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Original Research Article

Intradiscal Injection of Fibrin Sealant for the Treatment of Symptomatic Lumbar Internal Disc Disruption: Results of a Prospective Multicenter Pilot Study with 24-Month Follow-Up

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Abstract

Objective. Assess the safety and efficacy of intradiscal fibrin sealant in adults with chronic discogenic low back pain.

Design. Prospective, nonrandomized Food and Drug Administration approved pilot study.

Setting. Three centers in the United States.

Subjects. Fifteen adults with chronic, single, or contiguous two-level lumbar discogenic pain confirmed through meticulous provocation discography.

Interventions. Volume- and pressure-controlled intradiscal delivery of BIOSTAT BIOLOGX® Fibrin Sealant with the Biostat® Delivery Device into symptomatic lumbar disc(s).

Outcome Measures. Assessments were performed at baseline, 72 hours, and 1, 4, 13, 26, 52, and 104 weeks following intervention. Potential adverse events were evaluated with serial assessment of neurological status, radiographic, and magnetic resonance imaging (MRI). Efficacy measures included serial assessments of low back pain visual analog scale (VAS) measurements and the Roland-Morris Disability Questionnaire (RMDQ).

Results. Safety neurological assessments, X-ray, and MRI showed no significant changes. Adverse events were reported in nine subjects. Two instances of low back muscle spasm and one case of discitis were the only events considered related to the procedure or product.

Efficacy. Mean low back pain VAS scores (mm) decreased from 72.4 (95% confidence interval 64.6–80.3) at baseline to 31.7 (17.4–46.1), 35.4 (17.7–53.1), and 33.0 (16.3–49.6); mean RMDQ score improved from 15.2 (12.7–17.7) at baseline to 8.9 (5.3–12.5), 6.2 (3.4–9.1), and 5.6 (2.9-8.4) at 26, 52, and 104 weeks, respectively.

Conclusion. Intradiscal injection of BIOSTAT BIOLOGX Fibrin Sealant with the Biostat Delivery Device appears safe and may improve pain and function in selected patients with discogenic pain.

Key Words. Low Back Pain; Discogenic Pain; Intervertebral Disc; Injection; Fibrin Sealant

Introduction

Low back pain (LBP) affects millions of adults in industrialized society [1]. Estimates of the medical and socioeconomic costs of back pain in the United States range from $84.1 billion to $624.8 billion per year [2], with one-third of these costs directly attributed to medical treatment and the remainder to lost wages and work productivity [3]. The majority of these costs (75%) are ascribed to a small minority (~5%) whose LBP becomes chronic (lasting longer than 3 months) [3]. Among the various anatomical sources of chronic LBP (CLBP), the lumbar intervertebral discs are the most common source accounting for at least 40% of patients with CLBP in a working age population [4].

A common clinical misconception assumes that degenerated discs, if present, are the cause of CLBP. The actual interrelationship of disc degeneration and pain is complex and sometimes counterintuitive. Lumbar disc degeneration is a complex, age-related process influenced by several poorly understood genetic, biological, and mechanical factors. Reduced cell nutrition, apoptosis, and increased concentrations of pro-inflammatory cytokines and proteolytic enzymes in the nucleus pulposus (NP) accompany the progressive morphological changes in characteristic of disc degeneration and senescence [5–8], and adversely influence the reparative function of normal NP cells, favoring catabolic tissue degradation [9]. Catabolic tissue degradation results in reduced proteoglycan and water content within the NP, progressive fibrosis of the NP, decreased disc height, increased shear forces across the disc anulus [10], and increased load sharing by adjacent vertebral elements [11,12]. The changes in the mechanical properties of the disc construct combined with alterations in force distribution within the disc may make the disc susceptible to impaired disc function [10] and localized tissue damage [10,12].

CLBP has been associated with intervertebral disc degeneration, protrusion, and extrusion [13–15]. However, these imaging findings are also present in a majority of asymptomatic individuals [15–18]. Other potential causes of CLBP, including joint pain (e.g., zygapophyseal, sacroiliac), are not readily identified by spinal imaging. Consequently, the presence of disc degeneration on radiographic and neuraxial spinal imaging is not specific in patients with CLBP [15,17,18].

CLBP has, however, been correlated with the presence of concentric and radial fissures of the anulus fibrosus [19,20] and reactive endplate changes [21,22]. Thus, although degenerative disc changes are present in most people *without* CLBP, in those individuals *with* CLBP—particularly those with disc pain—evidence of disc degeneration is nearly always present.

In the early stages of disc degeneration, the highest concentration of nociceptive innervation is present in the peripheral (outer) disc anulus [23–25]. Fissures extending to the outer disc anulus can expose nociceptive nerves within the outer anular layers to elevated concentrations of hyperalgesic, pro-inflammatory cytokines from the NP [14].

As the morphological distinction between the anulus and nucleus degrades with advancing degeneration, *de novo* nociceptive neoneuralization may accompany neovascularization into the disc nucleus from the vertebral ring apophyses [24–26].

Chronic pain associated with outer anular fissures in discs with otherwise preserved nuclear and anular anatomy has been dubbed “symptomatic internal disc disruption” (IDD) [19] and correlated with the presence of anular granulation tissue and nerve fibers containing nociceptive neurotransmitters such as substance P [14].

At present, no universally recognized treatment provides long-term relief from symptomatic IDD [27]. Common conservative therapies, often prescribed to temporize symptoms during acute episodes of back pain, have not proven effective for IDD. Conservative treatments typically employ rest, heat, psychological, behavioral, physical, manual or manipulative therapies, pharmacological agents, and lifestyle modifications. Numerous minimally invasive interventional strategies have targeted the neural elements of the disc or aspects of disc biology through injection of intradiscal steroids [28,29], intradiscal neurotropic agents [30,31], intradiscal electrothermal energy [32,33], or radiofrequency energy [34]. Unfortunately, neither conservative nor interventional therapies have been consistently effective for pain associated with symptomatic IDD [35,36].

When conservative or interventional therapies fail, more aggressive surgical interventions, such as lumbar disc arthrodesis or arthroplasty, are often recommended. Unfortunately, lumbar disc arthrodesis has failed to consistently demonstrate superior outcomes to nonsurgical therapies [37], has been associated with reoperation rates as high as 26% [38], and has been implicated in the acceleration of adjacent level degeneration [39]. Although recent studies suggest that total disc arthroplasty provides modestly superior pain relief compared with arthrodesis [38,40], disc arthroplasty is associated with reoperation rates up to 11.4% [38,41], and the longevity of clinical benefits is unknown [38].

Consequently, intense interest surrounds the development of less invasive and less risky treatments for disc pain. A number of sophisticated strategies addressing specific aspects of disc degeneration and pain are in various stages of development [36]. These include injection of anti-inflammatory preparations [28,29,42], tissue growth factors [43,44], neurotropic agents [30,31], cells and extracellular additives [45,46], and engineered constructs of tissue scaffolds or synthetic polymer constructs [47].

A novel, minimally invasive intradiscal therapeutic strategy—intradiscal injection of a fibrin sealant—was devised to address the physical findings associated with

symptomatic IDD (i.e., anular fissures) as well as the histochemical changes associated with disc degeneration and progressive loss of nuclear matrix. Conceptually, intradiscal injection of fibrin may provide short-term pain relief by physically sealing anular nociceptors from inflammatory compounds in the nucleus that are known to stimulate nociception. The persistent presence of fibrin, as a degradable tissue scaffold, may also provide longer term relief by promoting natural cellular repair of anular fissures. One specific formulation of fibrin (BIOSTAT BIOLOGIX, Spinal Restoration Inc., Austin, TX, USA) demonstrated significant downregulation in the synthesis of inflammatory cytokines (i.e., Interleukin (IL)-1β, IL-6, IL-8, Tumor Necrosis Factorα) and proteolytic enzymes (i.e., Matrix Metalloproteinase (MMP)-1, MMP-3), and upregulated the synthesis of anabolic cytokines (e.g., IL-4) in animal and *in vitro* models of experimental disc degeneration [48,49]. In a porcine model of disc degeneration, intradiscal BIOSTAT BIOLOGIX maintained nuclear volume and mitigated the negative mechanical consequences of surgical denucleation [48].

Due to the viscous nature of liquid fibrinogen and the requirement for complete mixing of fibrinogen and thrombin to generate fibrin, a novel intradiscal delivery device was engineered to safely and uniformly distribute fibrin in the disc (Figure 1). The resulting Biostat® System combines BIOSTAT BIOLOGX Fibrin Sealant and the Biostat Delivery Device. The active ingredients of BIOSTAT BIOLOGX Fibrin Sealant include concentrated human fibrinogen, thrombin, calcium chloride, and synthetic aprotinin acetate. Aprotinin acetate prevents premature degradation of fibrin by upregulating the synthesis of the anti-inflammatory cytokines and downregulating the cellular secretion of inflammatory cytokines and proteolytic enzymes [48,49].

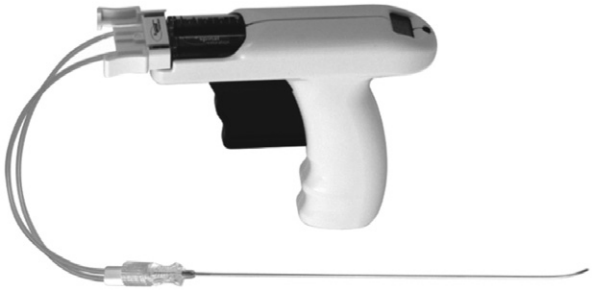

Figure 1 The Biostat Delivery Device is a hand-held delivery system that separates the reactive thrombin and fibrinogen solutions until just prior to delivery into the target disc. A digital pressure manometer allows the user to monitor intradiscal pressure during fluid delivery. When mixed, the liquid components can flow through the disc and anular fissures before rapidly transforming into a dense gel-like, three-dimensional microporous fibrotic matrix of fibrin.

In May 2008, a prospective multicenter pilot study was approved by the US Food and Drug Administration (FDA) to assess the safety of intradiscal injections of BIOSTAT BIOLOGX Fibrin Sealant, delivered with the Biostat System, in adults with discogenic LBP. Primary objectives of the study were to evaluate the safety of the Biostat System and intradiscal BIOSTAT BIOLOGX. Secondary objectives of the study were to evaluate the preliminary efficacy of the treatment using several different outcome measures and to inform the design of a larger, randomized clinical trial.

Methods

This study was conducted with Institutional Review Board approval at three centers (two spine pain centers and one community hospital) in the United States. All applicable Federal regulations, including the FDA good clinical practice requirements, as well as other generally accepted standards of good clinical practice, were followed at each center. Informed consent for participation in the study was obtained in accordance with FDA regulation 21 Code of Federal Regulations Part 50 and the Declaration of Helsinki. All study data were collated, processed, and audited by an independent clinical research organization (Regulatory & Clinical Research Institute, Inc., Minneapolis, MN, USA). Serious adverse events and adverse events related to the procedure or product were adjudicated by an independent Clinical Events Committee (CEC) composed of physicians knowledgeable in spine interventions and surgery. CEC members were compensated hourly but otherwise had no financial relationship with the sponsoring company.

Inclusion and Exclusion Criteria

All subjects had primary complaints of intractable axial LBP (without radicular pain or radiculopathy) for more than 6 months, refractive to pharmacological, conservative, and nonoperative modalities. All subjects had previously demonstrated a lack of relief from anesthetic lumbar medial branch blocks or intra-articular zygapophyseal joint blocks, and demonstrated no relief following interlaminar or transforaminal epidural steroid injection. The diagnosis of symptomatic IDD was made with pressure- and volume-controlled provocation discography performed in rigorous compliance with published standards [50]. The diagnosis of symptomatic IDD required recreation of concordant LBP at less than 50 psi over opening pressure, concomitant opacification of a posterior anular fissure extending to the outer posterior third of the anulus fibrosus, and at least one asymptomatic adjacent disc. Subjects with single and contiguous two level symptomatic discs were considered if all other inclusion criteria were satisfied.

Potential subjects were qualified according to extensive inclusion and exclusion criteria (Table 1). Painful discs with heights less than 67% of adjacent normal discs were excluded. Potential subjects were also excluded if they had ongoing workers' compensation claims, personal-injury or accident-related claims, or other health-related litigation.

Table 1 Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Age 18–75 (inclusive) and skeletally mature. 2. Voluntarily signs the subject informed consent form and agrees to the release of medical information for purposes of this study (HIPAA authorization). 3. Physically and mentally able to comply with the protocol, including ability to read and complete required forms, and willing and able to adhere to the follow-up requirements of the protocol. 4. Low back pain for at least 6 months. 5. Pretreatment baseline low back pain of at least 40 mm on a 100-mm visual analog scale. 6. Referred leg pain, if present, is of noncompressive origin, and there are no clinical findings of radiculopathy. 7. Low back pain is greater than leg pain (if present) as measured on a visual analog scale. If bilateral leg pain, back pain is greater than worst leg pain. 8. Low back pain unresponsive to at least 6 weeks of nonoperative treatment, which may include bed rest, anti-inflammatory and analgesic medications, chiropractic manipulations, acupuncture, massage, physical therapy, or home-directed lumbar exercise program. 9. Negative response to diagnostic medial branch block or facet joint injection. 10. No sustained relief with epidural injection of corticosteroids. 11. Diagnosis of symptomatic lumbar (L1/L2-L5/S1) internal disc disruption (IDD), which requires confirmation of discogenic pain at 1 or 2 contiguous levels through positive provocation discography performed using pressure manometry and identification of an adjacent normal disc. The disc provocation studies must precisely demonstrate concordant pain (<50 psi above opening pressure) and must demonstrate a fissure(s) in the outer one-third of the posterior or lateral anulus.	1. Cauda equina syndrome. 2. Active malignancy or tumor as source of symptoms. 3. Infection at the planned procedure site or active systemic infection. 4. Previous lumbar spine surgery. 5. Previous disc invasive treatment procedures at the affected level(s) (e.g., intradiscal electrothermal therapy, intradiscal radiofrequency thermocoagulation) in the past 12 months or intradiscal corticosteroid injection within the past 3 months. 6. Evidence of prior lumbar vertebral body fracture or trauma. 7. Disc bulge/protrusion at the symptomatic level(s) >4 mm. 8. Presence of disc extrusion or sequestration. 9. Clinical findings of lumbosacral motor or sensory radiculopathy. 10. Leg pain is greater than low back pain as measured on a visual analog scale. 11. Lumbar intervertebral foramen stenosis at the affected level(s) resulting in significant spinal nerve root compression or impingement. 12. Symptomatic central vertebral canal stenosis or absolute sagittal vertebral canal diameter <9 mm. 13. Loss of disc space height at the symptomatic level(s) greater than one-third of an adjacent normal disc (or of the expected height in the case of an L5-S1 disc). 14. Spondylolisthesis (≥grade 1) with or without spondylolysis at the symptomatic level(s). 15. Lumbar spondylitis or other undifferentiated spondyloarthropathy. 16. Dynamic instability on lumbar flexion-extension radiographs. 17. Positive response to diagnostic medial branch block or facet joint injection. 18. Positive response to diagnostic sacroiliac joint injection for those patients with pain in the sacral region 19. Sustained relief obtained with epidural injection of corticosteroids. 20. Symptomatic involvement of more than 2 lumbar disc levels. 21. Congenital or acquired coagulopathy or thrombocytopenia, or currently taking anticoagulant, antineoplastic, antiplatelet, or thrombocytopenia-inducing medications. 22. History of unexplained, easy, or persistent bruising or bleeding, bleeding from the gums, or bleeding problems experienced in previous surgical procedures. 23. Aspirin or aspirin-containing medication taken ≤7 days prior to the procedure. 24. Significant systemic disease, including unstable angina, autoimmune disease, rheumatoid arthritis, and muscular dystrophy. 25. Known or suspected hypersensitivity or allergy to drugs or components of the fibrin sealant, including aprotinin, used in the procedure. 26. History of, or current psychiatric condition, substance or alcohol abuse that would potentially interfere with the subject's participation in the study. 27. Ongoing or previous participation in another drug or device clinical study within the previous 2 months. 28. Subject known to be pregnant or nursing at time of enrollment or with plans to become pregnant within the planned length of follow-up (2 years). 29. Body habitus precludes adequate fluoroscopic visualization for the procedure or the procedure is physically impossible using the device. 30. Concomitant conditions requiring daily oral steroid usage for more than 30 days in the preceding 90 days. 31. Pending litigation against a health care professional, except where required by the insurer as a condition of coverage. 32. Prisoner or active military personnel who would not be available for follow-up. 33. Presence of ferromagnetic implants that would disallow MRI of the symptomatic disc(s). 34. Active or pending workers' compensation claims.

HIPAA = The Health Insurance Portability and Accountability Act of 1966; MRI = magnetic resonance imaging.

Procedure

Intravenous antibiotics were administered within 60 minutes prior to skin puncture. The skin was aseptically prepared with clorhexidine gluconate 4% and alcohol. Percutaneous target disc access was achieved through a standard posterolateral approach under local anesthesia using a styletted, curved-tip, 18-gauge intradiscal trocar introduced under real-time multiplanar fluoroscopic imaging, with or without using a second 14-gauge percutaneous sheath. Following multiplanar verification of trocar tip placement into the central third of the target disc nucleus, BIOSTAT BIOLOGX Fibrin Sealant was slowly injected using the Biostat Delivery Device following a standardized protocol. Slow (~0.2 mL/s) pressure-monitored intradiscal injection was performed until continued injection would result in one of three end points: sustained pressure above 100 psi, the entire volume of fibrin sealant (up to 4.0 mL maximum) was injected, or the subject could not tolerate continuation of the procedure. Anteroposterior (AP) and lateral fluoroscopy images were obtained with the intradiscal trocar(s) in place prior to injection and after removal of the intradiscal trocar(s) following injection.

Immediately following the procedure, subjects lay supine for at least 90 minutes prior to discharge. A neurological examination was performed prior to discharge. A gradual return to full activity was encouraged with normal activities of daily living resumed as tolerated after three days. Strenuous activities, heavy lifting, and repetitive bending were discouraged for the first 6 weeks following treatment.

Follow-Up

Clinical follow-up was performed at 72 hours and at 1, 4, 13, 26, 52, and 104 weeks following the procedure. The 26-week evaluation was specified as the primary efficacy end point with additional safety and efficacy evaluations planned at 52 and 104 weeks.

Safety Assessments

Safety assessments focused on three areas: detection of adverse events, radiographic changes, or neurological changes. Adverse events were defined as any undesirable clinical occurrence in a subject that appeared or worsened during the course of the clinical trial, regardless of whether it was considered to have a causal relationship to the procedure, delivery device, or biological material. An adverse event was considered serious if it resulted in death; inpatient hospitalization; significant, persistent, or permanent disability; medical or surgical intervention to prevent permanent damage or impairment of a body function; or was life-threatening.

Baseline plain radiographic films (standing neutral, flexion, and extension lateral views, and a standing neutral AP view) were used to document pretreatment lumbar spine morphology, disc height, and alignment. Roentgenographic imaging was repeated at 26, 52, and 104 weeks to assess the presence of any serial changes. Standardized measurements included disc height, translation (spondylolisthesis), neutral sagittal alignment, and angular motion in flexion and extension. Magnetic resonance imaging (MRI) scans were conducted at baseline and 1, 26, 52, and 104 weeks after the treatment procedure to qualitatively assess the condition of the treated disc(s), surrounding soft tissues, and bony structures. MRI reviews evaluated the appearance of the treated disc(s), presence of a bulge greater than 4 mm, presence of a disc herniation or extrusion, presence or absence of central canal stenosis, ganglionic impingement, or possible bony (e.g., ring apophysis) fracture. Fluoroscopic images from the procedure were examined to confirm appropriate trocar tip placement. All images were obtained using a standardized protocol and were assessed by independent neuroradiologists (Pharmascan, Inc., Belleair Beach, FL, USA).

The components of the neurological evaluation included serial assessment of motor, sensory, and reflex function, as well as the supine straight leg raise test.

Efficacy Measures

Efficacy outcomes instruments included a 100-mm visual analog scale (VAS) [51] for LBP, VAS for separate right and left leg pain, the Roland-Morris Disability Questionnaire (RMDQ) [52], a subject global assessment, a subject satisfaction questionnaire, subject employment status, post-procedure concomitant therapies and treatments, medication use for LBP, the Work Productivity and Activity Impairment questionnaire (WPAI) [53], and the EuroQol (EQ-5D) health-related quality-of-life questionnaire [54].

Statistics

Statistical treatment of the data was limited to descriptive statistical summaries, means with standard deviation (SD), 95% confidence intervals (CIs), and categorical frequencies. No formal prespecified hypothesis testing was planned or conducted because of the limited sample size of this investigation. Summaries include all available subject data.

Results

Fifteen subjects ranging from 18 to 65 years old (mean age 43.9, SD 10.7), including eight males (mean age 41.8, SD 6.4 years) and seven females (46.3, 14.4 years), were enrolled from June 4, 2008 through August 27, 2008. A total of 18 discs were studied in the 15 subjects (Table 2). Single-level procedures were performed in 12 subjects at L5/S1 (N = 10) and L4/L5 (N = 2). Two-level procedures were performed in three subjects at L4/L5 + L5/S1 (N = 2) and L3/L4 + L4/L5 (N = 1). The average volume of fibrin sealant injected per disc was 3.0 ± 0.8 mL with a range from 1.0 to 4.0 mL. In 11 of the 18 discs, injection was halted when sustained delivery pressure reached or exceeded 100 psi. In the seven remaining discs, the total

Table 2 Procedure summary

Number of subjects	15
Number of treated discs	18
Level treated, N (%)	
1 level	12 (80.0)
L4-L5	2 (16.7)
L5-S1	10 (83.3)
2 level	3 (20.0)
L3-L4/L4-L5	1 (33.3)
L4-L5/L5-S1	2 (66.7)
Final pull pressure (psi)	
Mean (SD)	92.9 (23.6)
Median	100.5
Min-Max	38–128
Delivered sealant volume (mL):	
Mean (SD)	3.0 (0.8)
Median	3.3
Min-Max	1–4
Reason stopped, N (%)	
Subject discomfort	0
Maximum pressure reached	11 (61.1)
Total volume delivered	7 (38.9)

SD = standard deviation.

volume available was injected into the disc. No injections were limited due to subject complaints of discomfort.

Fifteen subjects (100%) met 26-week primary end-point evaluation follow-up. One subject missed the 72-hour evaluation, and one subject missed the 1-week evaluation. Thirteen subjects (87%) were available for the first extended follow-up evaluation at 52 weeks, and 11 (73%) were available for the second extended follow-up evaluation at 104 weeks. One subject voluntarily withdrew prior to the 52-week evaluation, and one subject missed this evaluation and could not be contacted for the 104-week follow-up. Between 52 and 104 weeks follow-up, one subject voluntarily withdrew from the study, and another could not be contacted.

Adverse Events

There were 17 adverse events reported from nine subjects (Table 3). Three events were considered by the CEC to be possibly or probably related to the procedure. These related events include a single case of discitis and two instances of postprocedure lumbar muscle spasms experienced by two subjects within the first week after treatment. Two of the adverse events were considered serious because they resulted in hospitalization. These include the subject with discitis and one subject who underwent surgery to remove a kidney tumor that was identified at the 13-week follow-up. The CEC determined that the tumor was unrelated to the procedure after review of pretreatment imaging-identified findings consistent with a renal mass not noted on the original preprocedure radiology report.

One subject experienced new onset back pain occurring at 52 weeks. This corresponded to a fall-down steps prior to the 52-week follow-up and was 100% relieved by a sacro-iliac joint injection performed at another institution for “different pain than the study covered.” This was adjudicated by the CEC as pain unrelated to the study. Another subject experienced the onset of worsened LBP following a motor vehicle accident prior to the 104-week follow-up. This subject also complained of new neck pain and headache, which were ongoing at the final 104-week

Table 3 Adverse events and time course of reports

Body System	Onset/Discovery Interval (Weeks)								Total		
Specific Term	0	72-hour	1	4	13	26	52	104	Events	NSE	%*
Musculoskeletal									9	6	40.0
Muscle spasm		1	1						2	2	13.3
Buttock Pain				1					1	1	6.7
Sacroiliitis					1				1	1	6.7
Low back pain					1		2	2	5	4	26.7
Immunological									2	2	13.3
Lumbar discitis					1				1	1	6.7
Herpes genitalis			1						1	1	6.7
Genitourinary									1	1	6.7
Renal tumor					1				1	1	6.7
Other—nonspecific									5	4	26.7
Trip/fall			1	1			1		3	3	20.0
Motor vehicle accident					1			1	2	1	6.7

* % = NSE divided by total subjects (15).
NSE = Number of subjects with event.

follow-up. This was adjudicated by the CEC as pain unrelated to the study.

Neurological Examination

Neurological assessments of motor, sensory, and reflex did not change at any of the postprocedure follow-up time points in any subjects regardless of outcome. All straight leg raise examinations conducted were negative through the 26-week primary end-point evaluation and through the 52-week extended follow-up evaluation. Three subjects reported positive straight leg raise tests on both their right and left legs at the 104-week evaluation, although none of these subjects reported or demonstrated any associated clinical signs of radiculopathy.

MRI Assessments

Lumbar MRI at 1, 26, 52, and 104 weeks demonstrated no new disc bulges greater than 4 mm, disc herniation/extrusions, instances of central canal stenosis, ganglionic impingement, or vertebral fracture. Reactive endplate changes including Schmorl's nodes were observed in four subjects (three at one level, one at two levels) prior to injection. Pronounced increases in T2-signal and gadolinium-enhancement of the endplates were seen in the subject who developed L5/S1 discitis at 4-weeks. In two other subjects, asymptomatic reactive endplate changes were observed at 26 weeks (one subject, mixed Modic types I and II) and 52 weeks (one subject, "minimal," Modic classification not noted). One new asymptomatic Schmorl's node was seen in each of two separate patients, one with a baseline Schmorl's node at an adjacent level and the other without prior Schmorl's nodes. Both new Schmorl's nodes were detected on MRI at 26 weeks.

X-Ray Assessments

X-ray findings at 26, 52, and 104 weeks were similar to baseline with regard to translation, alignment, and angular motion. Disc heights remained at least two-thirds the height of adjacent discs and measured changes ranged between –2 mm and +2 mm of baseline height.

Efficacy Measures

Most subjects achieved significant reduction in LBP (VAS, Figure 2) and improvements in function (RMDQ, Figure 3) within 4 weeks of treatment. Except for a few episodic increases in pain or disability, relief was maintained to the primary 26-week end point. Many of the sporadic increases were caused by unrelated adverse events (i.e., auto accidents, falls, and the subject with renal cancer). Relief was generally maintained to the 104-week follow-up with evidence of some benefit decay at the later follow-up evaluations. One subject was completely unresponsive to treatment.

Clinically significant pain relief (≥30% reduction in LBP VAS) [55] was observed in 87% of subjects at the 26-week primary end point (Table 4). The mean individual reduction in baseline LBP VAS score was 40.7 mm (95% CI 25.4–56.0 mm), and the mean individual percent reduction in LBP VAS score was 55.6% (36.5–74.6%). Eight of 13 subjects (62%) at 52 weeks and 8 of 11 subjects (73%) at 104 weeks achieved at least a 30% reduction in LBP VAS score. Mean individual reductions in baseline LBP VAS scores were 37.3 mm (18.9–55.6 mm) and 38.5 mm (17.3–59.6 mm), while the mean individual percent reductions in LBP VAS scores were 51.2% (27.9–74.5%) and 49.9% (22.8–77.0%) at 52 and 104 weeks, respectively. Overall, mean LBP VAS scores decreased from 72.4 mm (95% CI 64.6–80.3 mm) at baseline to 31.7 mm (17.4–46.1 mm), 35.4 mm (17.7–53.1 mm), and 33.0 mm

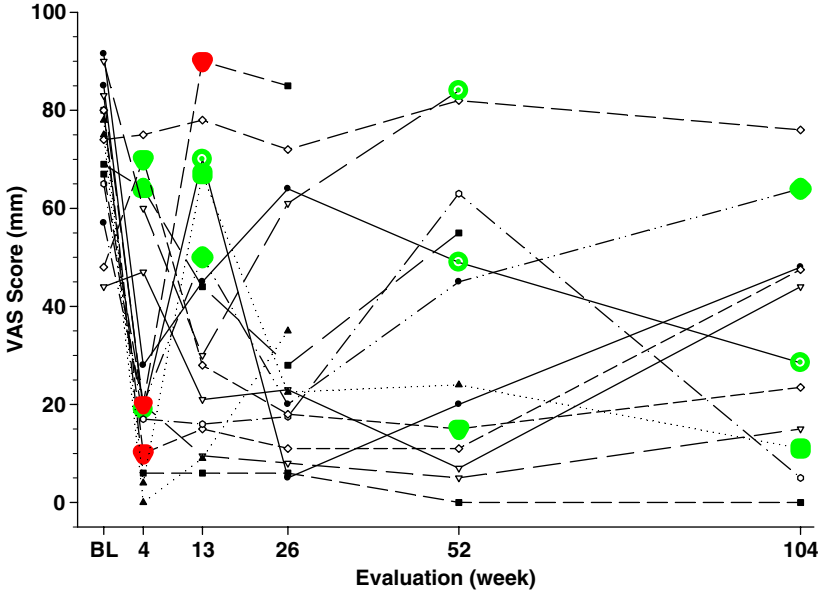

Figure 2 Individual subject visual analog scale (VAS) pain scores over time. Red symbol indicates a procedure-related adverse event in the preceeding interval. Green symbol indicates an unrelated adverse event in the preceeding interval.

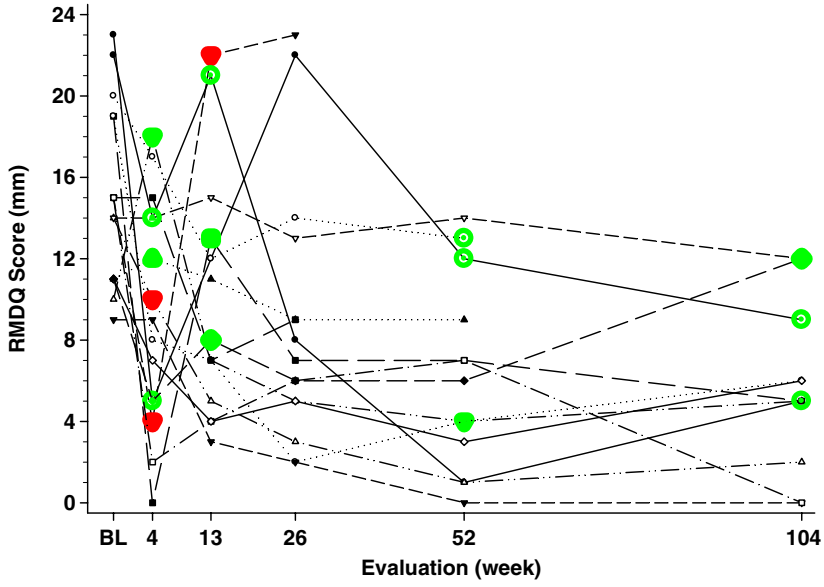

Figure 3 Individual subject Roland-Morris Disability Questionnaire (RMDQ) scores over time. Red symbol indicates a procedure-related adverse event in the preceeding interval. Green symbol indicates an unrelated adverse event in the preceeding interval.

Table 4 Pain relief (VAS) and functional improvement (RMDQ) efficacy outcome measures

	Evaluation					
Outcome Measure	Baseline N = 15	4 Week N = 15	13 Week N = 15	26 Week N = 15	52 Week N = 13	104 Week N = 11
VAS—low back						
Mean (SD)	72.4 (14.2)	30.7 (25.5)	38.6 (27.4)	31.7 (26.0)	35.4 (29.3)	33.0 (24.8)
Individual change, mean (SD)	—	–41.8 (8.4)	–33.9 (7.8)	–40.7 (7.1)	–37.3 (8.4)	–38.5 (9.5)
Individual % Change, mean (SD)	—	–52.9 (44.5)	–45.2 (38.3)	–55.6 (34.4)	–51.2 (38.5)	–49.9 (40.3)
Categorical results, number (%) of subjects						
>0% VAS increase	—	3 (20.0)	2 (13.3)	1 (6.7)	1 (7.7)	2 (18.2)
≥0 VAS reduction	—	12 (80.0)	13 (86.7)	14 (93.3)	12 (92.3)	9 (81.8)
≥30% VAS reduction	—	11 (73.3)	10 (66.7)	13 (86.7)	8 (61.5)	8 (72.7)
≥50% VAS reduction	—	10 (66.7)	8 (53.3)	10 (66.7)	7 (53.8)	6 (54.5)
≥75% VAS reduction	—	6 (40.0)	5 (33.3)	4 (26.7)	5 (38.5)	4 (36.4)
VAS—left leg, mean (SD)	15.0 (21.0)	14.2 (24.0)	15.4 (25.2)	21.9 (29.1)	14.5 (23.0)	11.1 (17.4)
VAS—right leg, mean (SD)	13.8 (13.2)	6.9 (19.9)	12.1 (25.4)	9.1 (22.6)	6.0 (19.0)	5.2 (8.0)
RMDQ						
Mean (SD)	15.2 (4.5)	9.3 (5.6)	10.1 (5.9)	8.9 (6.5)	6.2 (4.7)	5.6 (4.1)
Individual change, mean (SD)	—	–5.9 (7.5)	–5.1 (5.3)	–6.3 (6.1)	–9.0 (5.6)	–9.5 (5.6)
Individual % Change, mean (SD)	—	–31.9 (46.5)	–34.1 (34.0)	–41.9 (36.6)	–58.7 (30.0)	–60.6 (34.0)
Categorical results, number (%) of subjects						
≥0% RMDQ increase	—	2 (13.3)	2 (13.3)	1 (6.7)	0 (0.0)	1 (9.1)
≥0% RMDQ reduction	—	13 (86.7)	13 (86.7)	14 (93.3)	12 (92.3)	10 (91.9)
≥30% RMDQ reduction	—	8 (53.3)	10 (66.7)	11 (73.3)	11 (84.6)	9 (81.8)
≥50% RMDQ reduction	—	6 (40.0)	6 (40.0)	8 (53.3)	8 (61.5)	8 (72.7)
≥75% RMDQ reduction	—	3 (20.0)	0 (0.0)	3 (20.0)	4 (30.8)	4 (36.4)

— = not applicable; RMDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; VAS = visual analog scale.
The 26-week evaluation was the primary end point for efficacy.

(16.3–49.6 mm) at 26 (N = 15), 52 (N = 13) and 104 weeks (N = 11), respectively (Figure 4). Pronounced to complete pain relief (75–100% reduction in VAS score) was demonstrated in 4 of 15 (27%), 5 of 13 (39%), and 4 of 11 (36%) of subjects at 26, 52, and 104 weeks, respectively (Table 4).

Clinically significant improvements in function (RMDQ score, ≥30% reduction) [55] were achieved in 11 subjects (73%) at the 26-week primary end point (Table 4). The mean individual improvement in RMDQ score compared with baseline was 6.3 (95% CI 2.9–9.6), and the mean individual percent reduction was 41.9% (21.6–62.2%). At the 52- and 104-week evaluations, 11 or 15 (73%), and 9 of 15 (60%) evaluated subjects achieved at least a 30% improvement in RMDQ score. Mean individual improvements in baseline RMDQ scores were 9.0 (5.6–12.4) and 9.5 (5.6–13.5), and the mean individual percent improvements were 58.7% (40.5–76.8%) and 60.6% (37.7–83.5%), respectively. Overall, the mean RMDQ scores decreased from 15.2 (95% CI 12.7–17.7) at baseline to 8.9 (5.3–12.5), 6.2 (3.4–9.1), and 5.6 (2.9–8.4) at 26 (N = 15), 52 (N = 13), and 104 weeks (N = 11), respectively (Figure 4). Pronounced improvement of function (75–100% reduction in RMDQ) was demonstrated in 3 of 15 (20%), 4 of 13 (31%), and 4 of 11 (36%) subjects at 26, 52, and 104 weeks, respectively.

The EQ-5D index, which summarizes responses in five dimensions of health status (a value of 1 indicates the best possible health status), revealed an increase in the mean weighted index value of 0.476 (SD 0.191) at baseline to 0.637 (0.249) at the 26-week primary end-point evaluation and further increases to 0.717 (0.207) and 0.736

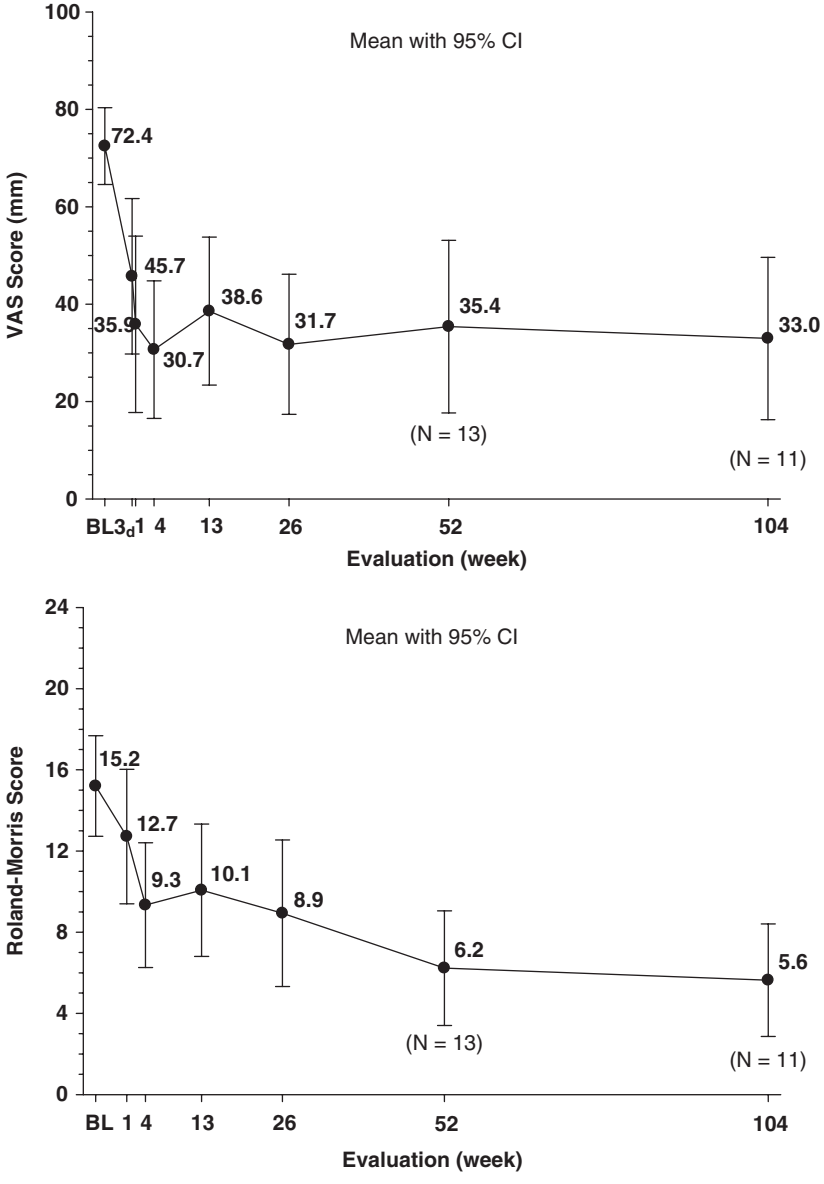

Figure 4 Mean visual analog scale (VAS) and Roland-Morris disability scores. CI = confidence interval.

(0.198) at the 52- and 104-week evaluations, respectively (Table 5). The mean EQ-5D VAS (anchored at 100 = best imaginable health state and 0 = worst imaginable health state) was 51.7 (25.9) at baseline and increased to 63.4 (23.9) at the 26-week primary end-point evaluation (Table 5). The EQ-5D VAS also increased at the 52- and 104-week extended follow-up evaluations to 69.7 (24.3) and 74.4 (17.1), respectively.

The global assessment question asked subjects to compare their current LBP to the pain before treatment and was assessed at 4-, 13-, and 26-week primary end-point evaluation, and at the 52- and 104-week extended evaluations. Eleven (73%), 10 (67%), and 11 (73%) of the 15 subjects responded that their pain was better or much better at the 4-, 13-, and 26-week evaluations, respectively (Table 5). At the 52-week evaluation, 11 of 13 subjects (85%) responded that their pain was better or much better compared with baseline. At the 104-week evaluation, 6 of 11 subjects (54.5%) responded that their pain was better or much better compared with baseline, and one subject (9%) responded "completely recovered." If subjects missing the 52- and 104-week evaluations are assumed not better, the percentages are 73% and 47%, respectively.

The subject satisfaction questionnaire asked subjects to rate their satisfaction with the treatment and whether or not they would recommend the treatment to a friend with the same condition. The questions were asked at 4-, 13-, and 26-week primary end-point evaluation, and at the 52- and 104-week extended evaluations. Twelve (80%), 13 (87%), and 10 (67%) of the 15 subjects expressed satisfaction at the 4-, 13-, and 26-week evaluations, respectively (Table 5). Fifteen (100%), 14 (94%), and 13 (87%) of the 15 subjects favored recommending the treatment to a friend at the 4-, 13-, and 26-week evaluations, respectively (Table 5). At 52 weeks and 104 weeks, 10 of 13 (77%) and 10 of 11 (91%) evaluated subjects expressed satisfaction with the treatment. All but one subject (at 52 weeks) favored recommending the treatment to a friend at the 52- and 104-week extended follow-up evaluations.

The WPAI questionnaire provided quantitative information on the impact of LBP on work productivity for working subjects and overall activity for all subjects (Table 5). The overall work impairment was reduced from 51% at baseline to 16% at 26 weeks, and the overall activity impairment was reduced from 70% at baseline to 40% at 26 weeks. Overall work impairment and activity impairment remained reduced compared with baseline for those subjects evaluated at 52 and 104 weeks. No significant changes were observed in employment status through the course of the study (Table 5).

No clear trend toward a reduction in medication use was observed at the 26-week primary end point. The majority of subjects continued to take analgesic medications throughout the follow-up period regardless of reported outcome (Table 5).

Discussion

The clinical safety of fibrin sealants has been established across a wide variety of therapeutic applications in humans [56,57]. Among numerous neurosurgical applications, fibrin sealants have been used for hemostasis during anterior cervical fusion [58] to treat postoperative cerebrospinal fluid leaks [59–62] and persistent cerebrospinal fluid leaks associated with long-term intrathecal catheterization [63], to treat symptomatic meningeal cysts of the sacral spine [64], to augment repair of peripheral nerves [65,66], and to provide a protective coating of cranial nerves during cranial base surgery [67]. Previous intradiscal applications of fibrin sealant have been reported following intradiscal electrothermal therapy [68] and percutaneous plasma discectomy [69]. This pilot study was the first to rigorously assess the safety and efficacy of intradiscal injection of fibrin sealant in patients with symptomatic IDD.

The Biostat Delivery Device was specifically designed to allow medical practitioners to effectively and safely deliver fibrin sealant into the IDDs associated with discogenic pain. In a proof-of-concept investigation performed in human cadaveric discs, the intradiscal flow patterns of fibrin sealant into anular fissures delivered with the Biostat Delivery Device closely approximated the distribution of radio-opaque contrast (Figure 5). The system uses a dual-lumen needle that prevents mixing of the reactive fibrinogen and thrombin solutions until the terminal 2 cm of the intradiscal needle. The Biostat Delivery Device also allows the medical practitioner to continuously measure intradiscal pressure during fibrin sealant delivery. The study protocol specified sustained intradiscal delivery pressures exceeding 100 psi were to be avoided. This pressure limit is commonly accepted in provocation discography. The limit is based on the lower end of pressures known to cause anular rupture in biomechanical studies that describe maximum anular rupture pressures of healthy and degenerated lumbar discs [70], and the relative strength of discs and their adjacent vertebra [71]. Delivery of fibrin sealant to a maximum transient pressure of 128 psi was tolerated without adverse event. There were no serious malfunctions of the delivery system.

The most significant complication in this study was a single case of discitis. Discitis is a known—but rare—complication associated with any intradiscal procedure. The subject in whom discitis developed described worsening back pain 10 weeks following intradiscal injection. The cultured pathogens from the infected disc aspirate at 13 weeks (*Haemophilus parainfluenzae* types 1 and 2, alpha-hemolytic *Streptococcus* sp., and nonpathogenic *Neisseria* sp.) were unusual in that they are not representative of typical skin flora that are more commonly associated with discitis following discography (*Staphylococcus epidermis*, *S. aureus*, and *Streptococcus* sp.) [72,73]. In particular, *Haemophilus parainfluenzae* is a member of the HACEK grouping of gram-negative coccobacillus (*Haemophilus* sp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella sp.*) [74].

Table 5 EQ-5D, subject global assessment, medications, employment status, and WPAI outcome measures

	Evaluation					
Outcome Measure	Baseline N = 15	4 Week N = 15	13 Week N = 15	26 Week N = 15	52 Week N = 13	104 Week N = 11
EQ-5D						
Index, mean (SD)	0.476 (0.191)	0.706 (0.167)	0.633 (0.188)	0.637 (0.249)	0.717 (0.207)	0.736 (0.198)
VAS, mean (SD)	51.7 (25.9)	68.1 (25.0)	65.4 (24.3)	63.4 (23.9)	69.7 (24.3)	74.4 (17.1)
Subject global assessment, N (%)						
Worse than ever	—	0 (0.0)	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
Much worse	—	1 (6.7)	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)
Worse	—	0 (0.0)	2 (13.3)	1 (13.3)	1 (7.7)	2 (18.2)
Same	—	3 (20.0)	2 (13.3)	1 (6.7)	0 (0.0)	2 (18.2)
Better	—	8 (53.3)	6 (40.0)	7 (46.7)	5 (38.5)	3 (27.3)
Much better	—	3 (20.0)	4 (26.7)	4 (26.7)	6 (46.2)	3 (27.3)
Completely recovered	—	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Satisfaction with treatment, N (%)						
Very satisfied	—	8 (53.3)	7 (46.7)	6 (40.0)	8 (61.5)	8 (72.7)
Somewhat satisfied	—	4 (26.7)	6 (40.0)	4 (26.7)	2 (15.4)	2 (18.2)
Somewhat dissatisfied	—	2 (13.3)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)
Very dissatisfied	—	1 (6.7)	2 (13.3)	3 (20.0)	3 (23.1)	1 (9.1)
Recommend treatment, N (%)						
Definitely yes	—	7 (46.7)	9 (60.0)	6 (40.0)	8 (61.5)	8 (72.7)
Probably yes	—	8 (53.3)	5 (33.3)	7 (46.7)	4 (30.8)	3 (27.3)
Probably no	—	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)
Definitely no	—	0 (0.0)	1 (6.7)	1 (6.7)	1 (7.7)	0 (0.0)
Medication for back pain N (%)*						
Any medication for back pain	13 (86.7)	12 (80.0)	11 (78.6)†	12 (75.0)	10 (76.9)	8 (72.7)
Opioids, including synthetic	12 (80.0)	10 (66.7)	9 (64.3)	10 (66.7)	9 (69.2)	6 (54.5)
Muscle relaxant	5 (33.3)	4 (26.7)	4 (21.4)	3 (20.0)	1 (7.7)	1 (9.1)
Other‡	4 (26.7)	1 (6.7)	2 (14.3)	5 (33.3)	2 (15.4)	3 (27.3)
Employment status N (%)						
Full-time/same duties	8 (53.3)	5 (33.3)	6 (40.0)	8 (53.3)	8 (61.5)	6 (54.5)
Full-time/reduced duties due to low back pain	3 (20.0)	3 (20.0)	3 (20.0)	3 (20.0)	2 (15.4)	1 (9.1)
Not working due to low back pain	1 (6.7)	3 (20.0)	2 (13.3)	1 (6.7)	1 (7.7)	1 (9.1)
Not working not low back pain related	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Unemployed seeking employment with full duties	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)
Unemployed not seeking work	3 (20.0)	4 (26.7)	2 (13.3)	3 (20.0)	2 (15.4)	2 (18.2)
WPAI						
Number of subjects employed	11	9	9	11	10	7
% work time missed due to low back pain, mean (SD)	8.7 (14.0)	13.1 (32.9)	0.8 (2.3)	0.4 (1.2)	4.7 (10.4)	0.0 (0.0)
% impairment while working due to low back pain, mean (SD)	48.2 (25.6)	35.6 (26.0)	16.7 (14.1)	15.5 (12.1)	21.0 (24.7)	14.3 (12.7)
Overall work impairment due to low back pain, mean (SD)	50.6 (27.6)	47.7 (30.1)	17.3 (14.4)	15.7 (12.5)	22.6 (27.3)	14.3 (12.7)
% activity impairment due to low back pain (all subjects), mean (SD)	70.0 (18.0)	46.0 (24.4)	38.7 (32.3)	40.3 (31.0)	27.7 (29.5)	28.2 (27.7)

* Totals exceed 100% because of subjects taking more than 1 medication.
† N = 14 at the 13-week follow-up.
‡ Includes OTC NSAID, acetaminophen, prescription NSAID, membrane stabilizing agent, and anxiolytic.
— = not applicable; EQ-5D = EuroQol; NSAID = non-steroidal anti-inflammatory drug; OTC = over the counter; SD = standard deviation; VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment.
The 26-week evaluation was the primary endpoint for efficacy.

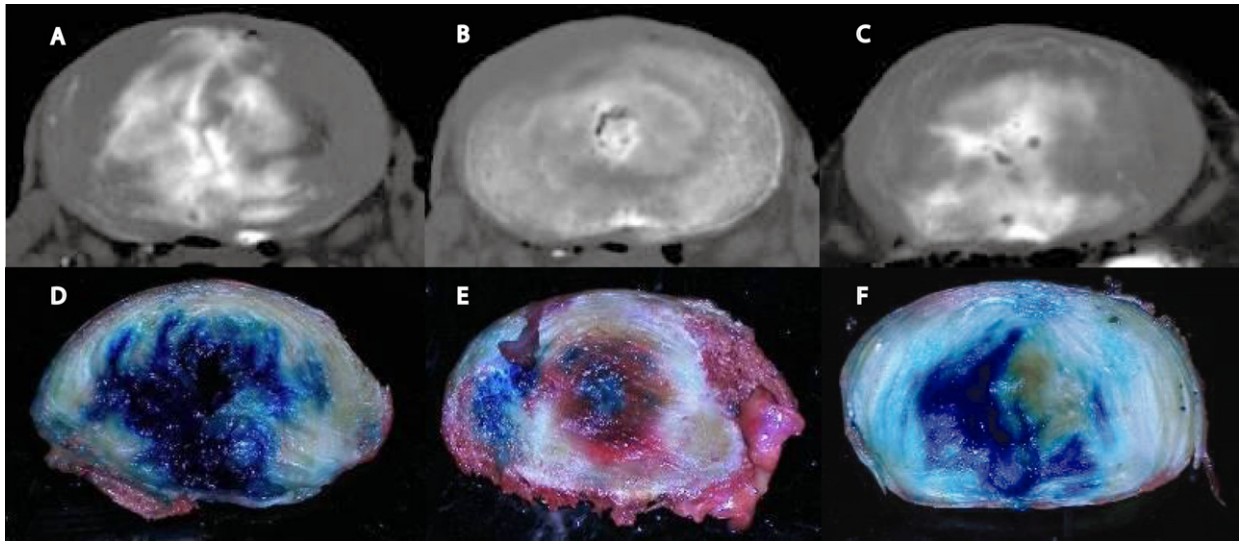

Figure 5 Flow characteristics of fibrin sealant into human cadaveric discs. Top row: computed tomography images of intradiscal contrast flow. Bottom row: corresponding fibrin sealant (stained with methylene blue) flow. (A, D) Middle of disc L4-L5; (B, E) superior margin at ring apophysis L3-L4; (C, F) middle of disc L3-L4.

These bacteria constitute normal oropharyngeal flora and are most notable for an association with culture-negative infective endocarditis. HACEK bacteria have, however, been cultured from disc aspirates in children and adults presenting with symptomatic and radiographic evidence of discitis [75–78]. There have also been reports of *H. parainfluenzae* infections of pacemaker leads [79], hip [80], and knee [81] implants. *H. parainfluenzae* infections causing psoas abscess [82], epidural abscess [83], and vertebral osteomyelitis [84] have also been described. These instances of opportunistic proliferation and haematogenous spread were often associated with nasal, oral, or dental pathologies but also occurred in otherwise healthy individuals. Detailed independent CEC review of the discitis case could not assign a definitive cause or source of the infection.

The other procedure-related adverse events were two cases of self-limited lumbar muscle spasm occurring within the first week following intradiscal fibrin injection.

No significant changes in other safety assessments, including serial radiographic, MRI, neurological status examinations were seen.

Secondary efficacy outcome assessments from this study were encouraging. Eighty-seven percent of the subjects achieved at least a 30% reduction in low back VAS score compared with baseline at the 26-week primary end point. Most outcome assessment instruments employed in this pilot study demonstrated improvements in the subjects' conditions, although the small number of subjects enrolled preclude definitive determination of efficacy.

This 15-subject pilot study was designed to provide a preliminary observation of the safety and efficacy of the Biostat System in the treatment of discogenic LBP due to symptomatic IDD. While the rigorous inclusion and exclusion criteria did thoroughly define the treated patient population and a wide battery of outcome assessment instruments were prospectively collected, conclusions are limited by the relatively small number of subjects enrolled, lack of a control group, loss of 2 of 15 subjects (13%) at 52 weeks and 4 of 15 (27%) subjects at 104 weeks, and other limitations of potential prospective bias inherent in the unblinded nature of this study.

Conclusions

This pilot study of intradiscal injection of fibrin sealant in patients with chronic discogenic LBP demonstrated encouraging safety and efficacy outcomes. Neurological assessments, consisting of motor, sensory, reflex, and straight-leg raise test evaluations were unremarkable at all postprocedure time points suggesting that the injection of fibrin sealant into the disc was not associated with the development of motor, sensory, or reflex deficits or radiculopathy. The treatment-related adverse events of postprocedure pain and muscle spasm are typical of those that may be expected for similar procedures, such as discography. Discitis is a known risk with any invasive disc procedure. The cause or source of the single case of discitis occurring in this study was not definitively identified. A majority of subjects demonstrated improvements in multiple patient outcome measurements, including measurements for pain, function, and health-related quality of life. These results support consideration of a more

rigorous, multicenter, randomized, blinded, placebo-controlled investigation of intradiscal injections of BIOSTAT BIOLOGIX Fibrin Sealant for the treatment of discogenic LBP.

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