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Annular Closure in Lumbar Microdiskectomy for Prevention of Reherniation: A Randomized Clinical Trial

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Abstract

BACKGROUND CONTEXT Patients with large annular defects following lumbar diskectomy for disk herniation are at high risk for symptomatic recurrence and reoperation.

PURPOSE To determine whether a bone-anchored annular closure device in addition to lumbar microdiskectomy resulted in lower reherniation and reoperation rates plus increased overall success compared to lumbar microdiskectomy alone.

DESIGN Multicenter, randomized superiority study.

PATIENT SAMPLE Patients with symptoms of lumbar disk herniation for at least 6 weeks with a large annular defect (6-10 mm width) following lumbar microdiskectomy.

OUTCOME MEASURES The co-primary endpoints determined a priori were recurrent herniation and a composite endpoint consisting of patient-reported, radiographic, and clinical outcomes. Study success required superiority of annular closure on both endpoints at 2 years follow-up.

METHODS Lumbar microdiskectomy with additional bone-anchored annular closure device (n=276 participants) or lumbar microdiskectomy only (control; n=278 participants). This research was supported by Intrinsic Therapeutics. Two authors received study-specific support more than $10,000 per year, eight authors received study-specific support less than $10,000 per year, and eleven authors received no study-specific support.

RESULTS Among 554 randomized participants, 550 (annular closure device: n=272; control: n=278) were included in the modified intent-to-treat efficacy analysis and 550 (annular closure device: n=267; control: n=283) were included in the as-treated safety analysis. Both co-primary endpoints of the study were met, with recurrent herniation (50% vs. 70%, P<.001) and composite endpoint success (27% vs. 18%, P=.02) favoring annular closure device. The frequency of symptomatic reherniation was lower with ACD (12% vs. 25%, P<.001). There were 29 reoperations in 24 patients in the annular closure device group and 61 reoperations in 45 control patients. The frequency of reoperations to address recurrent herniation was 5% with annular closure device and 13% in controls (P=.001). End plate changes were more prevalent in the annular closure device group (84% vs 30%, P<.001). Scores for back pain, leg pain, Oswestry Disability Index, and health-related quality of life at regular visits were comparable between groups over 2-year follow-up.

CONCLUSIONS In patients at high risk of herniation recurrence following lumbar microdiskectomy, annular closure with a bone-anchored implant lowers the risk of symptomatic recurrence and reoperation. Additional study to determine outcomes beyond two years with a bone-anchored annular closure device is warranted.

KEYWORDS annular closure, disk herniation, lumbar discectomy, randomized controlled trial, recurrent herniation, sciatica

INTRODUCTION

Sciatica is characterized by radiating buttock and leg pain in a lumbar nerve root distribution, which may be accompanied by sensory and motor deficits. The annual incidence of an episode of sciatica in the general population ranges from 1% to 5%.[1] The most common cause of sciatica is intervertebral disk herniation. Initial treatment of sciatica is conservative given the favorable natural history in most patients. In approximately 20% of patients, symptoms may persist despite conservative management.[2,3] These patients may continue conservative treatment or undergo surgical removal of herniated disk material, with surgery resulting in faster symptom relief.[4] However, recurrent symptomatic disk herniation occurs in 7% to 18% of patients within 2 years following surgery.[5-7] Recurrent symptomatic herniation is associated with poor clinical outcome and requires a technically demanding, expensive reoperation in most cases.[6,8] With almost half a million diskectomies performed in the United States per year,[9] this poses a significant problem not only for the affected individuals but for society overall.

Since the annulus fibrosus has limited healing capacity, a large annular defect following microdiskectomy is a major risk factor for herniation recurrence. Carragee et al. reported symptomatic herniation recurrence rates of 27% in defects larger than 6 mm, but only 1% in small annular fissures.[10] Thus, the clinical burden of herniation recurrence following microdiskectomy may be mitigated by development of treatments that reliably occlude large annular defects. A bone-anchored annular closure device (ACD) has shown promising results in a single-arm study to address recurrent herniation following lumbar microdiskectomy.[11,12] The aim of this randomized controlled trial was to determine whether bone-anchored ACD in addition to lumbar microdiskectomy resulted in lower reherniation and reoperation rates plus increased overall success.

METHODS

Trial Design and Oversight

We conducted a multicenter randomized controlled trial in patients who were operated for sciatica caused by lumbar disk herniation and who had a large annular defect following lumbar diskectomy. The primary objective of this trial was to determine whether implantation of a bone-anchored ACD following lumbar diskectomy reduced the risk of recurrent herniation compared to lumbar diskectomy alone. The clinical trial was approved by the local ethics review boards, and all participants provided written informed consent. This study was prospectively registered at ClinicalTrials.gov (NCT01283438). Details of the study rationale, design, and methods have been described previously.[13]

The authors designed the trial in collaboration with the Food and Drug Administration (FDA). The study was sponsored by Intrinsic Therapeutics, which manufactures the ACD and was involved in trial management and data monitoring. Two authors received study-specific support more than $10,000 per year, eight authors received study-specific support less than $10,000 per year, and eleven authors received no study-specific support. No authors, investigators or site staff have any equity, royalty or other financial interest in either Intrinsic Therapeutics or the Barricaid device. Data were analyzed by an independent statistician and radiographic assessments were performed by an independent core laboratory blinded to patient outcomes. All authors had full access to the data and the data analysis.

Participants

At 21 European hospitals, we enrolled patients 21 to 75 years of age, with imaging confirmation of single-level disk herniation between L1 and S1, with disk height ≥ 5 mm, and who failed ≥ 6 weeks of nonsurgical treatment. Magnetic resonance imaging (MRI) with T1- and T2-weighted axial and sagittal images, low-dose, multiplanar computed tomography (CT), and flexion/extension x-rays were performed. All patients had lumbar radiculopathy with positive straight leg raise or femoral stretch test, and Oswestry Disability Index score (ODI) and Visual Analogue Scale (VAS) leg pain score of at least 40/100 on each. Patients with spondylolisthesis (grade II or higher), previous surgery at the index level, and osteoporosis were excluded. Additional information on the inclusion and exclusion criteria are provided in **eTable 1**.

Interventions

Experienced spinal surgeons had performed at least three cases with additional ACD implantation prior to enrolling patients in this study. With patients under general anesthesia, magnification-assisted limited diskectomy was performed via an interlaminar transflaval approach.[14] After completion of the diskectomy, the annular defect was measured with sizing probes provided in an accessory kit and the final inclusion criterion was applied. If the annular defect was 4 to 6 mm tall and 6 to 10 mm wide, the patient qualified for randomization and no additional disk material was removed. This range of annular defect sizes was chosen to identify patients at high risk for recurrence that could also be treated within the range of available device sizes. In patients allocated to the control group, the procedure was concluded by standard incision closure. Patients allocated to ACD received bone-anchored annular closure under fluoroscopic guidance. The ACD is comprised of a flexible polymer mesh to close the annular defect and a titanium anchor to secure the mesh to an adjacent vertebral body (**eFigure 1**). The titanium anchor does not interfere with magnetic resonance imaging interpretation or the ability to detect reherniation. Postoperative care was provided according to the protocols of the participating surgical departments.

Follow-up and Outcomes

Patients returned for follow-up visits at 6 weeks, 3 months, 6 months, 1 year, and 2 years. CT, MRI, and flexion-extension x-rays were performed at 1 and 2 years (**eTable 2**). Outcomes of this trial were measured with the use of patient-reported data obtained from questionnaires, independent imaging assessment, and investigator reports of adverse events and reoperations. Patient-reported outcomes included ODI for back-related disability (0-100 scale),[15] VAS (0-100 scale) for back and leg pain,[16] and health-related quality of life with the Medical Outcomes Study 36-Item Short-Form General Health Survery (SF-36) scale.[17]

The trial included two co-primary endpoints. Study success required that outcomes with ACD were statistically superior to controls for both endpoints. One primary endpoint was incidence of recurrent herniation through 2 years. Recurrent herniation was confirmed during reoperation or by identification of protrusion, extrusion, or sequestration at any location of the index-level disk on imaging by independent radiologists.[18] The other primary endpoint was a composite consisting of: a) ≥15 point improvement in ODI compared to baseline, b) ≥20 point improvement in leg pain VAS compared to baseline, c) maintenance of ≥75% disk height compared to baseline, d) maintenance of device condition and neurological status, and e) freedom from index level reherniation, index level reoperation, and spontaneous fusion. Given that each primary endpoint was comprised of imaging findings even if no clinical symptoms were present, a *post hoc* modified composite endpoint was developed that included only symptomatic outcomes and was considered more clinically meaningful. This modified composite endpoint consisted of: a) freedom from symptomatic recurrent herniation, b) ≥15 point improvement in ODI compared to baseline, c) ≥20 point improvement leg pain VAS compared to baseline, d) maintenance of neurological status, e) freedom from device- or procedure-related serious adverse event, and f) freedom from index level reoperation.

Symptomatic herniation recurrence included recurrent herniation that was either surgically verified during reoperation, identified by the imaging core laboratory where the patient reported at least moderate (40/100) disability, radicular symptoms, and neurologic deterioration, or reported as an adverse event. The decision to reoperate during follow-up was collectively made by one of the investigators and the patient based on imaging findings, patient-reported symptoms, and patient preferences. The occurrence of adverse events was ascertained at each study contact and routinely monitored for accuracy. An independent data safety monitoring board (DSMB) adjudicated adverse events by seriousness and by relation to the procedure or implant.

Randomization and Blinding

Following lumbar diskectomy and intraoperative confirmation of eligible defect measurements, patients were randomly allocated in a 1:1 ratio, with a block size of four, to receive additional ACD or diskectomy alone. Simple randomization was performed intraoperatively with a central web-based system that enabled real-time computer generated random treatment assignment. Neither surgeons nor patients were blinded to treatment group except for patients in the Netherlands who were blinded to treatment group due to regional requirements.

Statistical Analysis

A Bayesian approach to sample size selection was used.[19] Interim analyses were performed after enrollment of 400 patients and repeated at increments of 50 patients thereafter until the predictive probability of trial success on each primary endpoint exceeded 90% or the maximum sample size of 800 patients was reached. Efficacy analyses were performed on a modified intention-to-treat (ITT) population, which included all randomized patients in whom the intended procedure was attempted. Safety analyses were performed on an as-treated population. An ITT (as randomized) population was included as a sensitivity analysis. Baseline patient characteristics are presented as means and standard deviations for continuous variables and numbers and percentages for categorical variables. Outcomes between the groups were assessed with Student's t-test for continuous data or Fisher's exact test for categorical data. Time-to-event data were analyzed using Kaplan-Meier methods with log-rank tests for group comparisons. Statistical significance was set at $P<.05$ and hypothesis testing was two-sided. Statistical analyses were performed using SAS v9.4 (SAS Institute) and R v3.3.2 (R Foundation for Statistical Computing).

RESULTS

Between December 2010 and October 2014, 554 patients were randomly allocated to ACD (n=276) or control (n=278). A list of participating centers is reported in **eTable 3**. In 4 patients allocated to ACD, implantation was not attempted due to proximity of the nerve root to the planned implant location. Therefore, the modified intention-to-treat population included 550 patients (272 ACD, 278 controls). Implantation of the ACD was unsuccessful in 5 patients, including 4 patients in whom the mesh did not fully enter the disc and 1 patient with nerve root injury during attempted implantation; thus, the as-treated population included 267 patients in the ACD group and 283 controls. Compliance with clinical follow-up at 2 years was 91% in each group (**Figure 1**).

Treatment groups were well matched at baseline (**Table 1**). The mean age of the study population was 43 years, and 59% were men, which is consistent with findings in previous reports of patients undergoing lumbar microdiskectomy.[4,20] The mean volume of nucleus removal was 1.3 ml in each group; surgery duration (70 vs. 52min, $P<.001$) and procedural blood loss (98 vs. 67 cc, $P<.01$) were higher with ACD vs. controls.

Herniation recurrence, diagnosed based on imaging or symptoms, was identified in 50% of patients in the ACD group and in 70% of controls at 2 years (mean difference: -20%, 95% CI: -12% to -28%, $P<.001$) (**Table 2**). Clinical success on the primary composite endpoint was 27% with ACD and 18% with controls (mean difference: 9%, 95% CI: 2% to 16%, $P=.02$). Thus, both co-primary endpoints of the study were met. Outcomes of the modified composite endpoint yielded similar conclusions, with 76% success in the ACD group and 66% in controls (mean difference: 10.2%, 95% CI: 2.3% to 18.1%, $P<.02$) (**eTable 4**).

The frequency of symptomatic reherniation was lower with ACD (12% vs. 25%, $P<.001$) (**Figure 2**). Mean leg pain severity decreased by 84% on average at the regular visits over 2 years with no difference between groups (**eFigure 2**). Back pain severity decreased by 66% on average at the regular visits through 2 years with no difference between groups (**eFigure 3**). At 2 years, mean ODI scores were comparable (**eFigure 4**). Health-related quality of life significantly improved with no differences observed between groups. Physical component summary scores increased from 29±6 to 49±9 with ACD and 29±6 to 47±9 in controls (**eFigure**

5). Mental component summary scores increased from 40±13 to 52±10 with ACD and 41±13 to 51±11 in controls (**eFigure 6**).

Index level reoperations were less frequent with ACD (9% vs. 16%, *P*=.01). There were 29 reoperations in 24 ACD patients and 61 reoperations in 45 control patients (**Figure 3**). The frequency of index level reoperations specifically to address an observed recurrent herniation was 5% with ACD (14 procedures in 14 subjects) and 13% in controls (42 procedures in 37 subjects) (*P*<.001). Of the 14 reoperations for recurrence in the ACD group, three were also associated with detachment of the mesh portion of the device from the anchor and a fourth was associated with a fracture of anchor head; in each of these cases, the detached portion was removed and the rest remained implanted. In the as-treated population, the frequency of serious adverse events adjudicated by the DSMB as related to either the implant or procedure was 7% in the ACD group and 17% in the control group (*P*=.001); this difference was primarily due to the lower incidence of reherniation in the ACD group. No difference in all-cause serious adverse events was observed when comparing ACD to controls (25% vs. 30%, *P*=.15). The frequency of adverse events, regardless of seriousness or relatedness, was 75% with ACD and 70% in controls (*P*=.29). Serious device- and procedure-related serious adverse events in the modified intent-to-treat population are reported in **Table 3**. Detailed listings of serious adverse events, serious device- and procedure-related adverse events, and adverse events regardless of seriousness or relatedness are reported in **eTables 5-7** for the as-treated population and **eTables 8-9** for the modified ITT population.

Assessment of all available CT images by the independent radiographic core lab identified endplate changes (disruptions in the smooth cortical margin of the bony endplate) following surgery with and without the ACD. Changes were more prevalent in the ACD group at

2 years (84% vs 30%, *P*<.001), though no correlation with any symptom or clinically adverse event was observed.

A sensitivity analyis of main study outcomes in an ITT population did not alter study conclusions (**eTable 10**).

DISCUSSION

This multi-center randomized controlled trial demonstrated that additional use of a bone-anchored ACD following lumbar microdiskectomy reduced the risk of symptomatic recurrence and associated reoperations. The number needed to treat to prevent a reherniation was less than 8 and to prevent an associated reoperation was less than 13. Further, these benefits were not offset by a higher risk of adverse events. Given that lumbar diskectomy is the most frequently performed spine surgery in the United States with close to half a million procedures each year,[9] the findings of this study have significant societal importance, as reoperations are known to be associated with poor outcome and extensive additional costs.[6,8]

The results of this study are generalizable to patients with large annular defects following lumbar microdiskectomy. While the symptomatic recurrence rate of 25% in the control group was markedly higher than the 7% to 18% recurrence rates frequently reported following diskectomy,[5-7] this was an anticipated result given the large annular defect inclusion criterion. McGirt et al.[7] reported that recurrence rates were 4 times higher in patients in the top quartile of annular defect size versus those in the lower quartile. In patients with annular defect size ≥ 6 mm, recurrence rates through 2 years follow-up were 18% in the study of Kim et al.[21] and 27% in the study of Carragee et al.[10] These findings have been corroborated in a meta-analysis that reported the risk of reherniation and reoperation following limited lumbar discectomy was approximately 3-fold higher in patients with large vs. small annular defects.[22]

The co-primary endpoints of the study must be interpreted within the context of a sample at high risk for recurrence as well as considering that the threshold for defining recurrence was stringent. The definition of reherniation included imaging evidence of protrusion, extrusion, or sequestration, even in asymptomatic patients. Indeed, the majority of recurrent disk herniations were classified as protrusions in asymptomatic patients. While both co-primary endpoints of the trial were met, each included information derived from imaging assessments. The clinical relevance of these endpoints is debatable given the known lack of association between MRI findings and symptoms in this population.[23,24] Given the inherent challenges with interpretation of the primary endpoints based on the asymptomatic reherniation rate of 42% in the entire sample, a *post hoc* modified composite endpoint was developed that was considered to be more clinically meaningful and demonstrated an increase of the success rate by 10% with ACD (76% vs. 66% in controls). Overall, additional ACD implantation reduced the risk for clinically important outcomes such as symptomatic herniation recurrence and reoperation, which are arguably the most important findings of this study.

Prevention of recurrent symptomatic herniation is a clinically meaningful pursuit since repeat diskectomy is technically demanding and considerably more expensive compared to primary diskectomy.[25] Several strategies to repair, replace, or regenerate the herniated nucleus pulposus have been evaluated yet none have resulted in a clinically proven therapy since the damaged annulus fibrosus had been largely ignored.[26,27] The annulus fibrosus has limited regenerative capacity, which is likely because exterior repairs are not matched to the demands of intradiskal tensile forces.[26] Efforts to develop a definitive annular repair mechanism to date have been unsuccessful. The implant that was evaluated in the current study is anchored into the adjacent vertebral body, which may provide a more durable repair. On balance, some clinical considerations with the ACD include longer procedure time and potential for device-related problems. As previously demonstrated following ACD implantation focal areas of bone resorption at the endplates were noted more frequently in the ACD group, but there was no relationship of these radiological findings with clinical parameters.[26]

Our study had several strengths including effective randomization, high follow-up rates, a sample size representing one of the largest studies in spine surgery, oversight provided by a DSMB, and study design collaboration with the FDA. There are also several important limitations of this research. The results of this trial are not generalizable to all patients undergoing lumbar diskectomy for disk herniation. Patients with inadequate disk height or small annular defects are not eligible for ACD implantation due to surgical access challenges and likely would not benefit from preventative annular closure. While patients in this study will be followed for 5 years, long-term outcomes with ACD are currently unknown. Finally, the possible influence of expectation bias cannot be ruled out since most patients and all surgeons were aware of treatment assignment. However, when comparing patient outcomes from sites where the principal investigator reported a financial relationship with the study sponsor versus those with no such relationship, there were no differences in study conclusions. This finding held true for the primary endpoint, reherniation rates, reoperation rates, VAS scores, and ODI scores. Further, imaging studies were evaluated by independent radiologists.

CONCLUSION

In this randomized controlled trial of patients at high risk of herniation recurrence following lumbar microdiskectomy, additional annular closure with a bone-anchored device lowers the risk for recurrent herniation and reoperation through 2 years follow-up.

Author Contributions: The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Barth, Bouma, Klassen, Thomé,

Acquisition and interpretation of data: All authors.

Drafting of the manuscript: Thomé.

Critical revision of the manuscript for important intellectual content: All authors.

Final approval of the version to be published: All authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

Data Access Statement: Dr. Thomé agrees to provide access to the data under reasonable request, including providing the data and cooperating fully in obtaining and providing the data on which the manuscript is based for examination by the editors or their assignees.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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FIGURE LEGENDS

Figure 1. Enrollment and Randomization of Patients. Intent-to-treat (ITT) population consisted of 276 patients assigned to anular closure device (ACD) and 278 patients assigned to Control. Modified ITT population consisted of 272 patients with attempted ACD implant and 278 patients assigned to Control. As-treated population consisted of modified ITT population where 267 patients received ACD and 283 received Control. In the as-treated population, failed ACD implantation in 5 ACD patients from the modified ITT population (including 1 with nerve root injury) resulted in assignment to the Control group. Compliance with clinical follow-up at 2 years was 91% in each group.

Figure 2. Freedom from Symptomatic Index Level Reherniation through 2 Years. Kaplan-Meier freedom from event estimates in the modified intent-to-treat population through the end of the 2-year follow-up interval (day 790) were 88.3% for annular closure device (ACD) and 75.6% for Control (log-rank *P* value<.001).

Figure 3. Freedom from Index Level Reoperation through 2 Years. (top panel) Kaplan-Meier freedom from index level reoperation for any reason estimates in the modified intent-to-treat population through the end of the 2-year follow-up interval (day 790) were 91.0% for annular closure device (ACD) and 83.4% for Control (log-rank *P* value<.01); (bottom panel) Kaplan-Meier freedom from index level reoperation for symptomatic reherniation estimates in the modified intent-to-treat population through the end of the 2-year follow-up interval (day 790) were 94.7% for ACD and 86.2% for Control (log-rank *P* value<.001).

TABLES

Table 1. Baseline Characteristics of the Patients.[a]

Characteristic	**Annular Closure (n = 272)**	**Control (n = 278)**
Age — yr	43±11	44±10
Male sex — no. (%)	156 (57)	171 (62)
Body mass index — kg/m^2	26±4	26±4
Smoking history — no. (%)	173 (64)	175 (63)
Medical history — no. (%) [b]		
Musculoskeletal	95 (35) [c]	91 (33) [d]
Head and neck	62 (23) [c]	54 (20) [d]
Gastrointestinal	53 (20) [e]	59 (21) [c]
Cardiovascular	49 (18) [c]	48 (17) [c]
Genitourinary	39 (14) [c]	35 (13) [c]
Skin	29 (11) [c]	30 (11) [c]
Respiratory	28 (10) [c]	44 (16) [c]
Visual-analogue scale for leg pain [f]	81±15	81±15
Visual-analogue scale for back pain [f]	57±30	56±31
Oswestry Disability Index score [g]	59±12	58±14
SF-36 Physical Component Summary score [h]	29±6	29±6
SF-36 Mental Component Summary score [h]	40±13	41±13
Index level — no. (%)		
L2-L3	2 (1)	1 (<1)
L3-L4	8 (3)	5 (2)
L4-L5	123 (45)	101 (36)
L5-S1	139 (51)	171 (62)
Spondylolisthesis, grade 1	6 (2)	8 (3)
Disk height — mm	8.9±2.1	8.9±2.2
Extrusion / sequestration — no. (%)	201 (74)	201 (72)

[a] Plus-minus values are mean±SD.
[b] Medical history variables reported with frequency of 10% or more in either group.
[c] Data from 2 patients not reported.
[d] Data from 1 patient not reported.
[e] Data from 3 patients not reported.
[f] Scores on the visual analogue scale (VAS) range from 0 to 100, with higher scores indicating more severe pain.
[g] Scores on the Oswestry Disability Index (ODI) range from 0 to 100, with higher scores indicating more severe disability.
[h] Physical Component Summary and Mental Component Summary scores from the Medical Outcomes Study 36-Item Short-Form General Health Survery (SF-36) scale range from 0 to 100, with higher scores indicating better health-related quality of life.

Table 2. Main Outcomes at 2 Years.[a]

Characteristic	Annular Closure	Control	*P* Value
Index level recurrent herniation — no. (%) [b]			
Symptomatic	31/250 (12)	65/257 (25)	<.001
Symptomatic and asymptomatic	125/250 (50)	180/257 (70)	<.001
Index level reoperation — no. (%) [c]			
Recurrent herniation	14/272 (5)	37/278 (13)	.001
Any cause	24/272 (9)	45/278 (16)	.01
Neurological function decline — no. (%) [d]	5/252 (2)	12/251 (5)	.09
Visual-analogue scale for leg pain [e,f]	12±21 [j]	14±21 [j]	.32
Visual-analogue scale for back pain [e,f]	18±23 [j]	19±24 [j]	.54
Oswestry Disability Index score [e,g]	13±14 [j]	14±15 [j]	.27
SF-36 Physical Component Summary score [e,h]	49±9 [j]	47±9 [j]	.07
SF-36 Mental Component Summary score [e,h]	52±10 [j]	51±11 [j]	.23
Serious adverse event — no. (%) [i]			
Device- or procedure-related	19/267 (7) [k]	47/283 (17)	.001
Any cause	66/267 (25)	86/283 (30)	.15

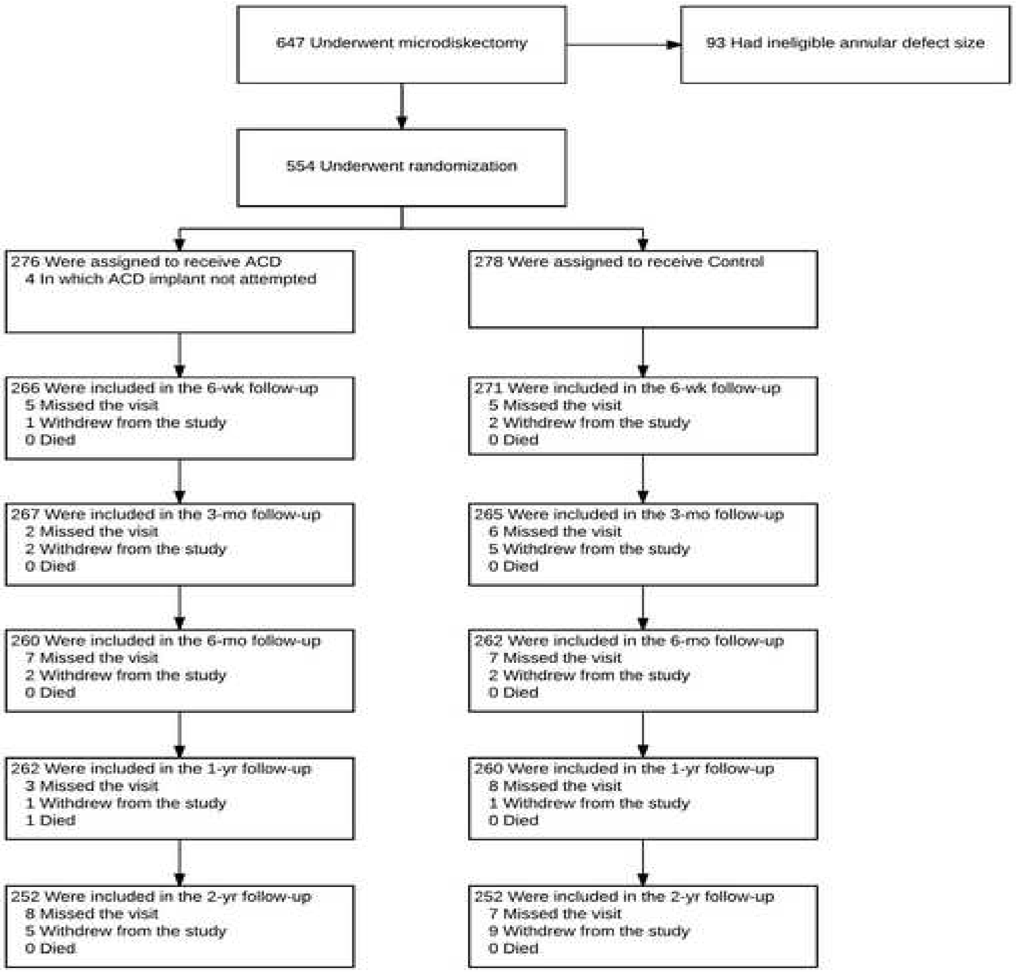
[a] Plus-minus values are mean±SD.
[b] Denominator includes patients in the modified intent-to-treat population with imaging at 2 years and patients with recurrent herniation at any time during follow-up.
[c] Denominator includes all patients in the modified intent-to-treat population.
[d] Denominator includes all patients in the modified intent-to-treat population with data at baseline and 2 years.
[e] Denominator includes all patients in the modified intent-to-treat population with data at 2 years.
[f] Scores on the visual analogue scale (VAS) range from 0 to 100, with higher scores indicating more severe pain.
[g] Scores on the Oswestry Disability Index (ODI) range from 0 to 100, with higher scores indicating more severe disability.
[h] Physical Component Summary and Mental Component Summary scores from the Medical Outcomes Study 36-Item Short-Form General Health Survery (SF-36) scale range from 0 to 100, with higher scores indicating better health-related quality of life.
[i] Denominator includes all patients in the as-treated population.
[j] N=252.
[k] N=8 subjects experienced a device-related SAE.

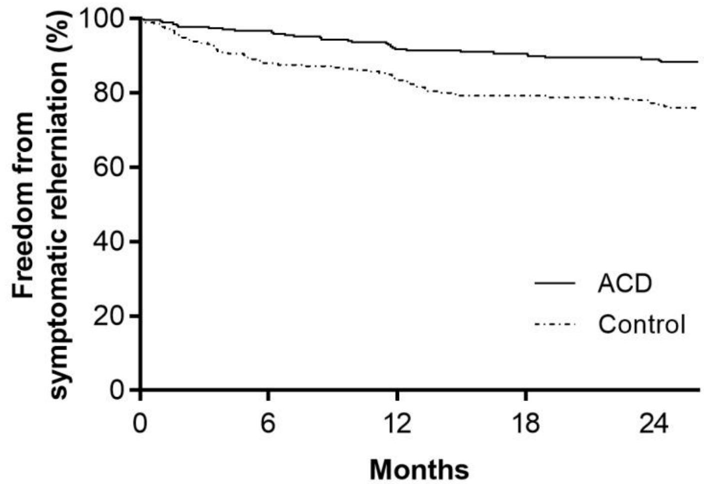
Table 3. Serious Device- and Procedure-related Adverse Events through 2 Years: Modified Intent-to-Treat Population.

Event	**Annular Closure (n = 272)**			**Control (n = 278)**			**Significance**	
	Events	**Patients**	**%**	**Events**	**Patients**	**%**	**Diff**	***P* Value**
ANY SERIOUS DEVICE- OR PROCEDURE-RELATED ADVERSE EVENT	**29**	**21**	**7.7%**	**56**	**45**	**16.2%**	**-8.5%**	**.002**
CARDIAC AND VASCULAR	0	0	0.0%	3	3	1.1%	-1.1%	.25
bleeding	0	0	0.0%	1	1	0.4%	-0.4%	
other	0	0	0.0%	2	2	0.7%	-0.7%	
DEVICE DEFICIENCY	7	7	2.6%					
device deficiency - anchor (whole device) migration	3	3	1.1%					
device deficiency - mesh migration - extradiscal	4	4	1.5%					
DISC HERNIATION	13	11	4.8%	43	38	15.5%	-10.7%	<.001
herniation - index level	11	9	4.0%	43	38	15.5%	-11.4%	
residual herniation - index level	2	2	0.7%	0	0	0.0%	0.7%	
MUSCULOSKELETAL - LUMBAR	1	1	0.4%	0	0	0.0%	0.4%	.50
other	1	1	0.4%	0	0	0.0%	0.4%	
NEURO - LUMBAR AND LOWER	1	1	0.4	0	0	0.0%	0.4%	.50

EXTREMITY			%					
nerve or spinal root injury: index surgery	1	1	0.4%	0	0	0.0%	0.4%	
PAIN - LUMBAR AND LOWER EXTREMITY	4	4	1.5%	2	2	0.7%	0.8%	.45
lower extremity only	2	2	0.7%	2	2	0.7%	0.0%	
lumbar	1	1	0.4%	0	0	0.0%	0.4%	
lumbar and lower extremity	1	1	0.4%	0	0	0.0%	0.4%	
WOUND ISSUE- SSI AT INDEX LEVEL	3	3	1.1%	8	6	2.9%	-1.8%	.50
dural injury/tear or csf leak	1	1	0.4%	1	1	0.4%	0.0%	
infection	1	1	0.4%	3	2	1.1%	-0.7%	
hematoma	0	0	0.0%	1	1	0.4%	-0.4%	
delayed wound healing	1	1	0.4%	0	0	0.0%	0.4%	
dehiscence	0	0	0.0%	1	1	0.4%	-0.4%	
deep	0	0	0.0%	2	2	0.7%	-0.7%	

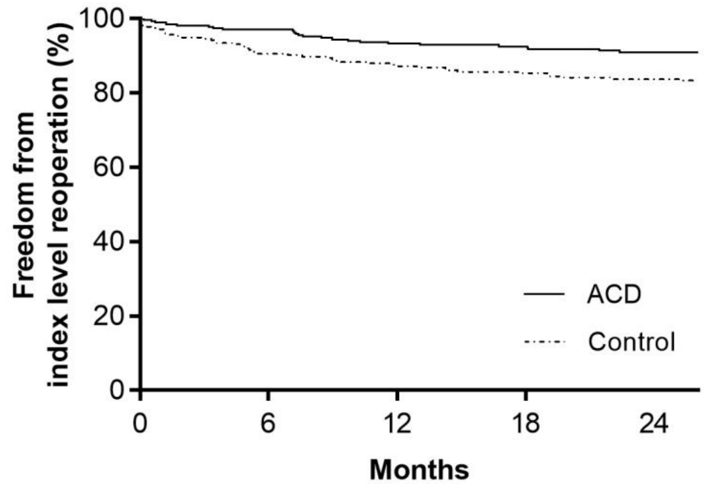
Figure 1.


647 Underwent microdiskectomy
93 Had ineligible annular defect size
554 Underwent randomization
276 Were assigned to receive ACD
4 In which ACD implant not attempted
278 Were assigned to receive Control
266 Were included in the 6-wk follow-up
5 Missed the visit
1 Withdrew from the study
0 Died
271 Were included in the 6-wk follow-up
5 Missed the visit
2 Withdrew from the study
0 Died
267 Were included in the 3-mo follow-up
2 Missed the visit
2 Withdrew from the study
0 Died
265 Were included in the 3-mo follow-up
6 Missed the visit
5 Withdrew from the study
0 Died
260 Were included in the 6-mo follow-up
7 Missed the visit
2 Withdrew from the study
0 Died
262 Were included in the 6-mo follow-up
7 Missed the visit
2 Withdrew from the study
0 Died
262 Were included in the 1-yr follow-up
3 Missed the visit
1 Withdrew from the study
1 Died
260 Were included in the 1-yr follow-up
8 Missed the visit
1 Withdrew from the study
0 Died
252 Were included in the 2-yr follow-up
8 Missed the visit
5 Withdrew from the study
0 Died
252 Were included in the 2-yr follow-up
7 Missed the visit
9 Withdrew from the study
0 Died



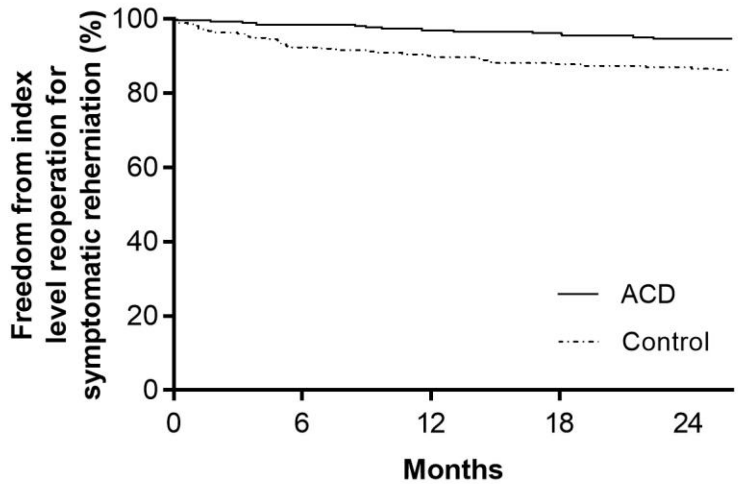
No. at Risk					
ACD	272	259	244	239	224
Control	278	239	223	206	190

Fig 2.jpg



No. at Risk					
ACD	272	260	248	244	237
Control	278	247	234	223	215

Fig 3a.jpg



No. at Risk

ACD	272	263	257	253	246
Control	278	251	240	229	223

Fig 3b.jpg