Randomized Controlled Trial

Percutaneous Intradiscal Hydrogel Implantation Versus Sham Control for Chronic Discogenic Low Back Pain: A Randomized Controlled Double-Blind Trial

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Background: Degenerative disc disease is a leading cause of low back pain. Conservative treatments like pain medication and exercise therapy have shown mixed results, while procedures like fusion surgery carry risks such as adjacent segment disorder and surgical morbidity. Therefore, there is a critical need for treatments that bridge the gap between conservative care and surgery.

Objective: To assess the efficacy of intradiscal hydrogel implantation compared with sham treatment of intradiscal injection of saline in patients with chronic discogenic low back pain.

Study Design: Prospective, double-blind, randomized, controlled, multicenter trial.

Setting: Two tertiary interventional pain care centers in Switzerland and in the Netherlands.

Methods: Forty-nine patients with chronic discogenic low back pain unresponsive to conservative treatment were randomized to receive either intradiscal hydrogel implantation or a sham treatment. Control Group patients could cross over to hydrogel treatment after 6 months. The primary outcome was pain improvement at 6 months. Secondary outcomes included disability, quality of life, employment status, Patient Global Impression of Change score, analgesic use, disc space height, and disc degeneration. Adverse events were continually assessed.

Results: At 6 months postprocedure, the Hydrogel Group patients had improved pain scores compared to Control Group patients, though not statistically significant (P = 0.070). Six out of 24 patients in the Hydrogel Group reported much improvement on their Patient Global Impression of Change scores, compared to 0 out of 25 in the Control Group (P = 0.008). Within-group disability improvements were statistically significant in the Hydrogel Group but not in the Control Group. No significant differences were found between groups in disability, quality of life, or employment status. Only one serious adverse event was reported—a patient from the Hydrogel Group was hospitalized due to a possible exacerbation of low back pain 6 days postprocedure.

Limitations: This trial's limitations include strict eligibility criteria and questions about the validity of intradiscal saline as a placebo.

Conclusions: This trial suggests that percutaneous intradiscal hydrogel implantation may reduce chronic discogenic pain and disability, with significant Patient Global Impression of Change improvements, though larger trials are needed to confirm efficacy.

Key words: Chronic discogenic low back pain, degenerative disc disease,; hydroge,; intradiscal injection, randomized controlled trial.

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The intervertebral discs have been identified as the source of pain in 26%–40% of all patients with low back pain (LBP) (1,2). Discogenic LBP is typically characterized by persistent, centralized pain, which worsens with axial loading and is associated with degenerative disc disease seen on magnetic resonance imaging (MRI) (1-4). Aging leads to disc dehydration due to proteoglycan loss, reduced elasticity, and nerve ingrowth, which all contribute to pain (5,6). Additionally, a decline in vascular channels reduces blood flow to the cartilaginous endplates, resulting in a decreased nutrient supply to the disc. This nutrient deficiency leads to the accumulation of lactic acid and a subsequent decrease in pH levels (6,7); studies suggest a direct correlation between low pH levels and discogenic pain (8,9).

Treatment options for discogenic LBP include conservative management such as pain medication, exercise therapy, and multidisciplinary biopsychosocial rehabilitation. However, studies have shown mixed results concerning their efficacy (10). More invasive options, like interbody fusion and disc arthroplasty, have demonstrated improvements in pain, but are associated with risks, including adjacent segment disorder and surgical morbidity (10,11). Therefore, there is a critical need for developing new treatment options that bridge the gap between conservative care and invasive surgery (12).

Implanting hydrogels into an intervertebral disc's nucleus pulposus represents a promising minimally invasive technique for treating discogenic pain (9,13). The hydrogel GelStix™ Nucleus Augmentation Device (Replication Medical, Inc.) (hereafter called hydrogel), which is primarily composed of hydrolyzed polyacrylonitrile, is inserted into the nucleus pulposus via a needle. Once implanted, it has the potential to absorb bodily fluids, providing hydration to the disc, which may result in an increase in disc volume (Fig. 1). This process promotes disc hydration and fluid exchange, and helps maintain a balanced pH level. Consequently, these effects contribute to disc preservation and are expected to result in pain relief (14).

The aim of our randomized controlled trial was to assess the efficacy of percutaneous intradiscal hydrogel implantation in patients with chronic discogenic LBP compared with a sham treatment.

Methods

Our double-blind, randomized, controlled, multicenter trial was conducted at 2 tertiary interventional pain care centers. Approval to conduct the trial was granted by the Research Ethics Committee of the Canton Ticino, Switzerland (CE 2982) and by the Medical Ethical Committee Arnhem-Nijmegen, the Netherlands (2016-2944). A detailed description of the trial protocol, including the eligibility criteria has been previously published (15). Eligible patients had discogenic LBP confirmed by MRI and discography; those who had prior spinal surgery, nerve root compression, or severe degeneration were excluded. The trial was registered at ClinicalTrials.gov (NCT02763956). Written informed consent was obtained from all patients prior to their enrollment in the trial.

Patients were randomized 1:1 to receive either hydrogel (Hydrogel Group) or sham treatment (Control Group), stratified by the treating center. Randomization was centrally managed by the by the Clinical Trial Unit of the Ente Ospedaliero Cantonale (CTU-EOC), Bellinzona, Switzerland, and was stratified by the treating center using blocks of 4. Both the hydrogel implantation and sham procedures were carried out in an identical manner. Blinding was maintained for patients, outcome assessors, and treating physicians, with only the proceduralist unblinded.

Patients who continued to experience substantial discogenic LBP at 6 months postprocedure (a Numeric Rating Scale [NRS-11] score ≥ 5) could request unblinding. If unblinding revealed they were initially assigned to the Control Group, they were offered the option to cross over to hydrogel treatment. Blinding was maintained for all other patients throughout the remainder of the trial, up to the 12-month follow-up.

Patient Selection and Data Collection

Patient recruitment started on June 27, 2016, and follow-up continued until the completion of this analysis on July 1, 2022.

Thirty minutes prior to the procedure, patients in both groups received an intravenous dose of one g cefazolin as a bacterial prophylaxis.

Percutaneous Intradiscal Hydrogel Implantation

The hydrogel implantation procedure has been described in detail previously (15). In summary, patients randomized to receive the investigational hydrogel (GelStix™ Nucleus Augmentation Device system, STX-1835S) underwent percutaneous intradiscal hydrogel implantation. Under sterile conditions and local an-

esthesia, an 18G needle tip (18GTXX165mm, Replication Medical, Inc.) was positioned in the center of the nucleus pulposus under fluoroscopic guidance. After the stylet was removed from the needle, the cap was removed and the holder threaded onto the needle. The spine interventionalist then pushed the piston of the holder to drive the hydrogel into the introducer needle. Once the holder was removed, the needle stylet was advanced through the needle to expel the hydrogel into the nucleus pulposus. This step was followed by fluoroscopic confirmation to ensure the needle tip was correctly positioned centrally within the nucleus pulposus. The procedure was repeated to insert additional hydrogel, with a maximum of 3 hydrogels per symptomatic disc.

At one site, 2 senior spine interventionalists (EK and PM) performed all procedures, while at the other site, a single senior spine interventionalist (JWK) performed all procedures. Each of these 3 senior spine interventionalists had over 10 years of experience in performing spinal pain intervention procedures.

The Sham Intervention

For the sham intervention, the spine interventionalist injected a total of 1 mL of saline (NaCl 0.9%) into the nucleus pulposus of the affected discs using a double-needle technique with a 25G inner needle and a 22G outer needle.

To maintain effective blinding, both the hydrogel and sham procedures were performed identically under fluoroscopic guidance, using the same equipment and needle technique, with patients shielded from visual cues during the procedure. Additionally, postprocedure instructions and follow-up protocols were standardized to avoid revealing treatment allocation.

All patients were instructed to avoid heavy lifting in the 2 weeks following the procedure. At 2 weeks postprocedure, patients in both groups began physiotherapy based on a trial-specific protocol; they received treatment once a week for 9 weeks (15). They were also taught how to perform the exercises at home and were asked to continue these exercises 3 times a week for 6 months. The continuation or modification of pain medication was allowed throughout the 12-month trial period.

Primary Outcome Measure

The primary outcome was the change in LBP score between baseline and 6 months, assessed using an 11-point NRS-based pain diary recorded over 5 days with entries made 3 times a day. Daily pain scores were averaged; peak pain scores were also calculated from the diaries.

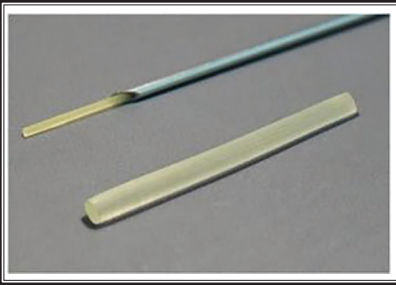

Fig. 1. *The hydrogel is water-soluble and enlarges in volume, absorbing the body's own fluids, after hydration.*

Secondary Outcomes Measures

Secondary outcomes included NRS-11 score changes at additional follow-up points (one week, and postprocedure months one, 3, and 12); Patient Global Impression of Change (PGIC), disability, as measured by the Oswestry Disability Index (ODI), and health-related quality of life assessed using the EuroQol Group EQ-5D-5L™ questionnaire. Additionally, the disc degeneration process and midsagittal disc height were evaluated using MRI at 12 months postprocedure, compared to baseline (≤ 6 months preprocedure). Pain medication consumption was recorded in the patient's pain diary. Employment status was recorded as an additional measure of treatment efficacy. Safety data were collected at each visit.

To assess the success of blinding, patients and their treating physicians (i.e., not the physician who performed the procedure) were asked before unblinding to indicate which treatment they believed they had received: hydrogel, sham, or if they were unsure. These responses were then compared with the actual treatments administered.

Statistical Analysis

All analyses were performed according to the intention to treat principle. Baseline characteristics were described as mean (SD) or as median (interquartile range [IQR]), or as count and percentage, and were stratified by group. The primary outcome—mean pain at 6 months postprocedure—and other pain scores over the total course of follow-up until 6 months postprocedure were compared using the independent-samples t test. To explore gender-specific effects, we additionally stratified the analysis of the primary outcome by gender and used linear regression analysis to test the interaction between gender and treatment. A significant interaction would indicate evidence of

a difference in effect of the hydrogel treatment between men and women. Secondary outcome measures were compared between groups using the independent-samples t test for continuous variables, and the Pearson χ^2 test for categorical variables. Within-group change-from-baseline of continuous outcomes was tested using the paired-samples t test. Results at 12 months postprocedure were compared between groups for the primary outcome. Other outcomes at 12 months postprocedure were described only for the Hydrogel Group, because of the possibility to cross over at 6 months for patients in the Control Group. All analyses were performed using R version 4.0.4 (The R Foundation).

Results

Patient Demographics

From June 2016 through June 2022, 272 patients were screened; 49 were enrolled (24 in the Hydrogel Group, 25 in the Control Group) (Fig. 2). Most exclusions were due to ineligibility (n = 186) or patient refusal (n = 37). Five patients withdrew or were lost to follow-up before the 12-month assessment. Baseline characteristics were similar between groups (Table 1). The most treated levels were L4-L5 and L5-S1 (Table 2).

Primary Outcome Measure

At 6 months postprocedure, the Hydrogel Group had a larger decrease in the mean NRS-11 pain score compared to the Control Group, though this difference was not statistically significant. The mean (SD) pain score decreased by 0.9 (2.2) points in the Hydrogel Group vs 0.1 (1.7) points in the Control Group (P = 0.070) (Fig. 3). The gender-specific analyses revealed that in men, the 6-month postprocedure mean (SD) decrease was 1.2 (2.8) in the Hydrogel Group compared to a decrease in pain intensity of -0.4 (1.8) in the Control Group (P = 0.126). In women, the mean (SD) decrease was 0.8 (1.8) in the Hydrogel Group compared to 0.2 (1.7) in the Control Group (P = 0.443). A linear regression analysis revealed no significant interaction between gender and treatment effect (regression coefficient: 1.1; 95% CI, -1.2 to 3.5; P = 0.342).

At postprocedure follow-ups of one week, one month, and 3 months, there were no significant differences in pain intensity between the groups (P = 0.518, 0.438, and 0.328, respectively). Of the patients initially assigned to the Control Group, 22 (88.0%) crossed over to receive intradiscal hydrogel at 6 months postprocedure. In the Hydrogel Group, the mean (SD) pain score had decreased by 1.9 (2.2) points at 12 months postprocedure, compared to a decrease of 1.1 (0.8) points in the Control Group, ignoring cross-over. For those who

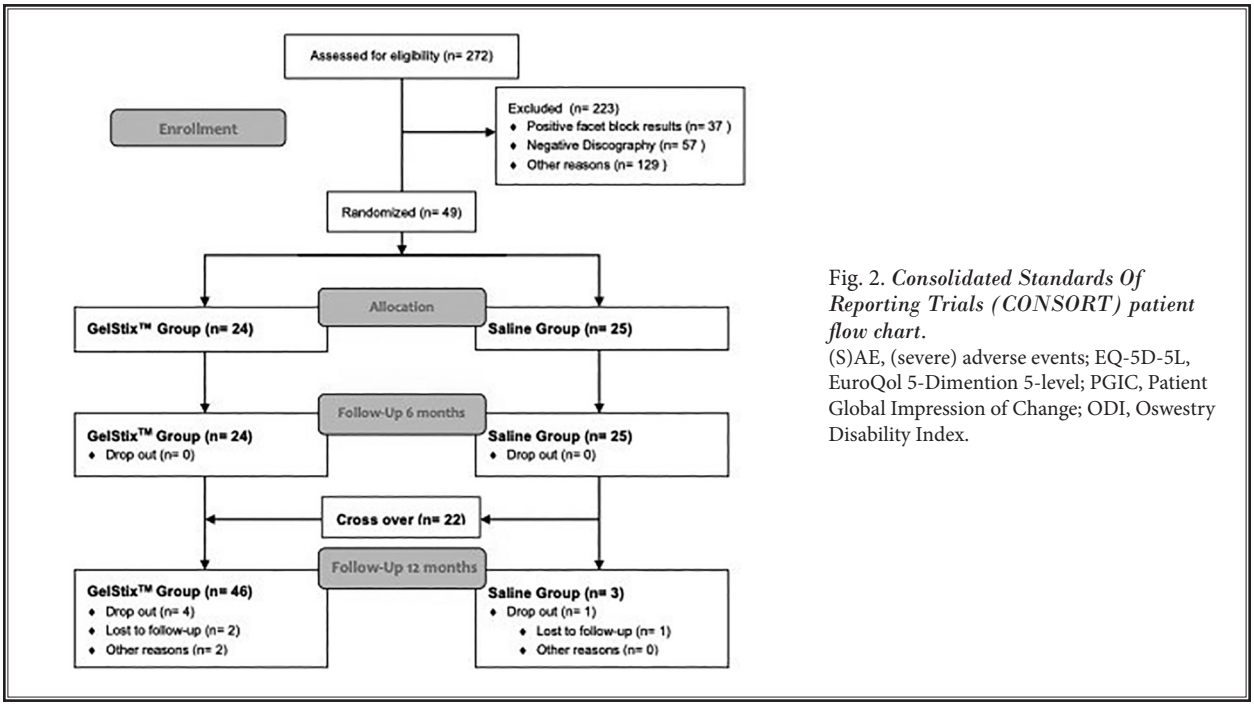

Fig. 2. *Consolidated Standards Of Reporting Trials (CONSORT) patient flow chart.*
(S)AE, (severe) adverse events; EQ-5D-5L, EuroQol 5-Dimention 5-level; PGIC, Patient Global Impression of Change; ODI, Oswestry Disability Index.

Table 1. *Demographic and baseline characteristics of patients stratified by treatment allocation.*

Characteristic	Hydrogel Group (n = 24)	Control Group (n = 25)
Women, n (%)	14 (58.3%)	12 (48.0%)
Age (y), mean (SD)	42.3 (10)	40.1 (10.3)
Pain NRS-11, mean (SD)	6.2 (1.5)	6.4 (1.2)
BMI (kg/m^2), mean (SD)	25.6 (38)	26.1 (4.0)
Smoking		
Never smoked	14 (58.3%)	15 (60.0%)
Past smoker	0 (0.0%)	3 (12.0%)
Current smoker	10 (41.7%)	7 (28.0%)
Cigarettes/d	10 (4- 14)	10 (5 – 10)
Duration (y)	16 (9 - 28)	27 (16 - 39)
Employment status, n (%)		
Full-time employment	8 (34.8%)	10 (44.0%)
Part-time employment	9 (39.1%)	6 (24.0%)
Unemployed	6 (26.1%)	7 (32.0%)
Restricted employment	0 (0.0%)	0 (0.0%)
Finger-to-floor distance, cm, median (SD)	15.4 (8.5)	18.8 (17.6)
Schober test unlimited	14 (58.3%)	13 (52.0%)
Chronic LBP duration (y), mean (SD)		
Previous treatment		
Bed rest	0 (0.0%)	3 (12.0%)
Lumbar brace	3 (12.5%)	5 (20.0%)
Chiropractic care	10 (41.7%)	8 (32.0%)
Physiotherapy	22 (91.7%)	24 (96.0%)
TENS	11 (45.8%)	13 (52%)
Acupuncture	5 (20.8%)	10 (40.0%)
Epidural injection	11 (45.8%)	10 (40.0%)
Facet joint injection	18 (78.3%)	23 (92.0%)
Steroid injection	7 (29.2%)	6 (25.0%)
ODI, mean (SD)	40.1 (14.4)	42.9 (12.3)
PCS	20.5 (9.0)	26.9 (10.2)
SFQ	24.2 (18.9)	24.8 (18.2)
PSEQ	26.8 (9.4)	25.4 (10.5)
HADS, mean (SD) (range 0-21)		
Anxiety	8.2 (3.6)	7.3 (4.8)
Depression	7.0 (4.1)	6.9 (4.1)
Pfirrmann Grade of treated disc level		
I	0 (0.0%)	1 (4.0%)
II	2 (8.3%)	3 (12.0%)
III	13 (54.2%)	16 (64.0%)
IV	9 (37.5%)	5 (20.0%)
Disc height of treated disc level, mm, mean (SD)	9.2 (1.7)	10.2 (2.6)
HIZ on treated disc level		
A	19 (67.9%)	15 (48.4%)
B	8 (28.6%)	10 (32.3%)
C	0 (0.0%)	2 (6.5%)
D	1 (3.6%)	4 (12.9%)
Schmorl's nodes on treated disc level. n/N (%)	0 (0%)	0 (0%)
Modic Type 1 vertebral endplate subchondral bone changes, n (%)	1 (3.6%)	2 (6.5%)
Modic Type 2 vertebral endplate subchondral bone changes, n (%)	5 (17.9%)	0 (0.0%)

LBP, low back pain; NA, not available; NRS-11, Numeric Rating Score (0-10); BMI, Body mass index; NSAID, nonsteroidal anti-inflammatory drug; ODI, Oswestry Disability Index; PCS, pain catastrophizing scale; SFQ, surgical fear questionnaire; PSEQ, pain self-efficacy questionnaire; HADS, Hospital Anxiety and Depression Scale; HIZ, high intensity zone (A= no HIZ, B= mildly hyper intensive, C= moderately hyper intensive, D= markedly hyper intensive)

Table 2. *Procedural characteristics.*

Characteristics	Hydrogel Group (n = 24)	Control Group (n = 25)
Segments treated, n (%)		
L2-L3	0 (0%)	0 (0%)
L3-L4	1 (4.2%)	5 (21.7%)
L4-L5	13 (54.2%)	13 (56.5%)
L5-S1	14 (58.3%)	13 (56.5%)
L2-L3 and L3-L4	0 (0%)	0 (0%)
L3-L4 and L4-L5	1 (4.2%)	1 (4.3%)
L4-L5 and L5-S1	3 (12.5%)	7 (30.4%)
Number of GelStix per level, n (%)		
L3-L4		
1	0 (0%)	1 (20.0%)
2	0 (0%)	1 (20.0%)
3	1 (100%)	3 (60.0%)
L4-L5		
1	0 (0%)	2 (16.7%)
2	4 (30.8%)	2 (16.7%)
3	9 (69.2%)	8 (66.7%)
L5-S1		
1	1 (7.1%)	0 (0%)
2	5 (35.7%)	2 (20.0 %)
3	8 (57.1%)	8 (80.0%)

Table 3. *Magnetic resonance imaging measurements at baseline and at 12 months postprocedure of all treated levels.*

	Baseline	12 months
Disc height in mm, mean (SD)	9.2 (1.7)	9.2 (1.9)
Pfirrmann Grade, n (%)		
I	1 (3.6%)	1 (4.0%)
II	5 (17.9%)	1 (4.0%)
III	13 (46.4%)	15 (60.0%)
IV	9 (32.1%)	8 (32.0%)
Modic signal on MRI, n (%)		
No Modic	22 (78.6%)	19 (76%)
Modic Type 1	1 (3.6%)	2 (8.0%)
Modic Type 2	5 (17.9%)	4 (16.0%)

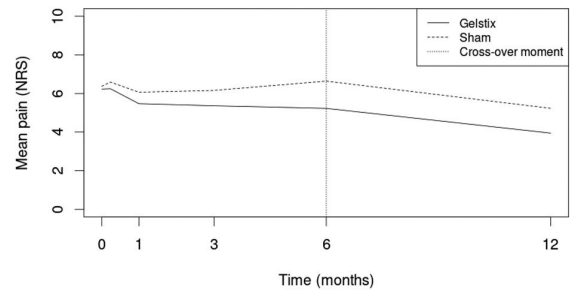

Fig. 3. *Mean Numeric Rating Scale pain scores over time for the Hydrogel and Control groups. The line graph shows the mean pain intensity measured at baseline and at one, 3, 6, and 12 months postprocedure. The vertical dashed line indicates the cross-over moment when patients from the Control Group were offered hydrogel treatment.*

crossed over at 6 months to the hydrogel treatment, the mean (SD) pain score decreased by 1.2 (1.8), while for the few who did not opt for hydrogel at 6 months, the mean (SD) pain score increased by 0.3 (1.8) points.

Secondary Outcome Measures

Figure 4 illustrates the distribution of PGIC scores. At the 3-month follow-up, 4 out of 24 patients (16.7%) in the Hydrogel Group reported at least "much improvement," compared to 2 out of 25 patients (8.0%) in the Control Group ($P = 0.417$). At the 6 month follow-up, 6 out of 23 patients (26.1%) in the Hydrogel Group reported "much improvement" or better, compared to none of the 25 patients (0.0%) in the Control Group ($P = 0.008$). At the 12 month follow-up, 11 out of 21 patients (52.4%) in the Hydrogel Group reported at least "much improvement."

At 6 months postprocedure, the Hydrogel Group had a statistically significant within-group reduction in ODI scores (mean decrease 6.3 (13.1); $P = 0.032$), while the Control Group did not (mean decrease 3.7 (15); $P = 0.234$). However, the between-group difference was not significant ($P = 0.428$). By the 12 month follow-up, mean (SD) ODI scores in the Hydrogel Group had decreased by 17.0 (18.7) points ($P < 0.001$).

There was no significant difference in mean (SD) quality of life scores (EQ-5D-5L) at 6 months postprocedure between groups (Hydrogel Group: 0.57 (0.29); Control Group: 0.48 (0.29); $P = 0.300$), nor were there significant within-group changes observed. At 12 months postprocedure, the Hydrogel Group's mean (SD) utility score was 0.66 (0.30). Employment status remained similar between groups at 6 months postprocedure ($P = 0.528$).

In the Hydrogel Group, the preoperative median (IQR) midsagittal disc height had a significant increase from 9.0 mm (8.4 mm– 10.5 mm) to 9.3 mm (7.4 mm–10.6) postoperatively. In contrast, the Control Group experienced a median (IQR) decrease in disc height from 9.9 mm (9.0 mm–11.0) to 9.8 mm (8.0 mm– 14.2 mm). However, the difference between the groups was not statistically significant ($P = 0.737$). Measurements were performed by a blinded radiologist (Table 3).

At baseline, 27 patients were taking analgesics (Table 4). Most patients were managing their pain with acetominophen. At baseline, 12 patients were using opioids, of whom half took strong opioids. We refrained from statistical testing due to the limited number of patients per type of analgesic.

Regarding blinding, 28.6% of the patients in the

Hydrogel Group correctly believed they had received the treatment, compared to 4.3% in the Control Group. Most patients in the Control Group (65.2%) believed they received a placebo. However, this difference was not statistically significant ($P = 0.085$). Similarly, treating physicians' guesses did not differ significantly between groups ($P = 0.384$); the majority in both groups were unsure of the treatment allocation.

At 6 months postprocedure, 6 patients (4 in the Hydrogel Group and 2 in the Control Group) reported an adverse event that was possibly related to the procedure. In the Hydrogel Group, one patient experienced LBP with MRI-detected edema at L4-L5, and another reported tired legs. Three patients (2 in the Hydrogel Group and one in the Control Group) experienced aggravated postprocedure pain. One patient in the Hydrogel Group experienced a severe adverse event. This patient was hospitalized at 6 days postprocedure for exacerbation of LBP, possibly procedure-related, which resolved after 2 days with analgesic treatment. At 12 months postprocedure, 2 patients reported adverse events. In the Hydrogel Group, one patient experienced tingling in the left leg at 6 months. An MRI revealed an L4-L5 disc protrusion compressing the L5 nerve root. This patient was treated with an epidural injection of lidocaine and dexamethasone, and the event was considered unlikely to be directly related to the hydrogel implantation, as it occurred at 6 months postprocedure. In the Control Group, one patient that crossed over to the hydrogel group, developed a herniated nucleus pulposus at the L4-L5 level, which was unlikely related since it occured 6 months postprocedure; the symptoms were successfully treated with an epidural injection.

Discussion

To our knowledge, this is the first prospective, double-blind, randomized controlled trial to evaluate the efficacy of intradiscal implantation of a solid hydrogel in patients with chronic lumbar discogenic

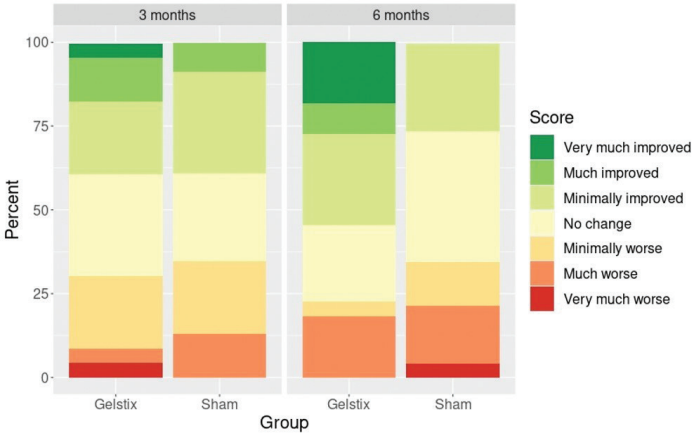

Fig. 4. *Distribution of Patient Global Impression of Change scores at 3 and 6 months postprocedure for the Hydrogel and Control Groups.*

Table 4. *Pain medication consumption during follow-up compared to baseline.*

	Baseline		1 Week		1 Month		3 Months		6 Months		12 Months	
	C	H	C	H	C	H	C	H	C	H	C	H
Acetaminophen	6 (24.0%)	4 (16.7%)	6 (24.0%)	8 (33.3%)	8 (32.0%)	7 (29.2%)	8 (32.0%)	7 (29.2%)	8 (32.0%)	6 (25.0%)	5 (20%)	4 (16.7%)
Anticonvulsants	1 (4.0%)	1 (4.2%)	1 (4.0%)	2 (8.3%)	1 (4.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4%)	0 (0.0%)	1 (4.0%)	0 (0.0%)
NSAIDs	3 (12.0%)	3 (12.5%)	6 (24.0%)	5 (20.8%)	6 (24.0%)	7 (29.3%)	7 (28.0%)	3 (12.5%)	7 (28.0%)	6 (25%)	4 (16%)	1 (4.2%)
Opioids, strong	3 (12.0%)	2 (8.3%)	2 (8.0%)	2 (8.3%)	2 (8.0%)	1 (4.2%)	2 (8.0%)	1 (4.2%)	2 (8.0%)	1 (4.2%)	2 (8.0%)	1 (4.2%)
Opioids, weak	3 (12.0%)	5 (20.8%)	5 (20%)	6 (25%)	2 (8.0%)	4 (16.7%)	2 (8.0%)	4 (16.7%)	4 (16.0%)	3 (12.5%)	0 (0.0%)	3 (12.5%)
Pyrazolone	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3)	0 (0.0%)	2 (8.3%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	3 (12.5%)	1 (4.2%)	2 (8.3%)
SNRI	1 (4.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.2%)	1 (4.0%)	1 (4.2%)	1 (4.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)
Tricyclic Antidepressants	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0(0.0%)	1 (4.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)

C, Control Group; H, Hydrogel Group; NSAID, nonsteroidal anti-inflammatory drug; SNRI, Serotonin-norepinephrine reuptake inhibitor
§ Weak opioids include tramadol. Strong opioids include fentanyl, oxycodone, and tapentadol.

pain unresponsive to conservative treatment. While the Hydrogel Group showed a larger reduction in pain at 6 months compared to the Control Group, the difference did not reach statistical significance (P = 0.070). However, patient-reported improvement, as measured by the PGIC, was significantly greater in the hydrogel group (P = 0.008), suggesting meaningful perceived benefit.

Additionally, the mean within-group improvement in disability, as assessed by the ODI questionnaire, was statistically significant in the Hydrogel Group but not in the Control Group. There were no statistically significant differences between the 2 groups regarding improvements in disability, health-related quality of life, or employment status. By postprocedure month 12, the Hydrogel Group had a significant decrease in ODI scores compared to baseline (P < 0.001), indicating that the benefits of hydrogel implantation may increase over time.

The high crossover rate (88%) from Control Group to Hydrogel Group at 6 months postprocedure reflects strong patient interest in the intervention. Post crossover, patients also experienced reductions in pain, which supports the possible clinical utility of the treatment.

Disc height increased slightly in the Hydrogel Group, but the difference was not statistically significant. These measurements should be interpreted cautiously given the small sample and measurement variability.

Our trial confirms that intradiscal hydrogel implantation is a generally safe procedure. Only one serious adverse event occurred, and adverse effects were mild and self-limiting in most cases. Temporary postprocedure pain flares were observed in both groups, which is common after intradiscal interventions. No acceleration in disc degeneration was observed at one-year MRI follow-up.

The intervertebral disc, which is avascular, relies on nutrient diffusion from blood vessels in the vertebral body (16). Nutrients cross the vertebral endplate to nourish the disc cells, which in turn release lactic acid and other byproducts back into the circulatory system (16). Risk factors like smoking, atherosclerosis, and vertebral endplate calcification can impair nutrient supply by reducing endplate permeability (17,18). This leads to lactic acid accumulation, decreased pH, altered cellular activity, and reduced proteoglycan synthesis. The resulting decline in proteoglycan content affects intradiscal pressure and the disc's ability to handle mechanical loads, contributing to disc degeneration (7).

Once implanted intradiscally, GelStix implants rapidly absorb water and expand due to their hydrophilic properties. When used to supplement the intervertebral disc in early to intermediate stages of disc degeneration, these hydrogels may enhance nucleus pulposus regeneration and improve segmental mechanical function (13,19). Intradiscal GelStix implantation increases the disc's pH, which helps natural proteoglycans bind to water, improving hydration. This process may help halt the disc degeneration cycle. This process might take time, and the benefits on pain intensity might therefore not appear immediately, which could explain the observed time-dependent reduction in pain in our trial.

Hydrogels composed of polyacrylonitrile based polymers also exhibit selective absorption of biomolecules. Its molecular sieving effect excludes large molecular-weight proteins while permitting entry of molecules below approximately 50 kDa. Absorption is diffusion controlled; moderately large molecules below the cut-off enter and are retained in the gel in a time-dependent manner. Proinflammatory cytokines associated with disc degeneration and nociceptive sensitization, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α,fall within the 17–50 kDa range; they would be expected to enter the gel slowly yet remain below the exclusion threshold (20,21). Over time, these molecules are likely to become entrapped within the hydrogel, thereby reducing their concentration and pathophysiological activity. This offers an additional mechanism for the delayed analgesic effect observed in this trial.

Several observational studies have evaluated intradiscal GelStix implantation in patients with discogenic pain, reporting improvements in both pain and function. Ceylan, et al (22) retrospectively analyzed data from 29 patients who underwent percutaneous intradiscal GelStix implantation and reported that the treatment significantly reduced pain and disability. Consistent with our trial, they observed a time-dependent decrease in the patients' Visual Analog Scale (VAS) pain scores and ODI scores with GelStix treatment, with better outcomes over time. The longer the follow-up time, the better the scores became. The mean (SD) VAS pain intensity scores decreased from 7.14 (0.64) at baseline to 3.69 (0.60) at one month and 2.48 (0.63) at 12 months postprocedure (P < 0.001) (22).

Singh, et al (23) implanted GelStix in 22 patients to assess its potential for reducing LBP in patients with discogenic pain confirmed by radiographic imaging and provocative discography. At the 4-week follow-up, VAS

scores decreased from 8.5 to 3.0 ($P < 0.0001$) and ODI scores decreased from 25.1 to 10.2 ($P < 0.0001$). Similar to our findings, this trial also observed a time-dependent decrease in both VAS and ODI scores throughout the one-year follow-up period (23).

For patients with early or intermediate-stage degenerative disc disease, various minimally invasive treatments have been employed, including intradiscal injection of methylene blue, corticosteroids, and thermal intradiscal/annular treatments (24–26). However, many of these treatments provide only short- to intermediate-term relief or have been discontinued due to insufficient evidence (27). For instance, pain relief from intradiscal glucocorticoid injections is generally short- to intermediate-term, lasting between 3 and 6 months (25).

The role of intradiscal hydrogel implantation for managing discogenic LBP remains to be defined. At present, no fully validated treatment for discogenic LBP exists, and most alternatives, including conservative care and fusion surgery, are supported by limited evidence (28). Given this context, even modest success with intradiscal hydrogel treatment can be considered a significant improvement. Additionally, intradiscal hydrogel implantation may offer a safer and more cost-effective option compared to fusion surgery.

The strengths of our trial include its methodological rigor, double-blind, randomized controlled trial design, and comprehensive patient selection process. It also benefits from long-term data, effective concealment of group allocation, and successful blinding of both patients and observers. Additionally, we employed provocation discography with manometric monitoring to select the target disc for treatment. While provocative discography is controversial, it remains the most reliable diagnostic test for confirming discogenic pain (28). Furthermore, all patients were treated according to a standardized physiotherapy protocol.

Limitations include the small sample size, strict eligibility criteria, and the extended recruitment period, which may affect generalizability. Also, the validity of intradiscal saline as a placebo remains debated, though widely used in similar trials. The 2-center trial experienced a lengthy recruitment period, likely due to the stringent eligibility criteria and patients' reluctance to a 50% chance of sham treatment. Stopping rules were implemented after including 49 patients due to logistical constraints, such as time and financial limitations. The current effect size was very unlikely to change significantly with the addition of new patients. However, the precision of that estimate and the statistical significance was likely to improve with new patients.

Another limitation is the potential issue of whether intradiscal saline injection serves as a true placebo. A meta-analysis indicated that epidural saline may be effective for managing low back and lower extremity pain (29). However, saline is commonly used as a sham intervention in other studies, such as the one by Cao, et al (30) which compared intradiscal corticosteroid injection to saline for discogenic LBP. In their study, neither pain intensity scores nor ODI scores showed improvement at 3 or 6 months following saline injection (30).

Conclusions

Our results suggest that percutaneous intradiscal hydrogel implantation may be an effective nonsurgical option for chronic discogenic pain. While the hydrogel group showed time-dependent improvements in pain intensity compared to the control group, this difference was not statistically significant. However, pain reduction in the hydrogel group continued to improve, with further gains observed at 12 months postprocedure. The significant improvement in PGIC highlights meaningful patient-perceived benefits, reflecting the treatment's clinical relevance. Additionally, the Hydrogel Group showed a significant within-group reduction in disability, unlike the Control Group. Despite these encouraging results, the small sample size warrants larger randomized controlled trials to confirm the treatment's efficacy.

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References

1. Cheung KM, Karppinen J, Chan D, et al. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. *Spine (Phila Pa 1976)* 2009; 34:934-940.
2. Verrills P, Nowesenitz G, Barnard A. Prevalence and characteristics of discogenic pain in tertiary practice: 223 consecutive cases utilizing lumbar discography. *Pain Med* 2015; 16:1490-1499.
3. Geurts JW, Willems PC, Kallewaard JW, van Kleef M, Dirksen C. The impact of chronic discogenic low back pain: Costs and patients' burden. *Pain Res Manag* 2018; 2018:4696180.
4. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1789-1858.
5. Garcia-Cosamalon J, del Valle ME, Calavia MG, et al. Intervertebral disc, sensory nerves and neurotrophins: Who is who in discogenic pain? *J Anat* 2010 ; 217:1-15.
6. Vo NV, Hartman RA, Patil PR, et al. Molecular mechanisms of biological aging in intervertebral discs. *J Orthop Res* 2016; 34:1289-1306.
7. Bibby SR, Jones DA, Ripley RM, Urban JP. Metabolism of the intervertebral disc: effects of low levels of oxygen, glucose, and pH on rates of energy metabolism of bovine nucleus pulposus cells. *Spine (Phila Pa 1976)* 2005; 30:487-496.
8. Liang CZ, Li H, Tao YQ, et al. The relationship between low pH in intervertebral discs and low back pain: A systematic review. *Arch Med Sci* 2012; 8:952-956.
9. Keshari KR, Lotz JC, Link TM, Hu S, Majumdar S, Kurhanewicz J. Lactic acid and proteoglycans as metabolic markers for discogenic back pain. *Spine (Phila Pa 1976)* 2008; 33:312-317.
10. Zhao L, Manchikanti L, Kaye AD, Abd-Elsayed A. Treatment of discogenic low back pain: Current treatment strategies and future options-A literature review. *Curr Pain Headache Rep* 2019; 23:86.
11. Fujii K, Yamazaki M, Kang JD, et al. Discogenic back pain: Literature review of definition, diagnosis, and treatment. *JBMR Plus* 2019; 3:e10180.
12. Remotti E, Nduaguba C, Woolley PA, et al. Review: Discogenic back pain: Update on treatment. *Orthop Rev (Pavia)* 2023; 15:84649.
13. Gullbrand SE, Schaer TP, Agarwal P, et al. Translation of an injectable triple-interpenetrating-network hydrogel for intervertebral disc regeneration in a goat model. *Acta Biomater* 2017; 60:201-209.
14. Yue J, Morgenstern R, Morgenstern C, Lauryssen C. Shape memory hydrogels – A novel material for treating age-related degenerative conditions of the Spine. *Eur Musculoskel Rev* 2011; 6:184-188.
15. Koetsier E, van Kuijk SMJ, Maino P, et al. Efficacy of the Gelstix nucleus augmentation device for the treatment of chronic discogenic low back pain: Protocol for a randomised, sham-controlled, double-blind, multicentre trial. *BMJ Open* 2022; 12:e053772.
16. Bibby SR, Urban JP. Effect of nutrient deprivation on the viability of intervertebral disc cells. *Eur Spine J* 2004; 13:695-701.
17. Battié MC, Videman T, Gill K, et al. 1991 Volvo Award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: An MRI study of identical twins. *Spine (Phila Pa 1976)* 1991: 16:1015-1021.
18. Kauppila LI. Atherosclerosis and disc degeneration/low-back pain--a systematic review. *Eur J Vasc Endovasc Surg* 2009; 37:661-670.
19. Gan Y, Li P, Wang L, et al. An interpenetrating network-strengthened and toughened hydrogel that supports cell-based nucleus pulposus regeneration. *Biomaterials* 2017; 136:12-28.
20. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood* 2011; 117:3720-3732.
21. Aggarwal BB. Signalling pathways of the TNF superfamily: A double-edged sword. *Nat Rev Immunol* 2003; 3:745-756.
22. Ceylan A, Asik I, Ozgencil GE, Erken B. Clinical results of intradiscal hydrogel administration (GelStix) in lumbar degenerative disc disease. *Turk J Med Sci* 2019; 49:1634-1639.
23. Singh SH. Lumbar intradiscal treatments: Early evaluation of patient

satisfaction in disc repair by nucleus augmentation (GelStixTM). *J Tissue Eng Regen Med* 2012. Abstract presented at the 3rd TERMIS World Congress 2012, 5-8 September 2012, Vienna, Austria. Available at: https://onlinelibrary.wiley.com/toc/19327005/6/s1

24. Kallewaard JW, Wintraecken VM, Geurts JW, et al. A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: The IMBI study. *Pain* 2019; 160:945-953.
25. Riegger M, Le H, van Kuijk SMJ, et al. Intradiscal glucocorticoid injection in discogenic back pain and influence on Modic changes: A systematic review and meta-analysis of RCTs. *Pain Physician* 2023; 26:E449-E465.
26. Helm II S, Simopoulos TT, Stojanovic M, Abdi S, El Terany MA. Effectiveness of thermal annular procedures in treating discogenic low back pain. Pain *Physician* 2017; 20:447-470.
27. Huygen F, Kallewaard JW, van Tulder M, et al. Evidence-based interventional pain medicine according to clinical diagnoses: Update 2018. *Pain Pract* 2019; 19:664-675.
28. Manchikanti L, Singh V, Pampati V, et al. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician* 2001; 4:308-316.
29. Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician* 2021; 24:S27-S208.
30. Cao P, Jiang L, Zhuang C, et al. Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. *Spine J 2011*; 11:100-106.