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Clinical Study

Factors affecting reoperations after anterior cervical discectomy and fusion within and outside of a Federal Drug Administration investigational device exemption cervical disc replacement trial

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Abstract

BACKGROUND CONTEXT: The excellent clinical re.sults of five US Federal Drug Administration (FDA) trials approved for cervical total disc replacement (TDR) (Prestige [Medtronic Sofamor Danek, Memphis, TN, USA], Bryan [Medtronic Sofamor Danek], ProDisc-C [Synthes, West Chester, PA, USA], Kineflex|C [SpinalMotion, Mountain View, CA, USA], and Mobi-C [LDR Spine, Austin, TX, USA]) have recently been published. In these prospective randomized studies, superiority or equivalency of TDR was claimed, citing an 8.7% (23/265), 9.5% (21/221), 8.5% (9/106), 12.2% (14/115), and 6.2% (5/81) (mean=9.02%) rate of additional related cervical surgical procedures within 2 years in control anterior cervical discectomy and fusion (ACDF) patients, respectively, compared with 1.8% (5/276), 5.8% (14/242), 1.9% (2/103), 11% (15/136), and 1.2% (2/164) (mean=4.34%) in patients receiving the cervical TDR. The rate of reoperation within 2 years after ACDF seems unusually high.

PURPOSE: To assess the rate of and specific indications for early reoperation after ACDF in a cohort of patients receiving the ACDF as part of their customary care. These results are contrasted with similar patients receiving ACDF as the control arm of five FDA investigational device exemption (IDE) studies.

STUDY DESIGN: Multisurgeon retrospective clinical series from a single institution.

PATIENT SAMPLE: One hundred seventy-six patients with spondylotic radiculopathy or myelopathy underwent ACDF by three surgeons between 2001 and 2005 as part of their clinical practices. All patients had at least 2 years of follow-up with final follow-up within 6 months of completion of this study.

OUTCOME MEASURES: Cervical reoperation rates at 2-year follow-up and at 3.5-year follow-up.

METHODS: Review of medical records and telephone conversations were completed to determine the number of patients who had undergone a revision cervical procedure.

RESULTS: At final follow-up, complete data were available for 159 ACDF patients. Of the 48 patients who underwent single-level ACDF and met criteria for inclusion in the IDE studies, one patient (2.1%) required additional surgery (adjacent-segment degeneration) within 2 years, the

FDA device/drug status: Approved (Bryan Cervical Disk; Prestige Cervical Disk Replacement; ProDisc-C); Investigational (Kineflex|C; Mobi-C).

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duration of follow-up of the five published IDE studies. Of the 159 patients who received single or multilevel ACDF at a mean follow-up of 3.5 years, 12 patients (7.6%) had undergone revision cervical surgery, with three patients (1.9%) undergoing same-level revisions (posterior fusion) and nine patients (5.7%) undergoing adjacent anterior level fusions. Patients who underwent revision same-level surgery typically had the intervention within the first year (mean, 11 months), whereas those requiring adjacent-level fusions typically had surgery later (mean, 29 months).

CONCLUSIONS: The present study identifies a 2.1% rate of repeat surgery within 2 years of a single-level ACDF performed during routine clinical practice, which is lower than that reported in the control arm of the Prestige, ProDisc-C, Bryan, Kineflex|C, and Mobi-C FDA trials (mean=9%). Even with longer follow-up including multilevel cases, our reoperation rate (7.6%) compared favorably with the IDE rates. This discrepancy may reflect different thresholds for reoperation in the control arm of a device IDE study compared with routine clinical practice. Additionally, patients enrolled in the single-level-only IDE trial may have received multilevel procedures outside of the study. This factor could result in a higher rate of subsequent surgeries at adjacent levels not addressed at the index procedure. These data suggest that we need to better understand factors driving treatment and, in particular, decisions to reoperate both in and outside of a device trial.

Keywords: ACDF; Reoperation; Cervical disc replacement; IDE; FDA

Introduction

Since its introduction by Robinson and Smith in 1955, anterior cervical discectomy and fusion (ACDF) has become a widely accepted surgical treatment for symptomatic cervical spondylosis [1–9]. Anterior cervical discectomy and fusion has been successfully demonstrated in numerous clinical series for the treatment of cervical radiculopathy or myelopathy [9–11]. Despite its widespread acceptance, the procedure has known complications including graft pseudarthrosis, instrumentation complications, and adjacent-level degeneration [11–15]. Radiographic pseudarthrosis rates after anterior cervical arthrodesis procedures range from 0% to 26% [16–21], although pseudarthrosis is not always symptomatic [22,23].

Anterior cervical fusion has been shown to cause significant alteration in adjacent-level kinematic including increased shear strains, higher intradiscal pressures, and increased adjacent-segment motion [24]. An increasing body of biomechanical and clinical evidence suggests that these altered mechanics may predispose to adjacent-level degeneration after fusion [11,25]. Recent biomechanical studies have suggested that in contrast to fusion, cervical disc replacement does not alter adjacent-segment motion and preserves adjacent-level intradiscal pressures [9,25]. In fact, the development of cervical disc replacement has been largely driven by the potential for these devices to mitigate the risks of adjacent-level degeneration as well as eliminate arthrodesis-related morbidities and complications [26–28].

Cervical total disc replacement (TDR) has been studied for the treatment of symptomatic spondylosis. Proponents suggest that the maintained motion at the operated level will reduce the incidence of adjacent-level degeneration and improve clinical outcomes compared with ACDF. Uncontrolled, case series performed outside of the United States have reported clinical success and safety with various designs of cervical TDR. To gain regulatory approval in the United States, the various cervical TDR devices are required to undergo prospective randomized trials that have typically used ACDF as a control. The clinical results of five US Federal Drug Administration (FDA) trials approved for cervical TDR (Prestige [Medtronic Sofamor Danek, Memphis, TN, USA], ProDisc-C [Synthes, West Chester, PA, USA], Bryan, [Medtronic Sofamor Danek], Kineflex|C [SpinalMotion], and Mobi-C [LDR Spine]) have been published [2,4–8]. In these prospective, randomized single-level studies, superiority or equivalency of TDR was observed with an 8.7% (23/265), 9.5% (21/221), 8.5% (9/106), 12.2% (14/115), and 6.2% (5/81) (mean=9.02%) rate of additional related cervical surgical procedures, respectively, within 2 years of the ACDF control versus 1.8% (5/276), 5.8% (14/242), 1.9% (2/103), 11% (15/136), and 1.2% (2/164) (mean=4.34%) in patients receiving the cervical TDR. The rate of reoperation within 2 years after one-level ACDF (8.7%, 9.5%, 8.5%, 12.2%, and 6.2%) seems high.

We hypothesize that the patient participation in these FDA investigational device exemption (IDE) clinical trials was a factor in the seemingly higher reoperation rate after ACDF. As such, the purpose of this study was to assess the rate of reoperation after ACDF in a cohort of patients treated as part of their customary care and not enrolled in an IDE study. We further aimed to understand the unique factors that affect the decision making of both the surgeon and the patient within an FDA IDE study.

Materials and methods

Inclusion criteria

Records of all patients who underwent ACDF at a single institution between 2002 and 2004 were reviewed. All

EVIDENCE & METHODS

Context
Randomized control trials (RCTs) comparing new techniques with controls are considered the gold standard for the assessment of efficacy and safety. It is often assumed that the control group within the RCT will be treated in a manner similar to usual practice, which would better justify surgeons applying the data to their own practices.

Contribution
By extracting data from published RCTs comparing fusion to cervical disc arthroplasty, the authors calculated reoperation rates for the control (fusion) patients. They compared these data with reoperation rates seen in their own practices. They found that control group reoperation rates were higher.

Implication
In order for results of RCTs to be validly applied, it is important that control groups represent, as closely as possible, contemporary gold-standard care. Atypical control groups, such as the use of stand-alone anterior cage fusions in lumbar disc replacement trials or the use of minimal amounts of iliac crest bone graft in graft replacement trials that do not represent the usual practice of spinal surgeons at-large can result in the acceptance of conclusions without ''real world'' applicability (effectiveness or external validity). While lower reoperation rates for cervical arthroplasty have been a purported advantage based on RCT data, the current authors have shown that control (fusion) group reoperations may be artificially higher than those found in usual practice. Thus, this advantage may be unfounded. RCTs that are not double-blinded—a necessary compromise in most studies—may, therefore, introduce bias via the control group due to well-recognized surgeon and patient factors.

—The Editors

patients were adults (older than 18 years) with symptomatic degenerative disc disease between C3 and C7 and intractable radiculopathy, myelopathy, or both. All patients reported a minimum 6-week history of neck and arm pain that was recalcitrant to nonoperative treatments such as physical therapy, a reduction in activities, anti-inflammatory medications, and injections. Surgery was performed in fewer than 6 weeks in patients experiencing progressive neurologic worsening despite nonoperative treatment. Similar inclusion and exclusion criteria reported by Mummaneni et al. [1], Murrey et al. [8], Anderson et al. [4], and others were used in single-level patients. Exclusion criteria included symptomatic C2–C3 or C7–T1 disc disease, previous surgery at the involved level, and a history of discitis or metastases.

Demographics

One hundred seventy-six patients with radiculopathy or myelopathy who had been treated with ACDF by three surgeons between 2001 and 2005 and who met inclusion criteria were studied. (Table 1) Forty-eight of these patients had undergone single-level ACDF and met the IDE studies inclusion/exclusion criteria. The remaining patients presented with spondylosis with radiculopathy or myelopathy, with clinical features consistent with those seen in the Prestige study, however, requiring multilevel ACDF. All patients had at least 2 years of follow-up, with final follow-up within 6 months of completion of this study. Review of medical records was completed to determine the number of patients who had undergone a revision cervical procedure at the same or adjacent level. Those patients who did not have follow-up within 6 months of completion of the study were contacted by phone to determine if any interval symptoms had developed and if any other surgical procedures had been performed.

Surgical technique and postoperative protocol

After a Smith-Robinson anterior cervical approach, the anterior longitudinal ligament was identified, and the level of the disc space was confirmed using a radiographic marker. The longus colli muscles were elevated subperiosteally off the lateral margins of the disc space. Dissection was not extended past the midportion of the vertebral bodies adjacent to the disc space. Care was taken not to injure or disturb the annular attachments of the adjacent disc spaces. An incision was made in the anterior longitudinal ligament and the anterior anulus fibrosus of the symptomatic level. The cartilaginous end plates were excised using curettes, and the lateral margins of the disc space were exposed. The posterior anulus fibrosus and the posterior longitudinal ligament were removed in select situations in which the disc fragment was noted preoperatively to be posterior to the posterior longitudinal ligament. The vertebral end plates were decorticated until bleeding cancellous bone was identified. An interbody graft was placed, and an anterior locking cervical plate was used. Postoperatively, all patients were encouraged to ambulate immediately after surgery, and physical activities were advanced at the discretion of the attending surgeon. The choice of an external orthosis was left to the attending surgeon.

Statistical analysis

All data sets were collected and entered into a coded spreadsheet. Statistical analysis was conducted with SPSS v11.5 software (SPSS, Inc., Chicago, IL, USA). Descriptive and frequency statistics were evaluated. Tests for parametricity between various data sets were conducted, and appropriate statistical independent and dependent tests were performed. Comparison of categorical variables between

Table 1
Patient demographics versus control studies

Demographics	Mummaneni et al. control [1]	Murrey et al. control [8]	Anderson et al. control [4]	Coric et al. control [6]	Hisey et al. control [7]	Present study
Variable	ACDF	ACDF	ACDF	ACDF	ACDF	ACDF
No. of patients	223	106	221	133	81	159
Average age (range)	43.9 (22–73)	43.5	n.s.	43.9 (23–62)	n.s.	47.4 (28–71)
Men, N (%)	122 (46)	49 (46.2)	n.s.	59 (44.4)	n.s.	76 (48)
Women, N (%)	143 (54)	57 (53.8)	n.s.	74 (55.6)	n.s.	83 (52)
Tobacco, N (%)	92 (34.7)	37 (34.9)	n.s.	62 (47)	n.s.	67 (42)
% Lost to follow-up (no. of patients), % (n)	25 (67)	5.2 (6)	0.5 (1)	13.5 (18)	7.4 (6)	10.7 (17)
Average follow-up (range), y	2	2	2	2	2	3.5 (2.0–6.9)

ACDF, anterior cervical discectomy and fusion; n.s., not stated.

the treatment subgroups was analyzed with χ^2 testing. Differences between groups were deemed to be statistically significant when $p \leq .05$.

Results

Demographics

Of the 176 patients who met study eligibility criteria, 159 (89.7%) were available for final follow-up (mean, 3.5 years; range, 2.0–6.9 years). Patient demographics were similar between the single-level patients in the present study and those reported by Mummaneni et al. [2] and Murrey et al. [8] (Table 1).

Surgical outcomes

Of the 48 patients who underwent single-level ACDF at the authors' institution and met criteria for inclusion in the IDE TDR studies, only one patient (2.1%) required additional surgery (for adjacent-segment degeneration) within 2 years of ACDF. At final follow-up (mean, 3.5 years; range, 2.0–6.9 years), a 4.2% (n=2) rate of adjacent-level surgery was noted after single-level ACDF. (Table 2)

Of the 159 patients who were treated with single-level and multiple-level ACDF, at 2 years of follow-up (the FDA IDE studies cutoff point), 1.3% (n=2) of patients had required revision surgery for symptomatic nonunions, and 3.1% (n=5) had surgery for adjacent-level degeneration. At final follow-up at a mean of 3.5 years, 12 patients (7.6%) had undergone revision cervical surgery, with three patients (1.9%) undergoing same-level posterior fusion for pseudarthrosis and nine patients (5.7%) undergoing adjacent-level anterior decompression and fusions. A higher percentage of reoperations (25%) was observed after three-level ACDF. Patients who underwent revision same-level surgery typically had the intervention within the first year (n=3; average, 11 months; range, 5 months–2 years), whereas those requiring adjacent-level fusions typically had surgery later (n=9; average, 2.4 years; range, 10 months–5.4 years) (Table 3).

Discussion

Proponents of cervical disc replacement have claimed that maintained motion at the operated level will reduce the incidence of adjacent-level degeneration and improve clinical outcomes compared with ACDF [5,6,10,24,29,30]. This claim was supported by FDA IDE studies of TDR compared with ACDF (Table 4). Review of a similar cohort of patients treated with ACDF at the authors' institution outside of any study suggests a lower risk of reoperation (2.1%) than that seen in the IDE studies. Even with multiple-level ACDFs in patients with more extensive pathology and with longer follow-up, our reoperation rate was lower than that reported in the three IDE trials. These discrepancies may reflect different thresholds for reoperation in the control arm of a device IDE study compared with routine clinical practice.

There are various factors that might explain the discrepancy in reoperation rates of patients undergoing ACDF within an FDA IDE trial and those treated as part of customary clinical practice. In the published FDA IDE trial, ACDF could only be performed at a single level. In reality, many patients with symptomatic cervical radiculopathy or myelopathy have multilevel degenerative changes, and the surgeon relies on available clinical information and his or her own judgment to decide which levels are responsible for symptoms and therefore are required to be addressed at surgery. This decision-making process is often quite

Table 2
Rates of reoperation per surgical level

	2-Year end point		Final follow-up (mean, 3.5 years)	
Surgical levels (no. of patients)	Adjacent level	Same level	Adjacent level	Same level
Level 1 (n=48), % (n)	2.1 (1)	0.0 (0)	4.2 (2)	0.0 (2)
Level 2 (n=95), % (n)	2.1 (2)	1.1 (1)	4.2 (4)	2.1 (2)
Level 3 (n=16), % (n)	12.5 (2)	6.3 (1)	18.8 (3)	6.3 (1)

Table 3
Overall rates of reoperation in patients

Surgical levels (no. of patients)	2-Year end point		Final follow-up (mean, 3.5 years)	
	Adjacent level	Same level	Adjacent level	Same level
Total % (N=159), % (n)	3.10 (5)	1.3 (2)	5.7 (9)	1.9 (3)

subjective and influenced by the age, training, and specialty of the surgeon [31,32]. The higher rate of adjacent-level operations within 2 years of ACDF in the IDE trial raises the question of whether patients with two-level disease that ordinarily may have received a two-level ACDF were channeled into a one-level procedure to allow entry into the clinical trial. This could result in a higher rate of subsequent surgeries at adjacent levels not addressed at the index procedure.

More recent arthroplasty studies and a long-term follow-up study of the previous Prestige FDA IDE trail at 5 years have shown reoperation rates with no significant differences between the investigational and control groups [5,6]. A recent Kineflex|C study and a subset of two other FDA IDE trials (Bryan and Discover) demonstrated no significant differences in adjacent-level reoperation rates between ACDF and arthroplasty groups at 2-year follow-up (Table 4) [5,6]. Also, the Prestige FDA IDE trial at 5-year follow-up showed no significant difference in adjacent-level reoperation rates between the ACDF group versus the arthroplasty investigational group (4.9% vs. 2.9%, respectively; p=.376) [33]. It is reasonable to assume that by 5 years from the procedure, any study-related biases (surgeon or patient) would be washed out and a truer representation of subsequent reoperations would be evident. The similar 5-year reoperation rate reported for ACDF and TDR in a cohort that had lower reoperation rates after TDR at 2 years would support the notion of the variations in decision making within the 2-year follow-up window of a clinical trial.

The criteria for reoperation after ACDF for a diagnosis of symptomatic adjacent-level disease or pseudarthrosis are even less clearly defined. The decision to proceed with additional surgery is based on the patient's subjective complaints of pain and disability rather than objective radiographic or functional criteria. Acknowledging failure of the index procedure and then electing to proceed to a second surgery are the end results of a complex interaction between the surgeon and patient. The patient's expectation of outcomes of both the index procedure and any subsequent intervention is largely set by the treating surgeon, and typically the patient's decision making is strongly influenced by the opinions of the surgeon. It seems plausible that the surgeon investigator might have a lower threshold for recommending repeat surgery in a symptomatic patient after the control procedure (ACDF) than after the novel experimental procedure (TDR). This might be particularly

Table 4
Summary of 2-year end point data in Federal Drug Administration investigational device exemption trials

Study author	Source of data	Treated levels	Prosthesis used	Total patients in arthroplasty group	Total patients in ACDF group	Overall % (secondary surgical procedures/ Total patients in arthroplasty group)	Overall % (secondary surgical procedures/ total patients in ACDF group)	p Value	Patients at 2-year follow-up (arthroplasty), n	Patients at 2-year follow-up (ACDF), n	Overall % (secondary surgical procedures in arthroplasty/Total patients at 2-year follow-up)	Overall % (secondary surgical procedures in ACDF/Total patients at 2-year follow-up)	p Value
Mummaneni et al. [1]	Article	Single	Prestige	276	265	**1.8 (5/276)**	**8.7 (23/265)**	.0003*	223	198	**2.2 (5/223)**	**11.6 (23/198)**	.0001*
Anderson et al. [4]	Article	Single	Bryan	242	221	**5.8 (14/242)**	**9.5 (21/221)**	.131	242	221	**5.8 (14/242)**	**9.5 (21/221)**	.131
Murrey et al. [8]	Article	Single	ProDisc-C	103	106	**1.9 (2/103)**	**8.5 (9/106)**	.033*	101	100	**2.0 (2/101)**	**9.0 (9/100)**	.029*
Coric et al. [6]	Article	Single	Kineflex|C	136	133	**11 (15/136)**	**12.2 (14/115)**	.777	119	115	**12.6 (15/119)**	**12.2 (14/115)**	.9203
Hisey et al. [7]	Article	Single	Mobi-C	164	81	**1.2 (2/164)**	**6.2 (5/81)**	.075	155	75	**1.3 (2/155)**	**6.7 (5/75)**	.0694

ACDF, anterior cervical discectomy and fusion; SSP, secondary surgical procedures.
Total mean overall SSP for arthroplasty and ACDF is 4.34% and 9.02%, respectively.
Mean overall SSP after 2-year follow-up for arthroplasty and ACDF is 4.78% and 9.80%, respectively.
*Statistical significance at a level of p<.05.

apropos when recommending a second surgical procedure for presumed symptomatic adjacent-level degeneration, which is the very condition TDR is designed to prevent while at the same time is believed to be a recognized complication of ACDF.

Another factor that might affect the decision to reoperate within a clinical trial is the bias that occurs when a patient is allocated to the control arm of the study. In many instances, patients enrolled in the cervical TDR trial specifically sought out a participating study center so that they might receive a TDR. When designated to the control arm of the study, the patient may naturally be quite disappointed. This likely will affect the patient's perception of any subsequent symptoms and well-being. If a patient received the control procedure (fusion) that they were trying to avoid by enrollment in a TDR trial, they may be more likely to attribute any symptoms to failure of the index procedure and therefore more readily consider revision strategies. On the other hand, a patient who received the TDR is likely to be quite emotionally vested in the success of the device.

The negative effect of being allocated to the control arm of a study is illustrated by other spine studies. For example, patients successfully fused with anteriorly placed threaded lumbar cages fared worse when this treatment was the control arm of a lumbar TDR study [34,35] than when this same treatment was the investigational procedure in the IDE trial of the use of Infuse (Medtronic Sofamor Danek) for spinal fusion [36].

A potential criticism of the study is that our data collection was collected in a retrospective fashion, whereas the other FDA studies used for comparison are high-quality prospective, randomized studies. We contend that the retrospective nature of our study is a strength, given the goals of the study. The retrospective nature allowed us to determine the reoperation rate in a cohort of patients over time based on clinical decisions made as part of customary care. An additional strength of our study was the 100% 2-year follow-up rate of all 159 patients. This allows us to report an accurate reoperation rate for the ACDF study cohort. This 2-year follow-up is comparable or slightly better when compared with the five FDA IDE ACDF control groups (74.7%, 100%, 94.3%, 86.5%, and 92.6%).

Anterior cervical discectomy and fusion has been reported to be a highly successful procedure with excellent clinical results and a relatively low rate of complications [9–11]. Long-term follow-up studies have analyzed the rate of adjacent-level degeneration and reoperation after ACDF and debated whether this reflects the natural history of the degenerative cascade or is the result of altered spinal mechanics imposed by the fusion [11,37]. Few studies have focused on the reoperations required within a short time of the index ACDF [38,39]. The present study reports that 7.6% of patients undergoing single-level or multiple-level ACDF required an additional cervical procedure at a mean of 3.5 years, with a majority requiring adjacent-level procedures. Reoperations likely relate to a combination of imprecision in our diagnostic techniques and shortcoming of the fusion procedure. The time course of additional surgeries after ACDF in our practice may be interpreted to suggest that the patient and surgeon may elect to wait a longer period before proceeding to address symptoms surgically than when patients are enrolled in an IDE clinical trial.

Although there are apparent deficiencies in the total disc arthroplasty literature, it is not our intent to lay blame solely on the arthroplasty literature. There are several factors that affect the dynamics of a clinical trial and the outcome. Randomized clinical trials pose the least potential for bias but cannot totally eliminate it. Whether intentional or unintentional, bias introduced into a study can significantly skew results [40]. There may be more difficulties with biases within surgical trials than with medical trials [41]. In surgical trials, the surgeon serves as the investigator and is active in the determination of the outcome and additional treatment [42]. This can set the stage for detection bias. This problem can occur if surgeons assess their own outcomes and recommend additional treatments based on this evaluation. Although it is impossible to blind the surgeon, it would be ideal for the assessor and patient to be blinded. The latter may be impossible because of informed consent of the procedure.

In conclusion, we report that the rate of reoperation within 2 years after ACDF is lower during patients' customary care than that reported when patients are enrolled in an FDA IDE clinical trial. The discrepancy between reoperation rates inside and outside of an IDE trial may reflect different thresholds for reoperation in the control arm of a trial compared with routine clinical practice. Additionally, patients enrolled in the single-level-only FDA trials may have received multilevel procedures outside of the study. As an increasing number of novel spinal technologies are undergoing FDA trials, it is important to understand variables beyond just the surgical technique or device implanted that might impact the results.

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