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Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease

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Abstract

BACKGROUND CONTEXT: Cervical total disc replacement (TDR) is intended to address radicular pain and preserve functional motion between two vertebral bodies in patients with symptomatic cervical disc disease (SCDD).

PURPOSE: The purpose of this trial is to compare the safety and efficacy of cervical TDR, ProDisc-C (Synthes Spine Company, L.P., West Chester, PA), to anterior cervical discectomy and fusion (ACDF) surgery for the treatment of one-level SCDD between C3 and C7.

STUDY DESIGN/SETTING: The study was conducted at 13 sites. A noninferiority design with a 1:1 randomization was used.

PATIENT SAMPLE: Two hundred nine patients were randomized and treated (106 ACDF; 103 ProDisc-C).

OUTCOME MEASURES: Visual analog scale (VAS) pain and intensity (neck and arm), VAS satisfaction, neck disability index (NDI), neurological exam, device success, adverse event occurrence, and short form-36 (SF-36) standardized questionnaires.

METHODS: A prospective, randomized, controlled clinical trial was performed. Patients were enrolled and treated in accordance with the US Food and Drug Administration (FDA)–approved protocol. Patients were assessed pre– and postoperatively at six weeks, 3, 6, 12, 18, and 24 months.

RESULTS: Demographics were similar between the two patient groups (ProDisc-C: 42.1±8.4 years, 44.7% males; Fusion: 43.5 ± 7.1 years, 46.2% males). The most commonly treated level was C5–C6 (ProDisc-C: 56.3%; Fusion=57.5%). NDI and SF-36 scores were significantly less compared with presurgery scores at all follow-up visits for both the treatment groups ($p<.0001$). VAS neck pain intensity and frequency as well as VAS arm pain intensity and frequency were statistically lower at all follow-up timepoints compared with preoperative levels ($p<.0001$) but were not different between treatments. Neurologic success (improvement or maintenance) was achieved at 24 months in 90.9% of ProDisc-C and 88.0% of Fusion patients ($p=.638$). Results show that at 24 months postoperatively, 84.4% of ProDisc-C patients achieved a more than or equal to 4° of motion or maintained motion relative to preoperative baseline at the operated level. There was a

FDA device/drug status: ProDisc-C (Synthes Spine, West Chester, PA, USA).

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statistically significant difference in the number of secondary surgeries with 8.5% of Fusion patients needing a re-operation, revision, or supplemental fixation within the 24 month postoperative period compared with 1.8% of ProDisc-C patients (p=.033). At 24 months, there was a statistically significant difference in medication usage with 89.9% of ProDisc-C patients not on strong narcotics or muscle relaxants, compared with 81.5% of Fusion patients.

CONCLUSIONS: The results of this clinical trial demonstrate that ProDisc-C is a safe and effective surgical treatment for patients with disabling cervical radiculopathy because of single-level disease. By all primary and secondary measures evaluated, clinical outcomes after ProDisc-C implantation were either equivalent or superior to those same clinical outcomes after Fusion.

Keywords: Cervical; Total disc replacement; ProDisc-C; ACDF; Arthroplasty; Randomized clinical trial

Introduction

Anterior cervical discectomy and fusion (ACDF) is considered by many to be one of the most successful spine procedures performed today and is a widely accepted option for the surgical treatment of cervical radiculopathy [1–6]. In 1958, Smith and Robinson [1] described the ACDF procedure where fusion was achieved by clearing the end plates of cartilage and subchondral bone, and the space was packed with iliac crest autograft. In the same year, Cloward [2] reported using a cylindrical bone dowel in place of morselized autograft with similar effect. The procedure remained largely unchanged until the 1990s when anterior cervical plates were widely introduced to add greater stability, and the increased commercial availability of allograft bone largely replaced autograft to reduce donor site morbidity. Over the past decade, despite reports of high fusion rates [3–6], there has been increased reporting of adjacent segment degeneration ranging from 3% to 8% per year as a consequence of ACDF [4,7–10]. The incidence of this adjacent segment breakdown was quantified by Hilibrand et al. [7], who retrospectively reviewed patient outcomes postoperatively and reported that 25.6% of patients developed new disease requiring surgical intervention at an adjacent level within 10 years after an ACDF. Although some argue that adjacent segment degeneration results from the natural progression of degenerative disc disease, it has been recognized that fusion causes increased stress at the adjacent levels [11–14], likely contributing to adjacent segment breakdown. In biomechanical cadaveric studies, cervical arthroplasty has been shown to maintain motion and mechanics within physiologic ranges at the index level and decrease stresses on adjacent segments [11,12]. In clinical studies after ACDF procedures, changes in segmental motion and increased strains in the intervertebral disc adjacent to fusion have been described [13,14]. Recently, clinical results of other cervical disc replacements have shown the maintenance of motion at the index level [15,16]. Long-term data will reveal whether substituting arthroplasty for fusion would both reduce the incidence of adjacent segment degeneration and the need for fusion at additional levels.

US Food and Drug Administration (US FDA) investigational device exemption (IDE) studies have been criticized for failing to always reflect a clinically meaningful result [17]. An IDE trial is a regulatory process focused on proving that the device performs equivalently to the predicate device. A composite of validated measures is combined to produce an "overall success." If there is a failure in any one category, the patient is a failure for the study. Because the focus is on the device, the substantial clinical benefit focused on the patient through health-related quality-of-life (HRQOL) measures could be different. Consequently, there has been strong motivation among the surgeon community to also evaluate the data for the minimum clinically important difference (MCID) in the HRQOL measures to better define the substantial clinical benefit of these devices [18–24]. MCID composite scores, similar to FDA overall success scores, are composed of validated measures to produce an overall success.

Early clinical results as part of the ProDisc-C IDE clinical trial have been reported previously as single-center European case series experiences [25,26]. These investigators have reported significant improvement in pain and outcome scores. This report presents the 2-year follow-up results of the prospective, randomized, controlled, multicenter US FDA IDE clinical trial to determine the safety and efficacy of the ProDisc-C total disc replacement (TDR) versus ACDF at a single level for the treatment of symptomatic cervical disc disease (SCDD) from C3 to C7. SCDD was defined as the presence of radicular pain and neurological deficit with at least one of the following conditions confirmed by imaging: herniated nucleus pulposus, spondylosis with the presence of osteophytes, and/or loss of disc height. The primary hypothesis of the study is that patients receiving a TDR would experience clinical success not inferior to control patients undergoing the current standard of care procedure, ACDF with allograft bone and anterior cervical plating. During the study, participating surgeons formulated an additional ad hoc hypothesis using clinical outcome measures already being collected as part of the trial as either primary or secondary endpoints. Focusing on HRQOL endpoints to define an MCID, it was hypothesize TDR would show superiority to Fusion.

Materials and methods

Study design

In an FDA-regulated IDE study (ProDisc-C IDE #G030059), 209 patients had surgery between August 2003 and October 2004 at one of 13 investigational sites across the United States. Approval was obtained from the Institutional Review Board at each site before the study was initiated. The study population consisted of 209 treated, randomized patients (ProDisc-C: 103; control: 106) with randomization conducted on a 1:1 ratio. The control group received anterior cervical discectomy and fusion. There were 13 primary investigators involved in the study and all had clinical practices heavily based in adult spine. Inclusion/exclusion criteria (Table 1) were met before enrollment. The main inclusion criteria were that the patient had SCDD causing intractable, debilitating radiculopathy from one vertebral segment between C3 and C7, was unresponsive to nonoperative treatment for at least six weeks, and had a neck disability index (NDI) score of 15/50 (30%) or more.

Statistical design

As traditionally used in IDE trials with regard to spinal implants, a noninferiority study design was used. The sample size was computed using the Blackwelder methodology, assuming that 75% of the patients in both the ProDisc-C and control groups would have a successful result and that a clinically insignificant difference in success rates between groups (δ) was 10%. Choosing a type I error of 5% (one-sided) and 80% power, the sample size was determined to be 102 in each group for a total of 204 patients. Allowing for a potential dropout rate of 10% resulted in a possible enrollment of 114 in each group, for a total possible enrollment of 228 patients.

Using a fixed randomization blocking method of four assignments per block, a contract research organization generated random allocations in a 1:1 ratio. After a patient signed the informed consent, surgical intervention was assigned. The surgeon and surgical staff were not blinded to group assignment as preparation requirements were needed for both procedures. The patient remained blinded to randomization until immediately postsurgery.

Statistical analysis

All patients who received the study devices and underwent the surgical procedures were included in the analyses. Primary statistical comparisons were based on the observed and recorded follow-up data.

The primary hypothesis of this IDE clinical trial is that, in regard to key clinical outcomes, the overall success rate of the investigational group (ProDisc-C) is not inferior to the overall success rate of the control group (Fusion). Overall success for each patient is determined by four-component endpoints: NDI success, neurological success, device success, and absence of adverse events related to the implant or its implantation. The overall study success rate is defined as the percentage of individual patients achieving success in all four-component endpoints. An exact version of Blackwelder's test for noninferiority was performed to test the primary hypothesis using a noninferiority margin of $\delta=0.10$ as recommended by the FDA.

An additional ad hoc hypothesis of the clinical trial tested with regard to the HRQOL measures is that the overall success rate of the investigational group is superior to the overall success rate of the control group. The HRQOL endpoints consist of six-component endpoints to determine overall success for each patient: NDI success, patient satisfaction measured by willingness to have the same surgery again, absence of device failure, absence of pseudoarthrosis (Fusion)/absence of fusion (ProDisc-C), visual analog scale (VAS) neck or arm pain improvement, and absence of strong narcotic or muscle relaxant use. The success rate is defined

EVIDENCE & METHODS

Context

Total disc arthroplasty and anterior cervical discectomy with fusion are two proposed procedures for the surgical treatment of cervical radiculopathy. This paper presents the two-year results of an FDA randomized trial comparing the two.

Contribution

There were no statistically significant differences between the two at two-years post-operatively for most outcome measures including VAS neck and arm, neurological success, neck disability index, and SF-36 scores. Longer operative time with increased blood loss were reported in the arthroplasty group; but while statistically significant, the actual differences were small. Small advantages were reported for the arthroplasty group regarding re-operation rate, strong narcotic use, and some measures of satisfaction; but the first two measures are to some extend determined by the unblinded surgeon discretion to prescribe further treatment (especially in light of equivalent validated outcomes) and satisfaction may reflect a new-technology effect.

Implications

Early data suggest disc arthroplasty has equivalent short-term outcomes in the setting cervical radiculopathy. Longer-term follow-up is needed as late failure of arthroplasty is a reasonable concern.

—The Editors

Table 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 18–60y	More than one vertebral level requiring treatment
SCDD in only one vertebral level between C3–C7 requiring: 1. Neck or arm (radicular) pain and/or 2. Functional/neurological deficit confirmed by imaging (CT, MRI, and X-ray) of at least one of the following: i. Herniated nucleus pulposus ii. Spondylosis (defined by the presence of osteophytes) iii. Loss of disc height	Marked cervical instability on resting lateral or flexion-extension radiographs: 1. Translation >3 mm and/or 2. More than 11° of rotational difference to that of either adjacent level Has a fused level adjacent to the level to be treated Radiographic confirmation of severe facet joint disease or degeneration
Unresponsive to nonoperative treatment for at least six weeks or has the presence of progressive symptoms or signs of nerve root/spinal cord compression in the face of conservative treatment	Known allergy to cobalt, chromium, molybdenum, titanium, or polyethylene Prior surgery at the level to be treated
NDI score ≥ 15/50 (30%)	Neck or arm pain of unknown etiology
Psychosocially, mentally, and physically able to fully comply with this protocol including adhering to follow-up schedule and requirements, and filling out forms	Clinically compromised vertebral bodies at the affected level as a result of current or past trauma, eg, by the radiographic appearance of fracture callus, malunion, or nonunion
Signed informed consent	Active infection—systemic or local
	Severe spondylosis at the level to be treated as characterized by any of the following: 1. Bridging osteophytes 2. Loss of disc height >50% 3. Absence of motion (<2°)
	Paget's (dual energy X-ray absorptiometry) disease, osteomalacia or any other metabolic bone disease (excluding osteoporosis discussed below)
	Severe diabetes mellitus requiring daily insulin management
	Pregnant or interested in becoming pregnant in the next three years
	Rheumatoid arthritis or other autoimmune disease
	Systemic disease including AIDS, HIV, or hepatitis
	Osteoporosis. A screening questionnaire for osteoporosis, SCORE, will be used to screen patients who require a DEXA bone mineral density measurement. If DEXA is required, exclusion will be defined as a DEXA bone density measured T score≤−2.5 (the World Health Organization definition of osteoporosis)
	Taking medications or any drug known to potentially interfere with bone/soft-tissue healing (eg, steroids)
	Active malignancy. A patient with a history of any invasive malignancy (except nonmelanoma skin cancer), unless treated with curative intent and there have been no clinical signs or symptoms of the malignancy for >5 years

SCDD, symptomatic cervical disc disease; NDI, neck disability index; SCORE, simple calculated osteoporosis risk estimation.

as the percentage of individual patients achieving success in all six-component endpoints. A one-sided Fisher's exact test was performed to test the hypothesis.

For between-treatment-group comparisons of continuous measurements such as NDI, VAS pain and SF-36 scores, the Wilcoxon rank-sum test was used. At each follow-up visit, paired *t*-tests were performed to compare the average improvement from baseline within the treatment groups for the patient's self-assessment data. Fisher's exact test was used to compare success rates between the treatment groups such as neurological success, device success, NDI success, the percentage of patients employed, and the percentage of patients indicating they would have the surgery again. The percentage of patients experiencing an adverse event was compared between the treatment groups using Fisher's exact test and the event rates per patient were compared using Poisson regression.

Device description

The ProDisc-C design is based on a ball-and-socket principle and comprises three components. There are two end plates manufactured from a cobalt chromium molybdenum (CoCrMo) alloy with a midline keel to provide fixation, titanium plasma spray coating for bony on-growth, and an ultrahigh–molecular weight polyethylene (UHMWPE) inlay. The upper end plate design allows for a highly polished concave bearing surface that articulates with the convex UHMWPE spherical dome. The design for the caudal end plate allows for the UHMWPE inlay to snap-lock into the plate providing the convex bearing surface and is preassembled during manufacturing. The design enables reconstruction of various heights and vertebral end plate sizes (Fig. 1).

Surgical technique

Patient positioning and approach

The patient is positioned supine on a radiolucent table with all bony prominences protected. A radiolucent Mayfield headrest or an occipital gel pad placed on a flat radiolucent bed may be used. A small roll is placed under the

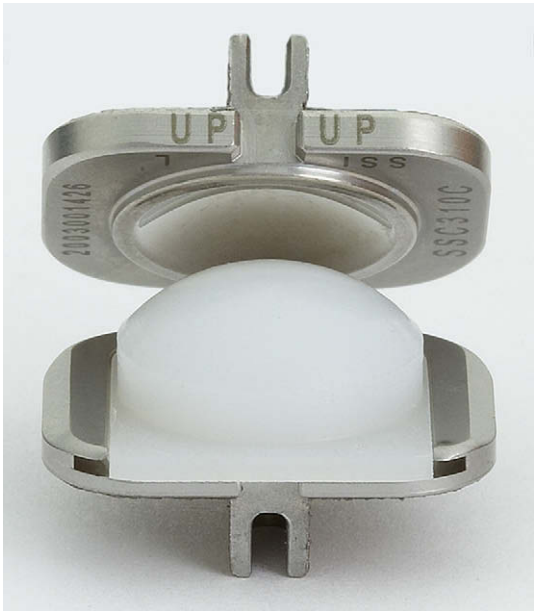

Fig. 1. The ProDisc-C total disc replacement. It comprises two cobalt chromium molybdenum alloy end plates with central keels and an ultra-high–molecular weight polyethylene convex inlay.

neck for stabiliy and support. A standard anterior approach to expose the cervical spine is used, with exposure limited to the operative level. The operative level is confirmed using a radiographic marker under fluoroscopy. The longus colli muscles are gently retracted as needed for exposure. Under fluoroscopic guidance, distractor pins are placed into the vertebral bodies near the superior end plate of the superior vertebra and inferior end plate of the inferior vertebra, with both pins parallel to the end plates of the operative-level disc. Minimal distraction is applied initially. The midline is determined with AP fluoroscopy and marked with an osteotome. The anterior longitudinal ligament and anterior annulus are resected, centered on the midline mark, to provide access to the disc space.

Anterior cervical discectomy and fusion procedure

For the control arm, standard ACDF technique is used. Allograft bone spacers (either surgeon-cut or commercially prepared) are used and when available, local bone is also packed around or within the allograft. No commercial DBM or BMP materials are used. An anterior cervical fixed angle plate is placed over the graft and secured to the adjacent vertebral bodies.

ProDisc-C procedure

Using curettes, the cartilaginous end plates are removed with attention to preserve the integrity of the bony end plates to provide a firm base for mechanical stability. The uncovertebral joints are preserved if possible. If significant hypertrophic uncovertebral joint spurs are present, they are removed. As needed, the posterior longitudinal ligament (PLL) is resected for decompression and remobilization. Violation of the end plates or excessive removal of uncovertebral joints is not advised. Once the discectomy is completed, an intervertebral distractor is used to remobilize the disc space and recreate normal disc space height in a parallel fashion. The vertebral body retainer is then adjusted to maintain this position.

The ProDisc-C system contains 16 trial implants corresponding to the 16 potential implant sizes. Appropriate-sized trials are placed into the disc space intraoperatively to determine the appropriate implant footprint, disc height, and position. The optimal position of the trial within the disc space is centered in the AP plane, extending to the posterior vertebral body cortex in the lateral projection. The largest footprint is selected to maximize coverage of the vertebral end plates, and the smallest appropriate height is selected to match a normal adjacent disc and allow motion. Correct sizing and placement are critical for optimal implant performance.

After ensuring that the trial is centered on midline and aligned in the sagittal plane, two different types of chisels are slid over the shaft of the trial to cut a channel in both the superior and inferior vertebral bodies for the keel of the implant. The trial and chisels are removed and the trough is cleaned of any bone debris with a nerve hook. The implant that correlates with the implant trial spacer is then assembled on the inserter. Under fluoroscopic control, the ProDisc-C implant is inserted into the prepared channels and advanced to the posterior margin of the vertebral bodies. The vertebral body distractor pins are removed and the holes created by the pins are filled with bone wax. Any bleeding bone, including the anterior keel trough cut, should be covered with bone wax. This was not specifically indicated in the protocol and instead was left to the discretion of the investigators at each site. Final implant position is verified with lateral and AP imaging. The surgical wound is then closed in a routine fashion (Fig. 2).

Postoperative care

Postoperative care was at the discretion of the surgeon including an appropriate rehabilitation program. ProDisc-C patients began ambulating immediately postoperatively. A hard or soft collar was used if deemed necessary for ACDF

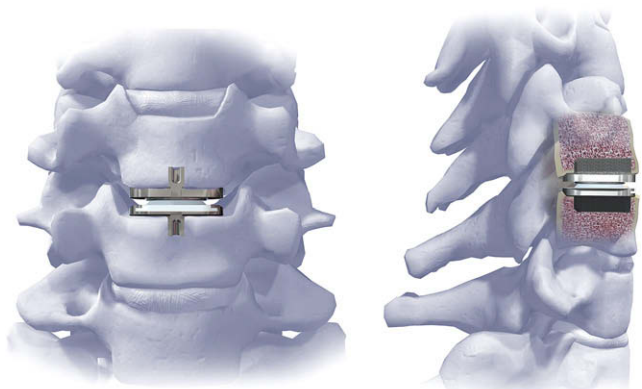

Fig. 2. Illustrations of the anterior and lateral views of the ProDisc-C in the cervical spine.

patients. Patients were told to avoid prolonged or strenuous activity until the surgeon directed otherwise and were instructed to immediately report any change in their pain or neurological status. Medication usage was not specified by the research protocol but was collected on the case report forms by schedule class of drugs. Strong narcotics were defined as Schedule 2 drugs (high abuse and high-dependency risk). Weak narcotics were defined as Schedule 3 drugs (lower abuse and moderate dependency risk). Nonsteroidal anti-inflammatory drug (NSAIDs) use as prophylaxis against new bone formation was not specified in the research protocol.

Clinical outcome measurements

The clinical status of each patient was evaluated pre– and postoperatively at six weeks and 3, 6, 12, 18, and 24 months. The clinical evaluation at each visit includes self-assessments, physical and neurological examination, and radiographic evaluation. The self-assessment questionnaires given are the NDI Questionnaire, SF-36 Mental and Physical Health Surveys (MCS and PCS), pain intensity and frequency on a 10-cm VAS in the neck and arm (VAS pain intensity and frequency), and satisfaction on a 10-cm VAS (VAS satisfaction). The physical and neurological examination evaluates range of motion (ROM), root tension, reflexes, muscle strength, and sensory deficits. Radiographic evaluation consists of anteroposterior (AP) and lateral, flexion-extension (F/E), and coronal right and left lateral bending films. For consistency, all the radiographic analyses were performed by Medical Metrics Inc. (Houston, TX), a provider of independent radiographic review services. For the ACDF procedure, fusion was confirmed if radiographic review confirmed all the following: strong evidence of fusion including more than 50% of the trabecular bridging or bone mass maturation and increased or maintained bone density at the site, no motion ($\leq 2^\circ$), no visible gaps in the fusion mass, no loss of disc height (>3 mm; comparing immediate postoperative to 24 month films), and no implant loosening (no halos/radiolucencies around the implant).

Results

The follow-up rate at 24 months for the entire study cohort was 96.5%. There was no statistically significant difference between ProDisc-C patients (98.0%) and control patients (94.8%) returning at 24 months.

Demographics and intraoperative data

Overall patient demographics showed no statistically significant differences between the treatment groups in age, gender, race, smoking status, body mass index (BMI), baseline NDI, surgical level, prior surgical treatment, or length of hospital stay (Table 2). The average age was 42.1 years in the ProDisc-C group compared with 43.5 years in the Fusion group. Female patients outnumbered male patients in both groups with 55.3% females in the ProDisc-C group and 53.8% females in the Fusion group. The most commonly treated level was C5–C6 followed by C6–C7, regardless of treatment. Intraoperative data (Table 2) showed the control group to be statistically significantly lower with regard to operative time (Fusion: 98.7 minutes vs. ProDisc-C: 107.2 minutes) and estimated blood loss (Fusion: 63.5 cc vs. ProDisc-C: 83.5 cc).

Table 2
Intraoperative data and patient demographics

Variable	ACDF (N = 106)	ProDisc-C (N = 103)	p Value
Intraoperative data			
Implant level, N (%)			
C3–C4	1 (0.9)	3 (2.9)	0.4764
C4–C5	6 (5.7)	10 (9.7)	
C5–C6	61 (57.5)	58 (56.3)	
C6–C7	38 (35.8)	32 (31.1)	
Intraoperative time (min)			
N	106	103	0.0078
Mean (SD)	98.7 (47)	107.2 (35.7)	
Estimated blood loss (cc)			
N	105	103	0.0094
Mean (SD)	63.5 (50.3)	83.5 (64.9)	
Length of hospital stay (d)			
N	106	103	0.7882
Mean (SD)	1.3 (0.83)	1.4 (1.18)	
Patient demographics			
Gender, N (%)			
Male	49 (46.2)	46 (44.7)	0.8897
Female	57 (53.8)	57 (55.3)	
Age (y)			
N	106	103	0.2025
Mean (SD)	43.5 (7.1)	42.1 (8.4)	
Race, N (%)			
Caucasian	97 (91.5)	88 (85.4)	0.1000
African American	1 (0.9)	4 (3.9)	
Hispanic	5 (4.7)	3 (2.9)	
Asian American	0 (0.0)	5 (4.9)	
Other	3 (2.8)	3 (2.9)	
Body mass index (kg/m^2)			
N	106	103	0.0896
Mean (SD)	27.3 (5.5)	26.4 (5.3)	
Smoking status, N (%)			
Never	49 (46.2)	51 (49.5)	0.9159
Former	20 (18.9)	18 (17.5)	
Current	37 (34.9)	34 (33.0)	
Prior surgical treatment, N (%)			
Any	10 (9.4)	11 (10.7)	0.8208
Discectomy	3 (2.8)	4 (3.9)	
IDET	0 (0.0)	0 (0.0)	
Laminectomy	5 (4.7)	2 (1.9)	
Laminotomy	0 (0.0)	0 (0.0)	
Other	4 (3.8)	7 (6.8)	

ACDF, anterior cervical discectomy and fusion; SD, standard deviation; IDET, intradiscal electrothermal therapy (ORATEC Interventions, Inc., Menlo Park, CA).

Clinical outcomes

Neurological success

Neurological success was defined as the maintenance or improvement in each of the neurologic evaluations including sensory, motor, and reflex functions. Failure in any one of the evaluations deemed the patient a neurological failure for that timepoint. At six months, there was a statistically significant difference favoring the ProDisc-C group compared with the Fusion group with 94.6% of patients achieving success compared with 85.1% (p=.0460). At 24 months, the neurological success rate was higher in the ProDisc-C group (90.9%) compared with the Fusion group (88.0%), but the difference was not statistically significant (p=.638).

Neck Disability Index

The NDI is a validated questionnaire [27] that assesses the patient's disability during activities of daily living. Baseline preoperative NDI values between both the treatment groups were not different (ProDisc-C: 53.9+15.0; control: 52.2+14.5; p=.43). Regardless of treatment, all patients showed statistically significant improvement in NDI scores at all follow-up periods compared with baseline (p<.0001; Fig. 3). At the 3-month timepoint, there was a statistically significant difference favoring the ProDisc-C group compared with the Fusion group (p=.05). Substantial improvement was maintained through 24 months in both the groups. At 24 months, the mean score of the ProDisc-C group was 21.4+20.2 points, whereas the mean score for the control group was 20.5+18.4 (p=1.0000).

As characterized by the FDA, the NDI success criterion was defined as a more than 15-point improvement from baseline value. The success rate was higher in the ProDisc-C group at all follow-up timepoints compared with the Fusion group, and was statistically significantly different favoring ProDisc-C at the three-month timepoint (p=.0005). At 24 months, 79.8% of ProDisc-C patients had a more than 15-point improvement and were considered successful compared with 78.3% of Fusion patients; the difference was not statistically significant. For determining MCID, NDI success criterion was defined as a 20% improvement from baseline value as previously validated for a similar clinical study [24]. At 24 months, 84.8% of ProDisc-C patients and 85.9% of Fusion patients were determined to have achieved success with no difference between the two treatments (p=.500).

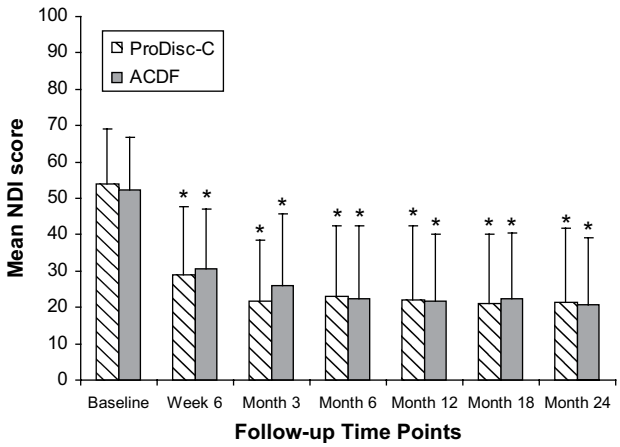

Fig. 3. Neck Disability Index (NDI) scores for each treatment over time. Error bars represent the standard deviation. *Significant difference from preoperative state with treatment group (p<.0001).

Secondary surgical procedures

Secondary surgical procedures were defined as any revision, removal, or re-operation of the implant or supplemental fixation. Overall, nine patients (8.5%) in the Fusion group and two patients (1.9%) in the ProDisc-C group required a secondary surgical procedure. Revision surgery was defined as any surgical procedure done to modify the original implant without removal of the entire construct. No patients in the ProDisc-C group required revision. Five patients (4.7%) in the Fusion group required revision surgery. Reasons for revision surgery included: one case of plate subsidence, one case of plate lift-off causing dysphasia, two cases of neck pain/pseudoarthrosis, and one case of additional fusion at adjacent level. Implant removal was performed in two ProDisc-C cases because of ongoing pain, and these patients were converted to fusion. No removals were required in the Fusion group. Re-operations were defined as any subsequent surgical procedure to the site, such as a decompressive laminectomy or foraminotomy. One patient (0.94%) in the Fusion group underwent re-operation for pain associated with pseudoarthrosis and there were no re-operations in the ProDisc-C group. A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted (eg, supplemental placement of a rod/screw system or a plate/screw system). Supplemental fixation was necessary in three Fusion patients (2.8%) for pain and/or pseudoarthrosis with posterior instrumentation. One of those cases was after a motor vehicle accident. There was no supplemental fixation in any ProDisc-C case.

Device success was defined as no revision, removal or re-operation of the implant or supplemental fixation. Using these criteria, there was a statistically significant difference favoring ProDisc-C compared with Fusion (p=.033) as success was achieved in 98.1% (101/103) of ProDisc-C patients and 91.5% (97/106) of Fusion patients.

Adverse events

Adverse Event (AE) success was defined as the absence of adverse events related to the implant or its implantation. An implant-related AE failure was defined as a failure attributable to the index level which was also associated with severe or life-threatening AE. This is defined as a medical occurrence that is fatal, life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or requires medical/surgical intervention. An implantation-related AE

failure was an event uniquely attributable to the implantation of the specific device. The number of patients achieving AE success was higher in the ProDisc-C group, 97.1% (100/103), compared with the Fusion group, 93.4% (99/106), but this difference was not statistically significant (p=.33). There were no incidences of vertebral body splits or fractures. The three ProDisc-C patients who did not achieve AE success had two implant-related and one implantation-related events: two patients reported continued pain and one patient elected removal of the device and conversion to a fusion and the other did not, and one patient who sustained a dural tear. The seven Fusion patients did not achieve AE success from implant-related (6) and implantation-related (1) events because of painful pseudoarthrosis requiring revision (2); plate subsidence/migration requiring revision (2); dysphagia (1); superficial wound infection (1); and foraminotomy as a result of persistent radicular pain (1).

Visual analog scale pain

VAS pain assessments recorded for both frequency and intensity for neck and arm pain indicated statistically significant improvement from preoperative levels regardless of treatment ($p < .0001$; Fig. 4). At 24 months, VAS scores were similar between ProDisc-C and Fusion for all parameters tested. VAS Neck Pain intensity results showed an average reduction from baseline in the ProDisc-C group of 46 mm compared with a 43-mm reduction in the Fusion group. VAS neck pain frequency averaged a 51-mm reduction from baseline in both groups. Similar results were seen for VAS arm pain scores at 24 months. VAS arm pain intensity scores were similar and showed a 43-mm average reduction (ProDisc-C) and a 44-mm average reduction (Fusion) from baseline. The frequency scores were also similar with a 49-mm reduction in the ProDisc-C group and a 50-mm reduction in the Fusion group from baseline. These differences were not statistically significant. An MCID in this area was defined as a 20% improvement in neck or arm pain frequency at 24 months. This was achieved successfully by 87.9% of ProDisc-C patients and 86.9% of Fusion patients ($p = 1.0$).

Patient satisfaction and Surgery again

VAS patient satisfaction (Fig. 5) was higher at all timepoints for ProDisc-C cases compared with Fusion cases. At 24 months, the mean satisfaction score was 83.39± 24.84 mm for ProDisc-C patients and 79.99±28.04 mm for Fusion patients. Patients' satisfaction scores were distributed in 20 mm intervals (<20, 20 to <40, 40 to <60, 60 to <80, 80–100). The percentage of patients considered to be completely satisfied (60–100) was 86.3% of ProDisc-C patients and 83.0% of Fusion patients.

Patients were asked whether they would have the same surgical treatment again (Fig. 5). At 24 months, 85.6% of the ProDisc-C patients and 80.9% of the Fusion patients responded "yes" (Fig. 6). At all timepoints, there was no statistically significant difference between patients responding "yes or maybe" in either treatment group. At 24 months, 95.9% of the ProDisc-C patients and 96.6% of the Fusion patients responded that they would definitely or maybe have the same surgery again.

Radiographic findings

Plain films were used to evaluate migration, device subsidence, disc height, presence of radiolucency, presence of visible gaps (Fusion only), presence of pseudoarthrosis (Fusion only), or bridging bone (ProDisc-C only). At all timepoints, radiographic data were analyzed. Only patients who reached their 24-month follow-up had their radiographic findings included in the final analysis, thereby excluding those who underwent secondary surgery. There was no evidence of migration, subsidence, change in disc height or visible gaps found in either group. In the Fusion group, one patient was found to have radiolucency (1.1%) and eight patients exhibited pseudoarthrosis (8.7%) defined as less than 50% bridging trabecular bone. Therefore, the fusion rate for those patients reaching 24 months without a secondary surgery was 90.2%. Three patients in the ProDisc-C group were found to have bridging bone at the index level (2.9%). Flexion/extension (F/E) ROM was also evaluated digitally on plain films by independent observers for the ProDisc-C group. Success was defined as more than or equal to 4° of motion on F/E and/or maintenance of motion at 24 months from preoperative baseline. At 24 months, F/E ROM averaged 9.36+5.95° in the ProDisc-C group. The F/E ROM criterion was met by 84.4% of the ProDisc-C patients.

Short form-36

SF-36 success was defined as any improvement from baseline in the composite score of the MCS and PCS components (Table 3). Regardless of treatment and at all timepoints, there was a statistically significant improvement of the overall SF-36 scores from baseline ($p<.0001$). At 24 months, 80.8% of ProDisc-C patients and 74.4% of Fusion patients were successful in the PCS. The MCS showed that 71.8% of ProDisc-C and 68.9% of Fusion patients were successful.

Narcotic use

Preoperatively, narcotic medications (Schedule 2 and Schedule 3) were used in 48.1% of Fusion patients and in 48.5% of ProDisc-C patients. In addition, 21.7% of Fusion patients and 19.4% of ProDisc-C patients were taking muscle relaxants. The use of these medications decreased considerably from baseline in both groups over the course of the postoperative evaluation period. Overall, at 24 months, 13.0% (73% decrease) of Fusion patients and 11.2% (77% decrease) of ProDisc-C patients remained on weak (Schedule 3) or strong (Schedule 2) narcotics. Additionally, 13% (40% decrease) of Fusion patients and 8.1% (58% decrease) of ProDisc-C patients were taking muscle

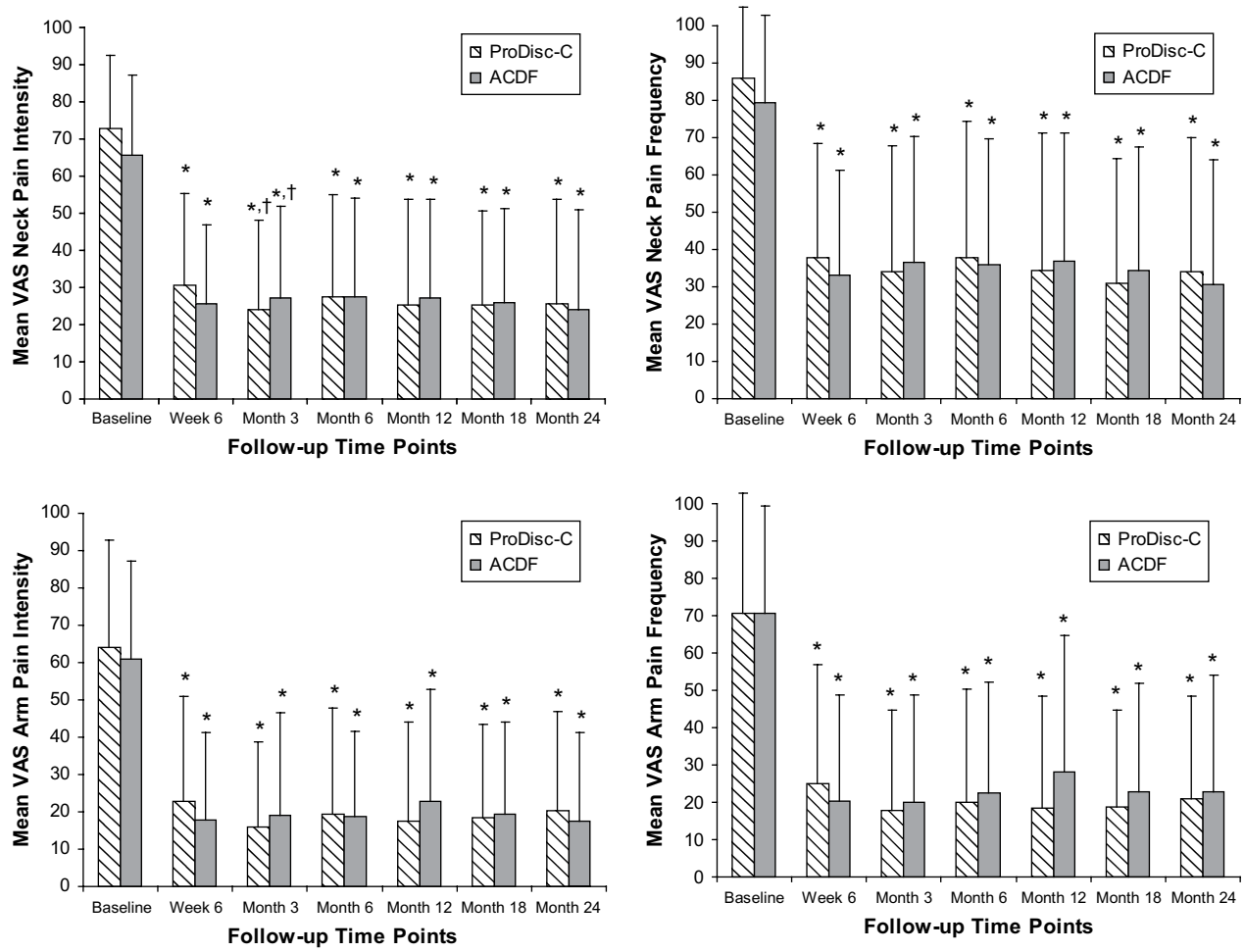

Fig. 4. Visual analog scale (VAS) pain scores. VAS pain intensity and frequency were collected for the neck and arm for each treatment over time. Error bars represent the standard deviation. *Significant difference from preoperative state within treatment group ($p<.0001$). †Significant difference between the treatment groups at specific time intervals ($p<.05$).

relaxants. Moreover, only 10% of ProDisc-C patients and 20.8% of Fusion patients remained on strong narcotics and/or muscle relaxants at 24 months. An MCID in this area was defined as the absence of strong narcotics and/or muscle relaxants at 24 months and the difference was statistically significant between the two treatment groups favoring the ProDisc-C group ($p=.05$). Interestingly, when looking at patients deemed a success by the FDA criteria at 24 months, only 1.4% (93.6% decrease) of ProDisc-C patients were still on strong narcotics compared with 4.3% (77.2% decrease) of Fusion patients. Also in successful patients, only 1.4% (91.7% decrease) of ProDisc-C patients were on muscle relaxants at 24 months compared with 7.2% (71.8% decrease) of Fusion patients. Interestingly, the results for patients considered failures by FDA criteria showed great disparity in medication usage between groups. In this group, there was a 35.2% decrease in strong narcotics and 9.2% decrease in muscle relaxants in the ProDisc-C group. In comparison, the Fusion group showed a 53.6% decrease in strong narcotics but a 61.7% increase in muscle relaxants.

Work and physical labor status

Status refers to the percentage of patients partaking in the activity both full and part time. There was no difference preoperatively between the Fusion group (84.9%) and the ProDisc-C (82.5%) group employment rate ($p = .71$). A lack of statistical difference continued throughout the 24-month postoperative evaluation period. At 24 months, the Fusion group reported 80.0% as employed and the ProDisc-C group 82.8% as employed ($p = .71$). Preoperative physical labor status showed no difference (Fusion: 52.2%; ProDisc-C: 57.1%) between patients asked to do moderate-to-heavy work. At 24 months, percentage of patients who were asked to do moderate-to-heavy labor had decreased slightly (Fusion: 44.7%; ProDisc-C: 48.1%) but the difference was not statistically significant ($p = .75$).

Overall success

The composite scores for the primary hypothesis and the additional hypothesis are presented in Table 4. For the primary hypothesis of FDA-defined criteria, 72.3% of ProDisc-C patients and 68.3% of Fusion patients were successful at 24

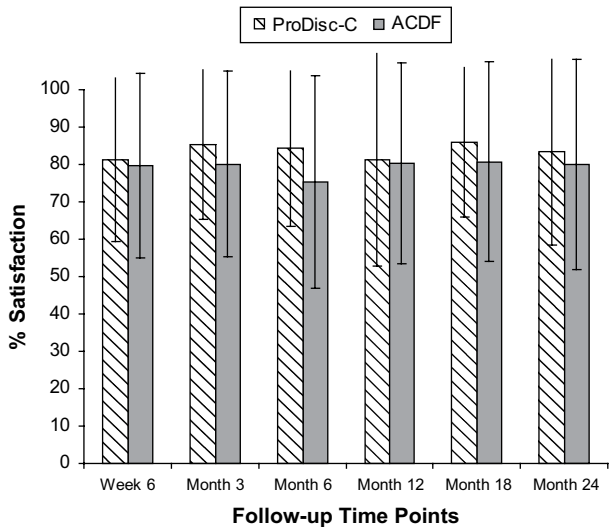

Fig. 5. Visual analog scale (VAS) satisfaction. VAS satisfaction represents how satisfied each patient felt at each timepoint. The mean and standard deviation at each timepoint for both the treatments is represented. There was no statistical difference between the treatments at any timepoint.

months (p=.0105), establishing noninferiority. For completeness, the originally defined FDA criteria used a 20% difference for NDI yielding success rates 77.2% for ProDisc-C patients and 74.3% for Fusion patients at 24 months (p = .0017), also establishing noninferiority. The additional MCID hypothesis found 73.5% of ProDisc-C patients and 60.5% of Fusion patients were successful at 24 months (p = .0472) proving ProDisc-C to be superior to ACDF.

Discussion

The results of this clinical trial clearly demonstrate that ProDisc-C is a safe and effective surgical treatment for patients with disabling cervical radiculopathy because of single-level disease. By all measures evaluated, clinical outcomes after ProDisc-C implantation were equivalent or superior to those same clinical outcomes after ACDF, considered by most clinicians to be a high bar for a control comparison. There was a significant difference in the number of secondary surgeries with 8.5% of ACDF patients needing a re-operation, revision, or supplemental fixation within the 24-month postoperative period compared with 1.8% of ProDisc-C patients (p=.033). In successful patients, there was a significant difference in medication usage with 90% of ProDisc-C patients not on strong narcotics or muscle relaxants, compared with 79.2% of Fusion patients (p=.05). As the FDA success criteria tend to focus on safety and efficacy of the device, whereas the surgeon community focuses on clinically relevant HRQOL outcomes, the discussion will consider these results in two lights—those required for FDA approval, and those deemed by the authors to be most clinically relevant.

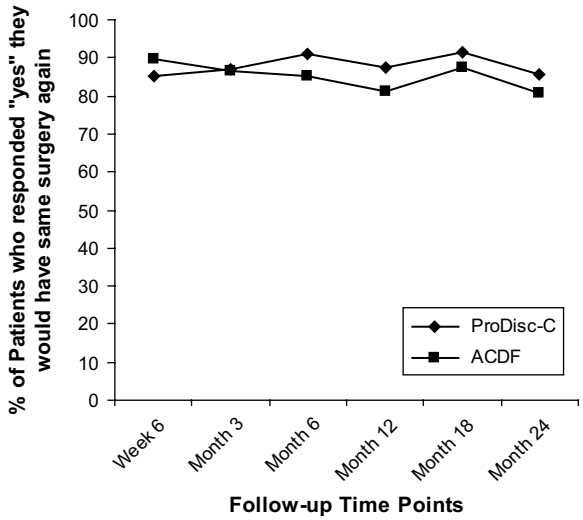

Fig. 6. Surgery again. Comparison of ‘‘yes’’ responses as to whether the patient would choose the same treatment option again.

The FDA-mandated criteria for success included 15-point improvement or more of NDI scores, neurological success, implant success, and adverse events. To achieve overall success, a patient was required to be successful in all four criteria. An overall success rate of 72.3% in the ProDisc-C group compares favorably with ACDF at 68.3%. Although the components of the composite score of success vary by study, the overall theme is that these studies are consistent in showing these devices to be safe and efficacious while providing greater surgical options. When looking at each component, there was also a common trend of significant improvement at earlier timepoints. Comparing NDI results, the ProDisc-C patients tended to fare better at six weeks, and fared significantly better at three months. Similarly, neurological success was equivalent at 24 months, but was noted to be significantly better at six months and trended to be better at one year. Both measures imply that ProDisc-C patients recover from their disability and achieve neurological success more quickly than do ACDF patients. Furthermore, only two patients in the ProDisc-C group required secondary surgery compared with nine patients in the fusion group, which was both statistically significant (p=.033) and substantially clinically relevant. Lastly, adverse events related to the implant or implantation were equally unlikely and not different (p=.33) between the study groups with 97.1% of the ProDisc-C group compared with 93.4% of the Fusion group not experiencing an incident. This was not surprising given the similarity in technique and treatment course between the study and control procedures.

In addition to success criteria required for FDA clearance, our hypothesis chose the components based on those that seemed the most clinically relevant to a patient's quality of life directly relate to the patient's pain and pain management. Multiple groups have proposed the idea of an MCID or essentially the delineation point at which patients begin to recognize a substantial clinical benefit from their treatment [18–24]. Although MCID composite scores are no more validated than FDA composite scores, they are composed of validated measures such as FDA composite

Table 3
SF-36 success rate by timepoint

Timepoint	ACDF (%)	ProDisc-C (%)	p Value
Week 6	56.9	72.1	0.0183
Month 3	70.0	86.6	0.0036
Month 6	75.0	80.4	0.2333
Month 12	76.7	81.0	0.3024
Month 18	74.5	79.1	0.3170
Month 24	70.0	79.2	0.0943

ACDF, anterior cervical discectomy and fusion.

scores. The minimal detectable difference for NDI has been validated at 10.5 points, 19 points, and 20% by others. We chose 20% difference for NDI because the previous study on ACDF was the closest model to our study. The demarcation was also set at a 20% difference from baseline for other applicable outcome parameters. The other measures chosen included patient satisfaction based on whether they would have the surgery again, 20% improvement in VAS arm or neck pain frequency, absence of device failure, absence of pseudoarthrosis (Fusion)/absence of fusion (ProDisc-C), and absence of strong narcotic or muscle relaxant use. Using these six components for a composite score, we were able to prove a statistically significant difference favoring ProDisc-C, 73.5%, compared with ACDF, 60.5%, when focusing on improving a patient's HRQOL (p=.0472).

Intraoperative data were largely comparable. There were two statistical exceptions with slightly longer operative time (107.2 minutes vs. 98.7 minutes) and slightly increased blood loss (83.5 cc vs. 63.5 cc) in the ProDisc-C group. As there were no training cases in this study as often seen in IDE trials, the increased operative time was attributed to time required to learn the new technique and time for additional use of fluoroscopy in ProDisc-C cases. Increased blood loss was attributed to bleeding from the keel cuts into cancellous bone required by the ProDisc-C technique. Although both were statistically significant, neither difference was felt to be clinically relevant.

Finally, radiographic outcomes were assessed indicating that, in general, ProDisc-C patients maintained motion in all planes at the operative level, averaging 9.36°. As reported in most other cervical TDR clinical trials, a small percentage of ProDisc-C patients developed motion-relevant heterotopic ossification (HO). Three did go on to fuse at the operative level; however, these patients achieved successful clinical outcomes for pain and disability relief. HO is a well-documented complication of large joint arthroplasty, especially hip arthroplasty [28], and has been successfully controlled with short-term use of NSAIDs in cervical TDR [29]. In this trial protocol, NSAID use was not required and as such was not routinely used by the investigators. Sites that routinely used NSAIDs for HO prophylaxis had zero incidence of this complication. Therefore, the postoperative ProDisc-C regimen has been altered to recommend two weeks of NSAID therapy. More notably, nine patients were radiographic failures in the ACDF group leading to a fusion rate of 90.2%. Although Fraser and Hartl [6] reviewed 21 articles on anterior approaches and reported a fusion rate of ACDF with plating to average 97.1%, most of these articles were retrospective, small series, self-assessed, often single surgeon's experience with no universal standards of fusion. In the prospective, randomized IDE study for Prestige ST, Mummaneni et al. [15] reported a fusion rate of 97.5% at 24 months, however, 25% of their ACDF patients were lost to follow-up and are not included. Our fusion rate was 90.2% on 94.8% of patients. To the best of our knowledge, this is the largest prospective series of ACDF with plating with the highest patient accountability ever reported. The consensus among surgeons is that ACDF is highly successful. This study has questioned that premise to some extent with regard to secondary surgery required, medication usage, and lower than anticipated fusion rates.

Table 4
Overall success criteria at 24 months

	FDA success criteria			MCID success criteria		
Timepoint	ACDF (%)	ProDisc-C (%)	p Value*	ACDF (%)	ProDisc-C (%)	p Value*
Neurologic exam	88.0	90.9	0.638			
NDI	78.3	79.8	0.467	85.9	84.8	0.500
Adverse events	93.4	97.1	0.330			
Device success	91.5	98.1	0.033	91.5	98.1	0.033
Surgery again (yes or maybe)				96.6	95.9	0.550
Absence of pseudoarthrosis/absence of bridging bone				91.1	97	0.067
VAS arm or neck pain				87.8	87.8	1.000
No strong narcotics and/or Muscle relaxants				81.5	89.9	0.073
Total	68.3	72.3	0.0105†	60.4	72.7	0.047

FDA, Food and Drug Administration; MCID, minimum clinically important difference; NDI, neck disability index; ACDF, anterior cervical discectomy and fusion; ACDF, anterior cervical discectomy and fusion; VIS, visual analog scale.

* Fisher one-sided exact test.

† Blackwelder's test for noninferiority.

In conclusion, ProDisc-C TDR is a viable surgical option for patients with SCDD and has been shown to have significant benefits to ACDF.

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