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Retrospective Study

Long-term Investigation of Annulargrams and Intra-annular Fibrin to Treat Chronic Discogenic Low Back Pain and Radiculopathy: 1-, 2-, and 3-Year Outcome Comparisons of Patients with and without Prior Surgery

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Background: Discogenic chronic low back pain (cLBP) and radiculopathy are the most prevalent causes of disability worldwide. Older spine treatments often lack reliability and are associated with adverse events. Among surgical treatment options, discectomies weaken discs, and fusions cause direct damage to adjacent discs, so both treatments accelerate disc degeneration. Other regenerative medicine treatments, including "stem cell" (centrifuged bone marrow aspirate, BMC), and platelet-rich plasma (PRP), lack fibrin's bio-adhesive properties. Specifically, fibrin is a strong bio-adhesive, so it immediately integrates into disc defects and binds there, becoming a part of the disc and facilitating new disc tissue growth.

Objectives: To evaluate the safety and efficacy of this new pragmatic algorithm that both diagnoses and treats cLBP by (i) first identifying annulus fibrosus tears (fissures) in the region of symptoms and (ii) subsequently treating those tears by introducing fibrin to seal them and facilitate new tissue growth.

Study Design: Retrospective cohort study that prospectively reported validated measures in a registry.

Setting: Private, single-center, specialized, interventional pain management institution.

Methods: The patients we decided to observe had suffered from cLBP with or without radiculopathy symptoms in their legs for greater than 6 months. Prior to enrollment, all patients underwent physical therapy and at least 4 invasive treatments without relief. Failed treatments included BMC or PRP injections, intradiscal or intraarticular zygapophyseal joints, or combinations of both. Fluoroscopically guided epidural injections of corticosteroids or PRP were additional failed treatments, as were radiofrequency neurotomies in the medial branch. Candidacy for enrollment was based on meeting the aforementioned criteria and by having magnetic resonance image (MRI) screenings (1.5 T) and plain-film radiographs performed 6 months before treatment. In addition, those MRI screenings and radiographs had to rule out the following concomitant conditions: (i) carcinoma, (ii) fracture, (iii) instability, or (iv) severe vertebral canal or intervertebral foramen stenosis.

Results: Significant improvement was demonstrated at one, 2, and 3 years after treatment in all outcome measures. The mean duration of low back pain prior to treatment was 11.2 years. Patients' mean age was 56 years. Thirty percent of the patients were female, and 70% were male. Both the failed surgery cohort and nonsurgery cohort demonstrated significant improvement after fibrin treatment, with the failed surgery cohort realizing greater relative improvement. Significant improvements in the Oswestry disability index (ODI), visual analog scale, and PROMIS® (mental and physical) scores were consistent across age, gender, comorbidity, and exposure status. At the 12-month follow-up, 50% of patients achieved minimal clinically important differences utilizing the ODI. No severe adverse events were reported.

Limitations: Limitations include patient demographic factors, outcome-measure sensitivity, and that the outcomes were reported prospectively and calculated retrospectively as one-, 2-, and 3-year time frames were attained. Although categorical analyses comparing the prior surgical cohort to the nonsurgical cohort were performed, other pre-enrollment treatments were not categorized for comparison.

Conclusions: Intra-annular fibrin bio-adhesive sealant demonstrates the ability to be an effective treatment for alleviating discogenic cLBP and radiculopathy for at least 3 years, even in patients who all failed multiple prior treatments, including discectomy, fusion, disc PRP, or BMC. The results suggest the benefits of fibrin sealant. Future investigations to consider include a randomized double-blind controlled trial and further categorical analyses.

Key words: low back, radiculopathy, fibrin, disc herniation, degenerative disc, regenerative, annulargram, annulogram

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This study focuses upon several vital areas in the domain of back-pain treatment: (a) the global impact of chronic low back pain (cLBP), (b) the potential benefits of diagnostic annulargrams, and (c) the potential benefits of injecting allogeneic fibrin sealant into the annulus fibrosus (AF). In the AF, allogeneic fibrin sealant makes use of the area's innate regenerative potential. Relatively little has been published on the use of fibrin injections for cLBP. For this reason, the present study retrospectively reviews prospectively and independently collected data concerning a large set of patients (n = 827), using validated patient-reported outcome measures (PROMs). Given the overwhelming data on cLBP's global severity (incidence, prevalence, and economic impact), as well as the limitations and side effects of the current standards of care, it is crucial to study this novel method of treatment that overcomes the significant issues associated with other treatment options.

A. Global Impact of cLBP

The global burden of cLBP has been well documented and discussed in the medical literature. In brief, low back pain (LBP) and neck pain are considered the largest causes of disability (1), and LBP is the leading cause of years lived with disability (1,2). LBP is a major public health burden because of its costly care (3-14) and associated indirect costs, including lost work and reduced productivity (15). LBP is considered chronic when it lasts for more than 12 weeks (15-18), and it increases linearly through ages 30 to 60 (9). In the United States alone, cLBP imposes an annual societal economic burden consisting of direct medical costs and indirect costs in lost work and reduced productivity that ranges from $84.1 to $624.8 billion (5,19,20). The World Health Organization (WHO) considers the management of cLBP a global problem, as documented by the 2018 Lancet Low Back Pain Series Working Group and others (21-26). Discogenic (originating in the disc) LBP is the most common cause of cLBP (27); therefore, treating discogenic cLBP is of great importance.

B. Improving Therapeutic Treatment Options

Because of the suboptimal outcomes associated with other current treatment options, intra-annular fibrin sealant merits investigation. Although the evidence supporting the use of opioids and spinal fusion surgeries is insufficient, they are utilized heavily in attempts to treat cLBP (28-32). Spinal fusion surgery fails to address the underlying cause or pathophysiology of symptoms; additionally, in one investigation, 98% of spine surgeons reported that they would avoid fusion on themselves for cLBP (32-34). Rather than treating the underlying biochemical cause of most cLBP cases, spinal fusions fuse vertebral bodies adjacent to the affected discs, thereby decreasing motion preservation (35,36) and often leading to adjacent segment degeneration and requiring additional surgical interventions (Fig. 1) (30,31,37). Nevertheless, in the US, elective spinal fusion surgeries between 2004 and 2015 increased nearly 63% (from 60.4 to 79.8 patients per 100,000), and hospital costs exceeded $10 billion in 2015 (38). Moreover, in 2014, 4% of the adult US population (11.5 million people) were prescribed long-term opioid drug therapy to manage their cLBP (39).

Another procedure often performed in an attempt to alleviate cLBP is spinal discectomy, performed through either microendoscopic or open surgery. Unfortunately, discectomies weaken discs by removing portions of the disc AF that provide support and integrity, consequently accelerating disc degeneration, which exacerbates cLBP (40, 41). In fact, the most common cause of cLBP that follows spinal discectomies is discogenic pain (42).

Although spinal surgical arthrodesis and disc arthroplasty are often provided as treatment options, they are now more scrutinized in light of research affirming adjacent segment accelerated degeneration (43-54) and confirming that pain is attributed significantly more often to biochemical etiology than to mechanical etiology. In addition to accelerated adjacent segment degeneration, surgical arthrodesis and disc arthroplasty are associated with a respective recidivism rate of 26% and 11% (55-60), and the longevity of disc arthroplasty is unknown. Since no spinal surgery of any variety can correct AF defects, nucleus pulposus (NP) leakage can go unchecked, which may lead to additional back pain. Failed spinal fusion pain may originate from both the fused discs and the adjacent discs. Surgical discectomy, whether minimally invasive or not, worsens AF defects and increases NP leakage because the procedure removes a portion of the disc AF (52). Suture or ligature allows NP leakage, which prevents surgery from repairing AF defects (62-65).

Research indicates that biologic injections are procedures for safely, potentially treating cLBP with dramatically reduced hospital time, cost, and invasiveness (66-74). Biologic injections into intervertebral discs have included autologous platelet-rich plasma (PRP) and centrifuged bone marrow aspirate (BMC) as well as allogeneic biologics (e.g., growth factors and fibrin). To date, many biologic injection studies have involved small sample sizes (generally, 30-60 patients). While these studies' results are promising, investigators have often excluded patients with more severely degenerated discs, recognizing that injectate leaks from AF defects (75-81). In live animals, 100% of radiolabeled precursor cells injected into discs leaked through AF defects and were subsequently identified within new large osteophytes adjacent to the injected discs (82).

C. Benefits of Diagnostic Annulargrams

To overcome the weaknesses of magnetic resonance images (MRIs) and other diagnostic tests, diagnostic annulargrams identify tears precisely by visualizing contrast flow patterns through the 17-25 layers of the AF in a dynamic rather than static manner (83). Unlike MRIs and discograms, annulargrams have been chosen to identify pathology for several reasons, one of which is that they precisely target the tissue meant to be treated, whereas discograms target the NP and displace it outwardly. Annulargrams also identify AF tears, from which most disc pathology (except for carcinoma) results. Additionally, annulargrams are primarily objective while discograms rely on patients' subjective responses during disc pressurization. Favorable results of ongoing investigations suggest that annulargrams deserve consideration as diagnostic tests for identifying low back pain etiology (66).

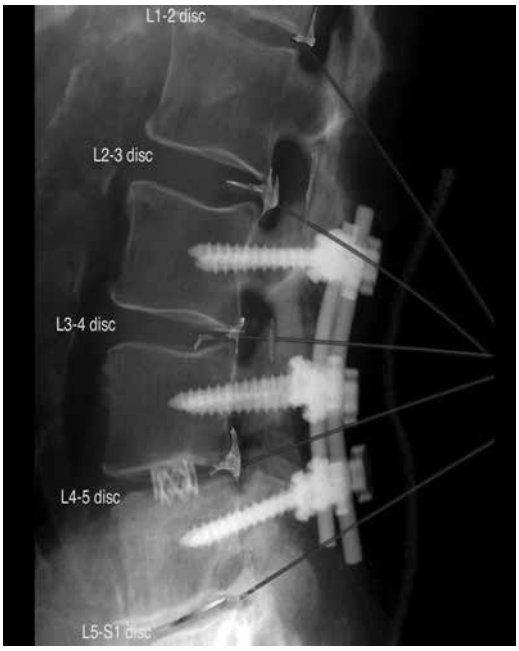

Fig 1. *Annulogram demonstrating posterior annulus fibrosus tears with epidural leaks at L1/2 through L5/S1 intervertebral discs.*

D. Benefits of Fibrin Injections

Fibrin, also referred to as Factor 1a, is a fibrous, nonglobular protein formed when thrombin makes contact with fibrinogen (84). Factor XIII completes the cross-linking of fibrin, causing it to harden to disclike firmness and contract (85). Contracted and cross-linked fibrin forms a mesh barrier that can be used to cover AF defects (86,87). Fibrin sealant, also referred to as fibrin "glue," is a unique hemostatic, sealant, and adhesive material that also possesses the unique ability to transform degenerated disc tissue into healthy disc tissue by initiating AF and NP growth (88). The mechanical properties of fibrin are unique, in that fibrin is a viscoelastic polymer, possessing both reversible elastic characteristics and irreversible plastic or viscous properties (89). Moreover, fibrin undergoes "strain stiffening," characterized by stiffness increasing as strain does, helping to prevent fibrin from suffering damage under harsh conditions, such as during disc shear forces (90). Additionally, fibrin possesses extreme extensibility

and compressibility, allowing fibrin AF defect plugs to deform without disruption (91). Gels based on fibrin are now used as scaffolds to optimize cellular activities, including differentiation, proliferation, and morphological changes (92,93). In summary, fibrin has become increasingly important as a unique biomaterial (94).

Fibrin hinders leakage, so intra-annular fibrin injections have the potential to transcend the shortcomings of other treatments, which are impeded by their leakage through AF defects (95). When introduced through intra-annular injections, allogeneic fibrin sealant occupies AF defects and coats annular nociceptors, while restoring mechanical strength within one hour of live human intra-annular injection (75). Therefore, fibrin serves as a physical barrier blocking NP and inflammatory mediators from nociceptors within the discs and as a barrier against affecting dura, meninges, and descending spinal nerves outside the discs (75).

Both in vitro and in vivo investigations of intradiscal allogeneic fibrin demonstrated promising results. In vitro studies demonstrated that allogeneic fibrin (250 mg/mL of fibrin) produced similar shear modulus qualities to that of the native AF (94). Another study showed that human AF cells cultured with fibrin on Type I collagen beads stimulated the synthesis of the anti-inflammatory cytokine interleukin-4 (96). In vivo studies have demonstrated that fibrin can be used to mechanically repair annular defects and stimulate new disc growth, restoring the biochemical and mechanical properties of the disc (75,96-98). Intradiscal fibrin prevented disc degeneration and stimulated proteoglycan content recovery in denucleated discs in a mammalian model (99). Specifically, these authors demonstrated through a prospective, randomized controlled trial of 220 porcine discs treated with either normal saline or concentrated allogeneic fibrin and aprotinin that the fibrin-treated discs were superior in all categories—proteoglycan composition, morphologic and histologic growth, cytokine content, and mechanical properties. That allogeneic fibrin sealant is safe for human use has been established across a wide range of applications, and the US Food and Drug Administration (FDA) has approved fibrin for multiple indications, including facial reconstruction, repairing blunt splenic trauma, and small bowel anastomosis (91-93).

Clinical research on intradiscal fibrin includes a multicenter, prospective clinical evaluation of 15 patients with discogenic LBP diagnosed by provocation discography and treated with intradiscal injections of allogeneic fibrin. At 26 weeks post-treatment, pain relief was demonstrated in 87% of the patients and functional improvement in 73% of the treated patients. At 52 weeks and 104 weeks, respectively, 73% and 60% of the patients reported combined pain and functional improvement (95).

Because fibrin was associated with these promising results, it was important to conduct a study that incorporated a large sample size and utilized fibrin as a disc sealant to investigate when intra-annular fibrin injections would reduce cLBP. The study would also need to measure the injections' effects through validated pain and quality of life scales in cases of multilevel degenerative disc disease (DDD). We sought to retrospectively evaluate the efficacy of intra-annular fibrin as a treatment for chronic low back pain (cLBP) and its associated radiculopathy using validated outcome scales that were collected prospectively and independently. Unlike many prior investigations, this study evaluated the amalgam of diagnostic and therapeutic refinements meant to improve patient outcomes, including: (a) diagnostic annulargrams used to identify annular defects, (b) targeting fibrin to those AF defects, and (c) treating each disc in the region of symptoms.

Methods

Study Design

This study incorporates 827 patients and tracks the same outcome measures at the baseline as well as at one, 3, 6, 12, 24, and 36 months after the procedure. All patients suffered from cLBP for a minimum of 6 months and had experienced the failure of prior treatments, such as surgery (including posterior-lateral interbody fusion [PLIF], laminectomy, laminotomy, and discectomy), intradiscal BMC injections, intradiscal PRP injections, BMC or PRP injections to the zygapophyseal (facet) joint, physical therapy, fluoroscopically guided transforaminal or interlaminar epidural corticosteroid injections, radiofrequency neurotomy, physical therapy, or medial branch blocks to rule out the posterior element of pain.

MRIs were obtained 6 months prior to treatment to rule out carcinoma, acute fracture, or severe vertebral canal or intervertebral foramen stenosis. If spondylolisthesis was observed by MRI, patients underwent lateral flexion/extension plain film radiographs to rule out instability.

Approval was obtained from the Institutional Review Board (IRB), and all patients, each of whom suffered from cLBP, reviewed, understood, and provided informed consent prior to their enrollment. Following

IRB approval, patients completed informed consent forms, were registered in the Regnerative Orthobiologics Registry (ROR) from October 2017 to September 2021, and reported baseline outcome data.

Inclusion criteria consisted of failure to experience relief after prior spine treatments, undergoing a lumbar assessment through MRI and x-ray screenings, and deciding to receive intra-annular fibrin injections. Exclusion criteria were met by patients presenting with carcinoma, fracture, spinal instability, spondylolisthesis that exceeded grade II, severe vertebral canal stenosis compressing the dura both anteriorly and posteriorly, and disc extrusions or non-contained disc herniations.

Interventions

Eight hundred twenty-seven patients with cLBP were enrolled in this study after undergoing screenings with MRI and x-rays. All patients followed the Discseel™ Procedure protocol:

(1) Annulargrams of each disc in the region of symptomology (no MRI or discograms); these annulargrams were diagnostic without being provocative, unlike discograms. The annulargrams consisted of a radiopaque contrast (GE Healthcare Technologies, Inc.) diluted with a Gentamicin antibiotic (Fresenius Kabi AG). This mixture (2-3 mL) was injected into each disc's AF, while visualization through 3-dimensional dynamic fluoroscopy was used to ensure intra-annular flow without vascular flow (extravascular flow) (100).

(2) Diagnostic annulargram tests in 4 discs in the region of symptoms; research affirmed that 3.2 discs were morphologically abnormal in over 90% of the patients with cLBP (95). Therefore, more than 3 discs were tested, unless extenuating circumstances prevented the testing of more than 3 discs. Each morphologically abnormal disc AF was treated with an injection of intra-annular, rather than intranuclear, fibrin sealant.

(3) The AF was targeted, avoiding the central NP, so that the contrast injection did not cause the outward displacement of the NP gel. Similarly, fibrin was injected only into the AF.

Following IRB approval, patients reported their pre-treatment baseline outcome measures into the ROR (October 2017 through September 2021) in order to assess pain, physical function, mental health, quality of life, and patient satisfaction. Subsequently, the patients underwent diagnostic annulargrams. Fibrin's precursors, including prothrombin, fibrinogen, aprotinin, and calcium, were reconstituted in the operating suite under aseptic conditions. Immediately afterward, patients underwent intra-annular allogeneic fibrin (Baxter Pharmaceuticals, LLC) injections to treat annular defects of all morphologically abnormal discs in the region of symptomology.

Under fluoroscopic visualization, the skin was marked, and local anesthesia was introduced to the skin puncture site only. Next, a 22-gauge trocar with a steel stylet and a curved tip was advanced under dynamic multiplanar fluoroscopic imaging into the midline posterior aspect of each disc's AF in the lumbar spine's region of symptomatology. Following the multiplanar verification of the trocar tip's placement within the posterior annulus, approximately 0.5-1 mL of radiopaque contrast diluted with gentamycin was injected slowly during dynamic fluoroscopic visualization, which was done to verify an intra-annular and extravascular flow pattern and identify AF defects. The needle position within the annular defects remained unchanged (Fig. 2).

Next, the fibrin precursors were merged while being introduced through the trocar needle toward the AF. The fibrin precursors transformed into fibrin during their introduction into the AF. Fibrin encircled the 22-

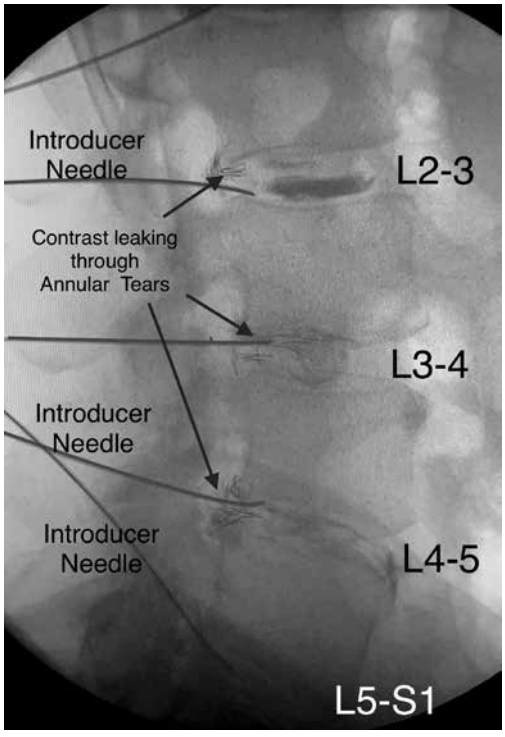

Fig 2. *Annulogram demonstrating normal L5/S1 disc, and posterior annulus fibrosis tears of L1/2 – L4/5 intervertebral discs.*

25 AF rings and adhered to the AF defects. The fibrin monomers assembled into fibrin polymers, with their bonds forming a 3-dimensional fibrin gel, stronger than innate AF tissue. Fibrin formation occurs before its components can leak out of AF defects. If the annulargram identified large AF defects with profuse leakage, the fibrin injection was performed more slowly. If the defects were smaller, fibrin was introduced more quickly, allowing it to reach discrete, smaller AF tears. Fibrin's desired occupation of AF defects was discerned by observing the displacement of the annulargram's radiopaque contrast in its wake; observing contrast flow assured extravascular fibrin introduction. This process was engineered into a strong adhesive system, analogous to the resin and catalyst of a 2-part epoxy. An optimal ratio of aprotinin molecules was included in the combination, prolonging fibrin's degradation and transformation of new disc tissue.

A mean of 3.7 discs were treated with 2.16 mL of allogeneic fibrin injected Into each disc.

Measures

The 4 most caudal discs (L2-3 through L5-S1) were assessed via diagnostic annulargrams in patients. The patients used the following validated outcome measures: the Oswestry Disability Index (ODI) (101), the Visual Analog Scale (VAS) for low back pain and for leg pain, the Numeric Rating Scale (NRS) (102-104), the Estimated Utility Score (EuroQol), PROMIS® Global Health Mental (GMH) and Global Health Physical (GPH) (105-107), and the modified North American Spine Society (NASS) patient satisfaction survey (108). Patients' reports were obtained at the baseline and at one, 3, 6, 12, 24, and 36 months after the treatment. Questionnaires were completed prospectively during office visits or through secure Web sites from the ROR.

Statistical Analysis

Descriptive analyses of the patient population included reporting means/medians (with standard deviations) for continuous variables; frequencies (with percentages) were used for categorical or discrete variables. An independent samples t-test, or nonparametric equivalent (109), was used to assess the differences in continuous variables, whereas a chi-squared or Fisher's exact test assessed the associations among categorical or discrete variables. Odds ratios and 95% confidence intervals were calculated to measure the strength of the association.

Longitudinal analysis of patient-reported outcome measures (PROMs) was performed at the baseline and at multiple follow-up time points (one, 3, and 6 months; one, 2, and 3 years). Linear mixed effect models were used to evaluate the PROMs over time and to make comparisons between surgical and nonsurgical patients. This modeling technique was chosen because it handled data robustly, whether or not those data met the assumption of normality. Additionally, the model controlled for the clustered nature of all observations that had been collected longitudinally and accounted for any missing data from patients who were lost to follow-up. All observations were analyzed using maximum likelihood estimations. Models included time as a fixed effect and the patient as a random effect to control for repeated measures. All parameter estimates from the models are reported as means and standard errors. The Bonferroni correction was used to adjust all P-values from the multiple pairwise comparisons.

Multivariable regression analyses were conducted to assess factors associated with follow-up and changes in ODI scores. A binary logistic regression model was built to evaluate the outcome of a follow-up ODI score of 20 points or lower, which indicated an outcome of minimal disability. In this analysis, only patients with baseline ODI scores of 30 points or higher were included in order to minimize any potential ceiling and floor effects.

For all analyses, statistical significance was defined as $P \leq 0.05$. All analyses were performed with SPSS® Statistics, version 23.0 (IBM Corp.®).

Results

Patients were enrolled and tracked using validated patient-reported outcome measures (PROMs) from October 2017 to September 2022. The patients (n = 827) were assessed for lumbar back pain to determine their potential eligibility for fibrin treatment. The ODI (101) was used to measure physical function, the VAS to assess low back and leg pain, and the EuroQol to measure quality of life. Other assessments were made using the PROMIS GMH and GPH (102-104) and Modified NASS patient satisfaction survey (108).

Descriptive patient characteristics of the study population are presented in Table 1. The mean age of the study population was 54 ± 14 years (range: 16 to 89), and the average body mass index (BMI) was 27.8 ± 5.2 (28% with BMI of 30 or above). Women made up 30% (n = 247) of the study population. For the study, the mean volume of fibrin used was 9.6 ± 3.4 mL. Twenty percent of the study cohort had indicated a

Table 1. *Baseline patient characteristics.*

Variable	Group	Total	Mean or Freq.	SD or Pct.	Min.	Max.
Age		826	54.8	14.1	16.0	89.0
BMI Score		667	27.8	5.2	16.2	57.9
Fibrin - Volume of Biologic (mL)		439	9.6	3.4	0.5	27.0
Gender	M	827	580	70%		
	F	827	247	30%		
Age	< 20	826	33	4%		
	30-39	826	96	12%		
	40-49	826	163	20%		
	50-59	826	200	24%		
	60-69	826	206	25%		
	70-79	826	110	13%		
	80+	826	18	2%		
BMI	< 25	667	194	29%		
	25-29	667	288	43%		
	30-34	667	126	19%		
	35+	667	59	9%		
Previous Back Surgery	N	827	667	81%		
	Y	827	160	19%		
Tobacco Use	Non-user	674	637	95%		
	User	674	37	5%		
	No Response					
Alcohol consumption	Never	674	175	26%		
	Occasionally	674	438	65%		
	Frequently	674	61	9%		
	No Response					

previous back surgery (fusion or discectomy) as part of their medical history.

All results of the entire cohort's patient-reported outcome scores over time, regardless of prior surgical history, are presented in Table 2. In all outcome measures collected, a significant improvement over time was found for the entire cohort (Figs. 3,4). Post-hoc analyses found a significant improvement at all follow-up time points compared to the baseline, except on the PROMIS® global mental health scale at the 3-year follow-up ($P = 0.170$).

Results of all patient-reported outcome scores over time are presented in Table 3, with a comparison of patients who received prior surgery to those who did not. Parameter estimates for each PROM report a significant improvement over time in both cohorts. Significant differences were observed at some time points between the patients who had received surgery previously and the patients who had not, with patients who had no history of previous surgery generally having better outcomes at each time point (Figs. 5,6).

Results of the modified NASS patient satisfaction survey over 36 months are presented in Table 4. NASS scores were interpreted both as a raw 4-response and as a binary "satisfied" (1 and 2) intervention versus "not satisfied" (3 and 4). The results across time were consistent, with more than two-thirds of the patients showing similar outcomes when comparing those who had prior surgery to those who did not (Fig. 7).

This study showed 50% of patients attained minimal clinically important differences (MCIDs) in pain relief and physical function at 12 months as assessed by the ODI. Of those who attained MCIDs at 12 months, 40% of the patients had improvement of 75% or more in their ODI scores and 74%

Table 2. *Results of patient-reported outcome scores over time.*

Outcome	Time	Mean	SD	95% CI		*P*-value	Time 1	Time 2	Mean Diff.	*P*-value
				Lower	Upper					
ODI	PRE	36.8	16.1	35.5	38.1	0.000				
	1M	31.2	17.1	29.6	32.8		PRE	1M	-5.6	0.000
	3M	25.1	16.4	23.5	26.8		PRE	3M	-11.7	0.000
	6M	25.7	17.8	23.9	27.5		PRE	6M	-11.0	0.000
	12M	24.2	19.3	22.0	26.4		PRE	12M	-12.6	0.000
	24M	23.3	19.3	20.3	26.2		PRE	24M	-13.5	0.000
	36M	21.8	19.5	18.0	25.6		PRE	36M	-15.0	0.000
VAS.Back	PRE	5.8	2.4	5.6	6.0	0.000				
	1M	3.9	2.4	3.7	4.2		PRE	1M	-1.8	0.000
	3M	3.5	2.5	3.3	3.8		PRE	3M	-2.3	0.000
	6M	3.7	2.7	3.5	4.0		PRE	6M	-2.1	0.000
	12M	3.6	2.8	3.3	3.9		PRE	12M	-2.2	0.000
	24M	3.5	2.9	3.1	3.9		PRE	24M	-2.3	0.000
	36M	3.4	3.0	2.9	4.0		PRE	36M	-2.4	0.000
VAS.Leg	PRE	4.4	2.9	4.2	4.7	0.000				
	1M	3.3	2.7	3.0	3.5		PRE	1M	-1.2	0.000
	3M	2.9	2.7	2.6	3.2		PRE	3M	-1.5	0.000
	6M	3.0	2.7	2.7	3.3		PRE	6M	-1.4	0.000
	12M	2.9	2.9	2.6	3.3		PRE	12M	-1.5	0.000
	24M	2.6	2.7	2.1	3.1		PRE	24M	-1.9	0.000
	36M	2.5	2.7	1.8	3.1		PRE	36M	-2.0	0.000
pGMH	PRE	46.4	8.7	45.6	47.1	0.000				
	1M	48.6	9.0	47.7	49.5		PRE	1M	2.2	0.002
	3M	49.8	9.5	48.9	50.7		PRE	3M	3.4	0.000
	6M	49.3	9.7	48.3	50.3		PRE	6M	2.9	0.000
	12M	50.1	9.9	48.9	51.3		PRE	12M	3.8	0.000
	24M	49.4	10.2	47.9	50.9		PRE	24M	3.0	0.010
	36M	49.6	9.2	47.3	51.9		PRE	36M	3.3	0.170
EuroQOL	PRE	0.63	0.09	0.62	0.64	0.000				
	1M	0.67	0.10	0.66	0.68		PRE	1M	0.04	0.000
	3M	0.69	0.10	0.68	0.70		PRE	3M	0.06	0.000
	6M	0.69	0.11	0.68	0.70		PRE	6M	0.06	0.000
	12M	0.70	0.11	0.69	0.71		PRE	12M	0.07	0.000
	24M	0.70	0.12	0.68	0.72		PRE	24M	0.07	0.000
	36M	0.71	0.11	0.68	0.73		PRE	36M	0.07	0.000

had improvement of 50% or more in the same area. There were no serious adverse events recorded throughout the study. An MCID is often described as "the smallest difference in the score in the domain of interest, which patients receive as beneficial and would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management" (110). MCID was defined as a 10-point reduction from the baseline ODI score.

Multiple regression analysis was performed to identify any potential factors associated with the ODI at follow-up (defined as a one- or 2-year follow-up). The ODI was analyzed as a continuous variable, both as the follow-up score and the change in ODI from

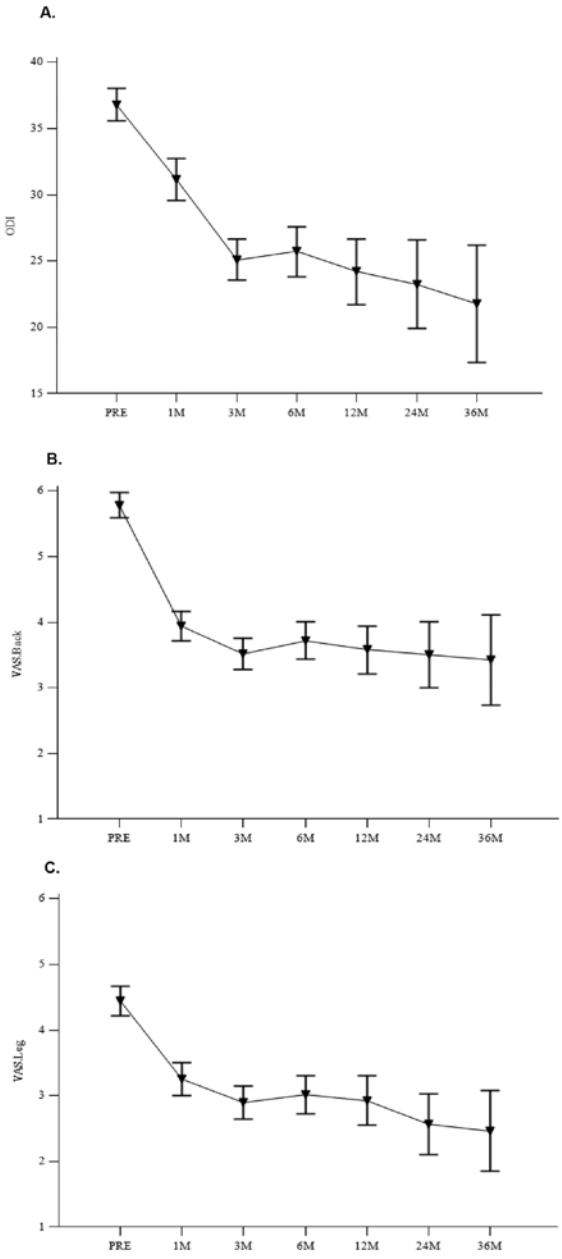

Fig. 3. *Results of all patient-reported outcome scores over time.*
*Error bars indicate 95% confidence intervals

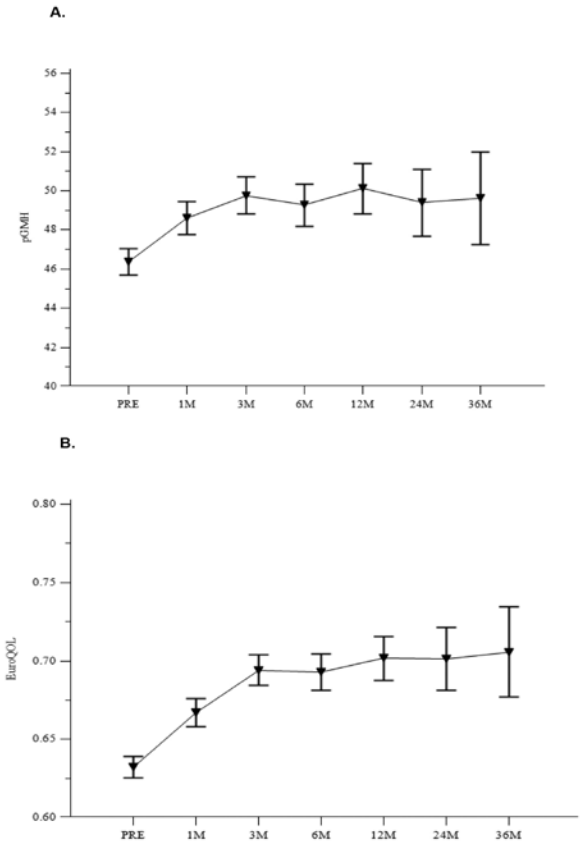

Fig. 4. *Results of all patient-reported outcome scores over time.*
*Error bars indicate 95% confidence intervals

the baseline. Higher ODI at baseline was associated with increased ODI scores at follow-up (Beta: 0.42, P = 0.018). Women were likelier to have lower ODI scores at follow-up (Beta: -8.81, P = 0.042). Similarly, looking at changes in the ODI from the baseline showed that an increased baseline ODI score was associated with a larger change in ODI score (Beta: 0.58, P = 0.001), and women were likelier to have seen an increased change in their ODI scores from the baseline (Beta: 8.81, P = 0.042) after adjusting for all other variables in the model.

The second model looked at the outcome of achieving an ODI score of 20 or less at follow-up in a logistic regression model. After patients with a baseline score of 30 or greater were excluded, it was demonstrated that a baseline ODI score was not a significant factor in the achievement of a ≤ 20 outcome (P = 0.605). Adjusting for all other factors in the model showed that women were over 3 times more likely to achieve that score (OR: 3.42, P = 0.009). Patients who had had a previous surgery were less likely to achieve a score of 20 or lower at follow-up (OR: 0.42), though this factor was not statistically significant (P = 0.092). Age and BMI did

Table 3. *Results of patient-reported outcome scores over time - surgery vs non-surgery.*

Outcome	Time	SURGERY				*P*-value
		Non-Surgery		Surgery		
		Mean	SD	Mean	SD	(B)
ODI	PRE	35.7	15.9	40.9	16.1	0.001
	1M	30.0	17.4	35.4	15.4	0.005
	3M	24.0	16.6	30.6	14.1	0.002
	6M	23.9	17.4	33.5	17.4	0.000
	12M	21.1	18.3	35.4	18.7	0.000
	24M	21.5	19.6	29.6	17.0	0.024
	36M	21.6	19.7	23.1	19.6	0.778
	P-value (W)	$P < 0.001$		$P < 0.001$		
VAS.Back	PRE	5.7	2.4	6.2	2.4	0.018
	1M	3.8	2.4	4.5	2.5	0.018
	3M	3.4	2.5	4.4	2.4	0.002
	6M	3.6	2.7	4.4	2.5	0.022
	12M	3.2	2.8	5.0	2.6	0.000
	24M	3.2	2.9	4.5	2.7	0.014
	36M	3.5	3.1	3.0	2.7	0.503
	P-value (W)	$P < 0.001$		$P < 0.001$		
VAS.Leg	PRE	4.3	2.9	5.1	2.8	0.001
	1M	3.1	2.7	3.9	2.7	0.005
	3M	2.7	2.6	3.8	2.6	0.002
	6M	2.8	2.7	4.0	2.7	0.002
	12M	2.5	2.8	4.4	2.9	0.000
	24M	2.2	2.5	3.8	2.9	0.006
	36M	2.3	2.7	3.4	2.9	0.241
	P-value (W)	$P < 0.001$		$P < 0.001$		
pGMH	PRE	46.8	8.8	44.5	7.9	0.009
	1M	48.9	9.0	47.3	9.0	0.130
	3M	50.1	9.5	48.0	9.6	0.079
	6M	49.8	9.8	47.1	8.9	0.034
	12M	51.2	10.1	46.2	8.2	0.001
	24M	49.5	10.7	49.0	8.4	0.771
	36M	49.1	9.5	53.1	6.6	0.259
	P-value (W)	$P < 0.001$		$P < 0.001$		
EuroQOL	PRE	0.64	0.09	0.61	0.09	0.013
	1M	0.67	0.09	0.65	0.10	0.018
	3M	0.70	0.10	0.66	0.10	0.002
	6M	0.70	0.10	0.65	0.10	0.000
	12M	0.72	0.11	0.65	0.09	0.000
	24M	0.71	0.12	0.67	0.11	0.080
	36M	0.70	0.12	0.76	0.07	0.126
	P-value (W)	$P < 0.001$		$P < 0.001$		

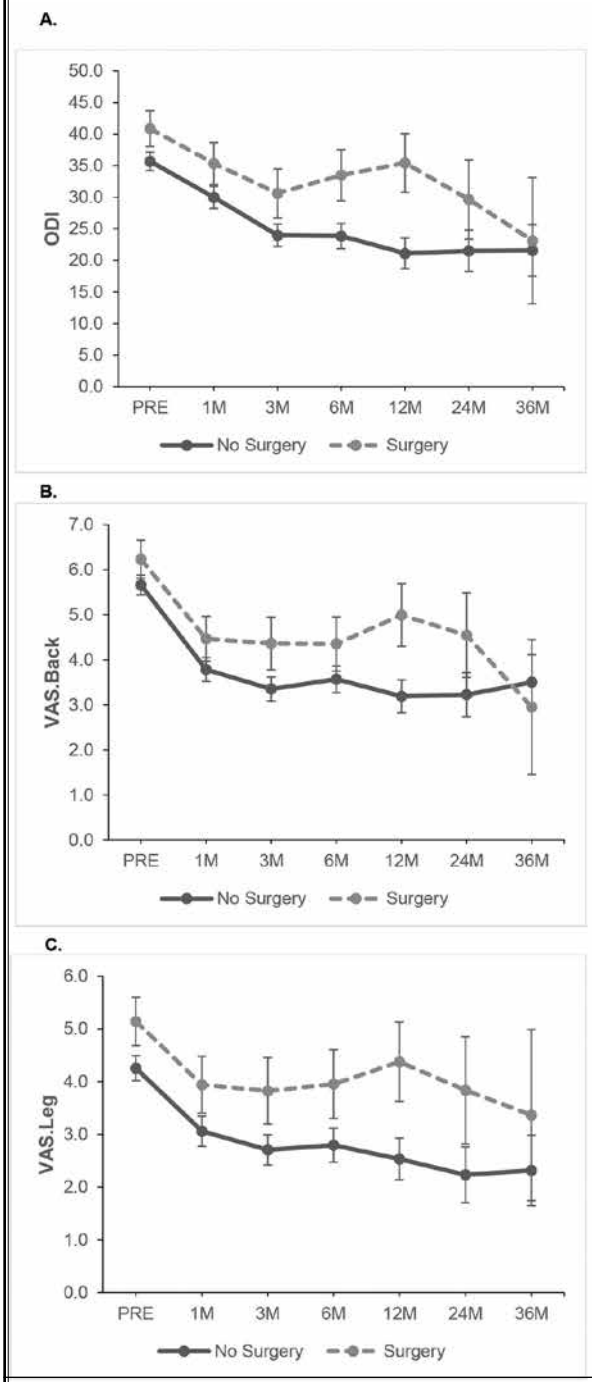

Fig. 5. *Results of all patient-reported outcome scores over time – surgery vs non-surgery.*
*Error bars indicate 95% confidence intervals

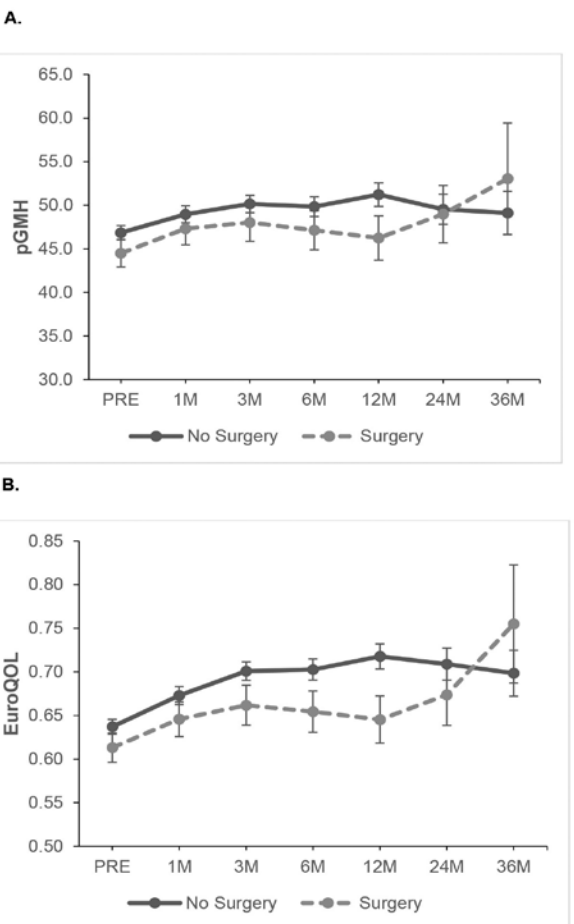

Fig. 6. *Results of all patient-reported outcome scores over time – previous surgery vs no surgery.*
*Error bars indicate 95% confidence intervals

not appear to impact the scores over time in any of the regression models. Fibrin improved patients' ODI function scores by > 30% at 6 months and was sustained to 3 years (Table 5).

Discussion

Annulargrams conducted at the time of the procedure are cost- and time-efficient, since they are performed concurrently with the procedure to provide physician guidance. In a future study, we will investigate the potential cost savings of this approach and the pragmatic algorithm that requires no more than an MRI screening. Additionally, to address this study's limitations, it is necessary to use a prospective randomized controlled trial to investigate the potential long-term benefits of introducing fibrin, which facilitates growth of disc AF (111,112), in discogenic cLBP treatments. The primary outcomes of this study have demonstrated that fibrin sealant is a viable option as a tool in physicians' arsenals for treating discogenic cLBP. Infection rates following interventional spine procedures are low (113), and no infections or other adverse events were observed in this study.

Table 4. *Results of patient-reported North American Spine Society (NASS).*

Patient Satisfaction												
Outcome	**Score**	**3M**		**6M**		**12M**		**24M**		**36M**		
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***P*-value**
NASS	4. I am the same or worse compared to before surgery	93	23%	72	21%	57	24%	26	20%	19	24%	0.221
	3. Surgery helped me but I would not go through it again for the same outcome.	34	8%	43	12%	18	7%	15	12%	2	3%	
	2. Surgery improved my condition enough so that I would go through it again for the same outcome	185	46%	158	46%	106	44%	51	40%	34	43%	
	1. Surgery met my expectations	93	23%	74	21%	60	25%	36	28%	25	31%	
Outcome	**Score**	**3M**		**6M**		**12M**		**24M**		**36M**		
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***P*-value**
NASS	Not satisfied (3 or 4)	127	31%	115	33%	75	31%	41	32%	21	26%	0.829
	Satisfied (1 or 2)	278	69%	232	67%	166	69%	87	68%	59	74%	

The NASS Patient Satisfaction Index:
1. The procedure met my expectations.
2. I improved less than I had hoped, but I would undergo the same procedure again for the same results.
3. The procedure helped, but I would not undergo the same procedure again for the same results.
4. I am the same or worse than before the procedure.

Table 5. *Multiple regression analysis.*

Outcome	**Parameter**	**Beta**	**SE**	**95% CI**		***P*-value**
				Lower	**Upper**	
ODI Post-Fibrin*	Baseline ODI	0.42	0.17	0.07	0.76	0.018
	Female (vs. Male)	-8.81	4.27	-17.29	-0.34	0.042
	Age	-0.04	0.16	-0.37	0.29	0.803
	BMI	0.00	0.01	-0.02	0.01	0.892
	Fibrin - Volume of Biologic (cc)	-0.38	0.57	-1.51	0.75	0.507
	Surgery	4.01	4.48	-4.89	12.91	0.373
	Smoker (vs. Non-Smoker)	1.52	7.03	-12.42	15.46	0.829
ODI Change vs. PRE	Baseline ODI	0.58	0.17	0.24	0.93	0.001
	Female (vs. Male)	8.81	4.27	0.34	17.29	0.042
	Age	0.04	0.16	-0.29	0.37	0.803
	BMI	0.00	0.01	-0.01	0.02	0.892
	Fibrin - Volume of Biologic (cc)	0.38	0.57	-0.75	1.51	0.507
	Surgery	-4.01	4.48	-12.91	4.89	0.373
	Smoker (vs. Non-Smoker)	-1.52	7.03	-15.46	12.42	0.829
Outcome	**Parameter**		**OR**	**95% CI**		***P*-value**
				Lower	**Upper**	
ODI ≤ 20 at Post-Fibrin**	Baseline ODI		0.99	0.95	1.03	0.605
	Female (vs. Male)		3.42	1.36	8.59	0.009
	Age		1.00	0.96	1.03	0.819
	BMI		0.96	0.89	1.03	0.219
	Fibrin - Volume of Biologic (cc)		1.09	0.96	1.23	0.180
	Surgery		0.42	0.15	1.16	0.095
	Tobacco User (vs. Non-User)		2.67	0.59	11.99	0.200

n = 108
* Post-op defined as 1Y or 2Y follow-up
** Patients with baseline ODI ≥ 30 were included to minimize ceiling/floor effects. Best outcome defined for ODI (≤ 20 for minimal disability).

Validated patient-reported outcome scales were used to evaluate the efficacy of fibrin sealant intra-annular injections; we included a mental component with PROMIS®. "PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of patient measures that evaluates and monitors physical, mental and social health in adults and children" (107). The goal of PROMIS® is to look at the physical, mental, and social domains of health and use the outcomes to improve the health of the population (114).

One major issue that could have been significantly detrimental to mental health was the COVID-19 pandemic, due to the consequent uncertainty of economic consequences; the fear of oneself and one's family, friends, and co-workers contracting the virus; and the unpredictability of survival for those who contracted the disease. COVID-19 had a significant impact on people's lives and mental health. In a 2020 study, the COVID-19 outbreak was associated with psychological distress, especially during the beginning states of the pandemic (115). Our data revealed declines in the mental health components of PROMIS® during this period at the height of the outbreak; this trend was consistent with other research demonstrating that COVID-19 had a negative effect on mental health scores (116-118). While it is unknown what specific impact COVID-19 had on the patients in this study, the aforementioned studies demonstrated consistency with the drop found in ours. While this study did not include a specific COVID-related mental health analysis, the slight decrease that occurred after month 12 and the increase after month 24 corresponded to the timing of the onset of the Sars-CoV-2 pandemic.

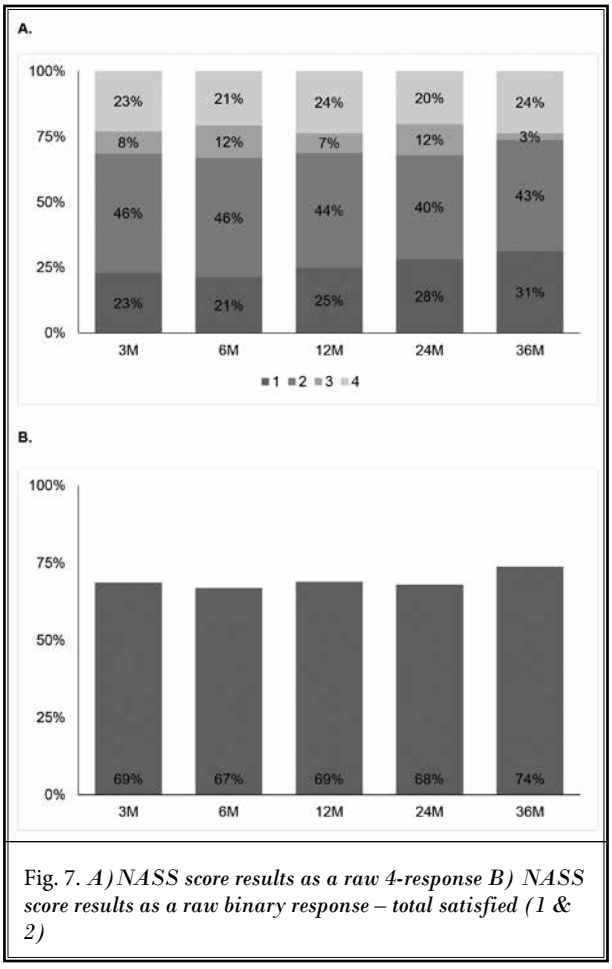

Fig. 7. *A) NASS score results as a raw 4-response B) NASS score results as a raw binary response – total satisfied (1 & 2)*

Limitations

While this study incorporated many patients and those patients reported their outcomes prospectively, it was not a prospective study. Additionally, this case study did not contain a control arm; rather, patients functioned as their own control through baseline measures. Moreover, patients electing to undergo intra-annular fibrin sealant injections could lead to potential selection bias. This study included a large number of patients recruited from all those who, within specialized clinics, met the inclusion and exclusion criteria. Future studies should investigate the benefits of fibrin sealant for discogenic cLBP in more general populations. Compliance with validated self-reported outcome measures was evaluated at the previously mentioned time points: baseline (83.43% compliance), one month (53.85% of the baseline), 3 months (49.18% of the baseline), 6 months (45.60% of the baseline), 12 months (41.69% of the baseline), 24 months (39.56% of the baseline), and 36 months (39.78% of the baseline). Missed follow-up in some patients could have altered some outcome measures. At both the baseline and 12 months later, office visits occurred. Future studies should incorporate either more office visits to increase compliance or more effort to ensure high compliance throughout each time point. It is often presumed that if there were poor outcomes at any given time point, patients would have certainly notified the procedure-performing author (KP). However, this presumption cannot be assumed; consequently, this may be another source of bias. This study demonstrated an imbalance of male-female ratios (30% women); such an imbalance in studies can be a potential source of gender bias. To help balance these possible sources of bias, prospective reporting of patients' outcome measures was collected by an independent organization, the Regenerative

Orthobiologics Registry (powered by OBERD; Universal Research Solutions, LLC), and independent statisticians analyzed these data.

Although cLBP is defined as 3 months of LBP (16,17), all patients suffered from cLBP for a minimum of 6 months, and follow-up on these patients lasted for up to 36 months. The sample size of this study was much larger than most biologic studies and provides promising results for treating cLBP with fibrin sealant. In future publications, randomized controlled trials (RCTs) with large sample sizes and 2-3 years of follow-up will be critical to reveal the long-term benefits and efficacy of intra-annular allogeneic fibrin annular injections as treatments for discogenic cLBP.

Conclusions

Intra-annular fibrin bio-adhesive sealant demonstrates the ability to effectively alleviate discogenic cLBP and radiculopathy for at least 3 years, even in patients who failed multiple prior treatments, including discectomy, fusion, disc PRP, or BMC. Results suggest the benefits of fibrin sealant; however, future investigations to consider include a randomized double-blind controlled trial and further categorical analyses.

Author Contribution

Authors KP, KB, PE, FH, JN, AS, CW were involved in all phases of the study and writing of the manuscript. WM was involved in data analysis, data review, editing, and submitting the final manuscript.

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