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RANDOMIZED TRIAL

Comparison of Clinical Outcomes of 1- and 2-Level Total Disc Replacement

Four-Year Results From a Prospective, Randomized, Controlled, Multicenter IDE Clinical Trial

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Study Design. A prospective, randomized, multicenter Food and Drug Administration Investigation Device Exemption study using total disc replacement as surgical treatment of degenerative disc disease at 1 or 2 contiguous levels of the cervical spine.

Objective. To evaluate the safety and effectiveness of total disc replacement at single or 2 contiguous levels through 48 months of follow-up.

Summary of Background Data. Cervical total disc replacement has been shown to be a safe and effective alternative to anterior cervical discectomy and fusion at 24 months. Its motion-preserving capabilities may avoid accelerating adjacent segment pathology and thereby lower the rate of associated complications.

Methods. Patients were randomized in a 2:1 ratio (total disc replacement [TDR]: anterior cervical discectomy and fusion [ACDF]) at 24 sites. Ultimately, 164 patients received TDR at 1 level and 225 patients received TDR at 2 contiguous levels. An additional 24 patients (15 one-level, 9 two-level) were treated with TDR as training cases.

Outcome measures included neck disability index, visual analogue scale neck and arm pain, Short Form 12-item Health Survey (SF-12) Mental Composite Score (MCS) and Physical Composite Score (PCS), range of motion, major complication rates, and secondary surgery rates. Patients received follow-up examinations at regular intervals through 4 years after surgery.

Results. Preoperative characteristics were statistically similar for the 1- and 2-level patient groups. Four-year follow-up rates were 83.1% (1-level) and 89.0% (2-level). There was no statistically significant difference between 1- and 2-level TDR groups for all clinical outcome measures. Both TDR groups experienced significant improvement at each follow-up when compared with preoperative scores. One case of migration was reported in the 2-level TDR group.

Conclusion. A 4-year *post hoc* comparison of 1- and 2-level TDR patients concurrently enrolled in a 24-center, Food and Drug Administration Investigation Device Exemption clinical trial indicated no statistical differences between groups in clinical outcomes, overall complication rates, and subsequent surgery rates.

Key words: anterior cervical discectomy and fusion, Mobi-C Cervical Artificial Disc, artificial disc, degenerative disc disease, multilevel, total disc replacement.

Level of Evidence: 1

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Surgical treatment of symptomatic cervical radiculopathy is commonly achieved with anterior cervical discectomy and fusion (ACDF). ACDF has been a standard treatment of symptomatic degenerative disc disease (DDD) since the mid-1900s.[1–5] Results of ACDF procedures are effective in eliminating or reducing DDD symptoms, and the procedure has low complication rates.[1,4] ACDF also eliminates segmental motion and has been shown to induce higher intradiscal pressure and increased segmental motion at segments adjacent to treated levels.[6–9] Over time, these effects are hypothesized to be a primary reason for the elevated rates of radiographical adjacent segment pathology (RASP) and related symptoms reported in ACDF-treated patients.[10] However, until recently, ACDF was the only available option to surgically treat patients with 2-level DDD.

Total disc replacement (TDR) is thought to avoid accelerating RASP by preserving cervical mobility.[11] One-level TDR has been shown to be a safe and effective treatment of symptomatic DDD across a number of TDR devices.[12–16] Evidence is minimal for multilevel TDR, especially in large, controlled clinical trials, and few studies have compared the results of single-level and multilevel TDR to determine whether a reduction in efficacy occurs when more than 1 segment is treated with TDR.[17]

TDR is now a Food and Drug Administration (FDA)-approved alternative to ACDF, and 2-year postoperative results have shown TDR to be at least as safe and effective as ACDF at 2 levels, with statistically better outcomes for both pain and function than ACDF.[18] The clinical trial conducted by Davis *et al*[18] investigated both 1 and 2 levels simultaneously under the same FDA study protocol. As such, this investigation allows for direct comparison between 1- and 2-level outcomes for TDR patients.

Here, we present 4-year data from the 1-level and 2-level arms of this clinical trial to more fully characterize the safety and effectiveness of TDR. We aim to determine whether safety and efficacy are maintained when the number of treated levels is increased from 1 to 2 levels in patients receiving TDR.

MATERIALS AND METHODS

Patients underwent surgery between April 2006 and March 2008 at 24 clinical sites across the United States as part of the FDA Investigation Device Exemption (IDE) randomized, controlled 2-arm clinical trial. Enrollment criteria included a diagnosis of DDD with radiculopathy or myeloradiculopathy at 1 or 2 contiguous levels from C3 to C7. Enrolled patients were unresponsive to nonoperative treatment for at least 6 weeks or demonstrated progressive symptoms requiring immediate surgical intervention. Further inclusion and exclusion criteria are included in the study by Davis *et al*.[18]

Patients were randomized in a 2:1 ratio (TDR:ACDF). Ultimately, 164 patients received the Mobi-C Cervical Artificial Disc (LDR Medical; Troyes, France), Figure 1, at 1 level and 225 patients at 2 contiguous levels. An additional 24 patients (15 one-level, 9 two-level) were treated with the TDR as training cases. Treating surgeons were not blinded to the treatment, whereas patients were blinded to their treatment assignment until after surgery; continued blinding of the patient was not possible due to radiographs.

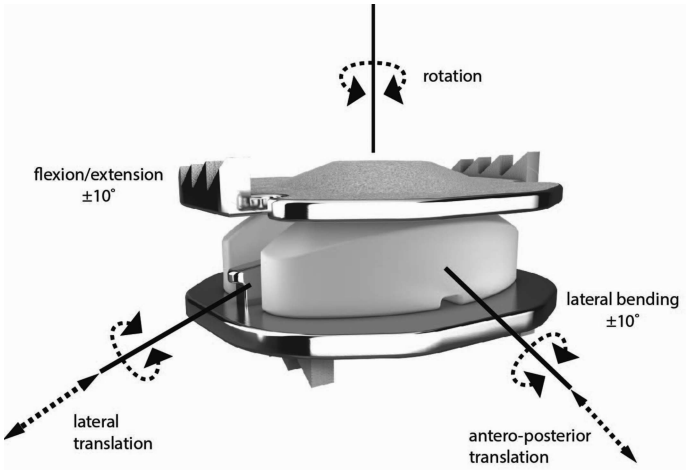

Figure 1. Mobi-C Cervical Artificial Disc with 2 CoCrMo alloy endplates and an UHMWPE mobile insert facilitating 5 independent degrees of freedom.

Postoperative care was left to the discretion of the treating surgeon. Patients were examined preoperatively and at follow-up periods of 6 weeks and 3, 6, 12, 18, 24, 36, and 48 months. TDR and ACDF groups were asked to refrain from taking nonsteroidal anti-inflammatory drugs a week before surgery until 3 months postsurgery.

Clinical Outcomes

Measured outcomes included neck disability index (NDI), visual analogue scale (VAS) for neck and arm pain, Short Form 12-item Health Survey (SF-12) Mental Composite Score (MCS) and Physical Composite Score (PCS), neurological function, and patient satisfaction. Mean change in VAS arm pain score was determined from the most symptomatic arm at preoperation carried through 48 months. Neurological function was evaluated by the treating surgeon through tests of reflex, motor, and sensory function. Patient satisfaction was assessed using a questionnaire that asked whether they were "very satisfied," "somewhat satisfied," "somewhat dissatisfied," or "very dissatisfied" with their surgical treatment. Patients were also asked whether they would "definitely," "probably," "probably not," or "definitely not" recommend their respective treatment to a friend with the same symptoms and indications.

Radiographical Outcomes

Radiographical outcomes included radiographical success, range of motion (ROM), heterotopic ossification (HO), and RASP. All radiographical determinations were made through Medical Metrics, Inc. (MMI, Houston, TX) by a team of independent radiologists. Radiographical success for the TDR group was defined as at least 2° angular motion in flexion/extension or no evidence of bridging trabecular bone across the disc space. ROM was assessed at preoperative and postoperative time points using lateral flexion/extension and anteroposterior right/left lateral bending radiographs at each treated level. RASP was determined by the Kellgren-Lawrence Scale of disc degeneration.[19,20] Any patient with an increase of at least 1 grade of degeneration at either adjacent level was considered to have RASP. HO was determined using classifications defined by Mehren *et al*[21] and McAfee *et al*.[22]

Adverse Events (AEs), Serious Adverse Events, and Subsequent Surgical Intervention

Adverse events (AEs) were any clinically adverse signs, symptoms, syndromes, or illnesses that occurred or worsened during or after the initial surgery, regardless of cause or device relatedness. All AEs were evaluated and classified by the Clinical Events Committee comprising 2 orthopedic surgeons and 1 neurosurgeon.

Subsequent surgical intervention was defined as any subsequent surgery that involved an index-level segment. Adjacent-level subsequent surgical procedures that did not involve a treated level did not automatically indicate a study failure; however, such events were recorded and included in the study analysis.

Statistical Methods

The original statistical plan for the FDA IDE study did not preplan analysis for 1 *versus* 2-level TDR; however, the resulting patient subgroups provided a unique opportunity to compare 1- *versus* 2-level patients in a *post hoc* statistical analysis. A mixed-design analysis of variance test was used to determine statistical significance for all continuous outcome measures between groups at each time point. Fisher exact tests were used to determine statistical significance of binary variables such as "overall success" or incident rates. Wilcoxon signed rank test was used to compare the change in score from preoperative to follow-up visit within treatment groups.

RESULTS

Patient Accountability and Preoperative Characteristics

The 1-level arm randomized 169 patients to the TDR group; 5 patients withdrew from the study prior to surgery, resulting in 164 patients receiving a 1-level TDR. An additional 15 nonrandomized patients received a 1-level TDR as training cases. For the 2-level arm, 232 patients were randomized to the TDR group; 7 subjects withdrew from the study prior to surgery, resulting in 225 patients receiving treatment with a 2-level TDR. An additional 9 patients underwent a 2-level TDR as training cases (Figure 2). At 48 months in the TDR group, the follow-up rates were 83.1% (128/154) for the 1-level arm and 89.0% (186/209) for the 2-level arm. There were no significant differences in patient characteristics at preoperation.

Neck Disability Index

NDI scores improved through 48 months compared with preoperative scores for both 1- (54.0) and 2-level (53.9) treated patients ($P < 0.0001$). Mean NDI scores were 16.3 at 48 months for 1-level and 17.2 for 2-level patients (Table 1 and Figure 3).

VAS Neck and Arm Pain

Both TDR groups demonstrated statistically significant improvement in VAS neck pain and VAS arm pain scores at every postoperative time point compared with preoperative values ($P < 0.0001$). No significant differences in VAS neck pain or VAS arm pain scores were observed between the 1- and 2-level TDR groups (Table 1 and Figure 4A, B).

SF-12 MCS and PCS

Each patient group showed significant improvement in SF-12 MCS and SF-12 PCS scores from preoperative values at all postoperative time points ($P < 0.0001$). At 48 months, there was no difference in amount of improvement from

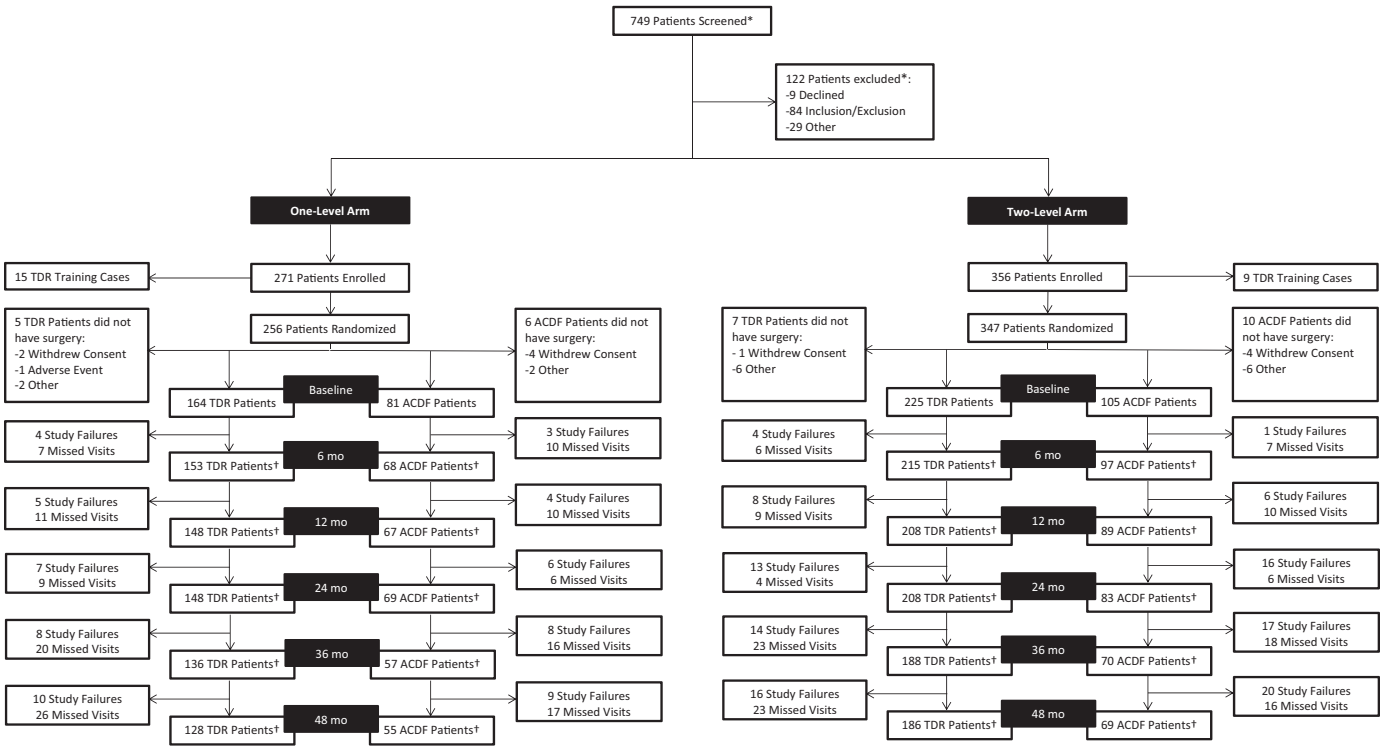

Figure 2. Flow diagram of the patient population from enrollment to 48 months postsurgery. *Patients were screened as part of the 1- or 2-level arm. †Patients with any data available at the time point. TDR indicates total disc replacement; ACDF, anterior cervical discectomy and fusion.

TABLE 1. IDE Outcomes for the 1- and 2-Level Arms at 48 Months

Outcome	One-Level TDR	Two-Level TDR
NDI (Δ)	37.5 ± 19.62	36.5 ± 21.3
VAS neck pain (Δ)	52.3 ± 32.8	52.6 ± 30.2
VAS arm pain (Δ)	56.6 ± 32.6	56.0 ± 30.7
SF-12 MCS (Δ)	9.3 ± 14.2	10.8 ± 11.8
SF-12 PCS (Δ)	15.9 ± 11.1	13.4 ± 11.5
Patient satisfaction (%)	88.6	85.0
Patient recommendation (%)	87.8	85
Secondary surgery rate (%)	3.0	4.0

Values given are mean ± SD unless otherwise indicated.

TDR indicates total disc replacement; NDI, neck disability index; VAS, visual analogue scale; SF-12, Short Form 12-item Health Survey; MCS, Mental Composite Score; PCS, Physical Composite Score.

preoperative SF12-MCS/PCS reported by 1- *versus* 2-level treated patients (Table 1 and Figure 5A, B).

Satisfaction

There was no difference in reports of satisfaction between 1- and 2-level TDR patients, with 88.6% of 1-level and 85.0% of 2-level patients reporting "very satisfied" at 48 months.

There was no significant statistical difference in the number of 1-level *versus* 2-level patients that would "definitely recommend the surgery to a friend" (1-level: 87.8%, 2-level: 85.0%).

Major Complications

There was no significant statistical difference in the number of AEs deemed a major complication by the Clinical Events Committee between the 2 groups, with 4.3% in 1-level TDR patients *versus* 4.0% in 2-level TDR patients experiencing a major complication. There was 1 case of migration in the 2-level TDR group prior to 24 months and was previously reported.[18]

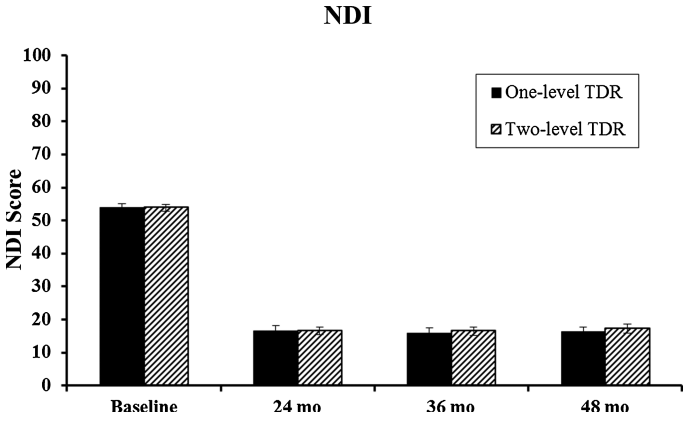

Figure 3. Mean NDI scores of 1- and 2-level cohorts at preoperation and 24, 36, and 48 months. Two-level TDR patients showed significant improvement in NDI score at all postoperative time points compared with preoperative time points. One-level and 2-level TDR groups demonstrated similar improvement. Error bars represent standard error of the mean. NDI indicates neck disability index; TDR, total disc replacement.

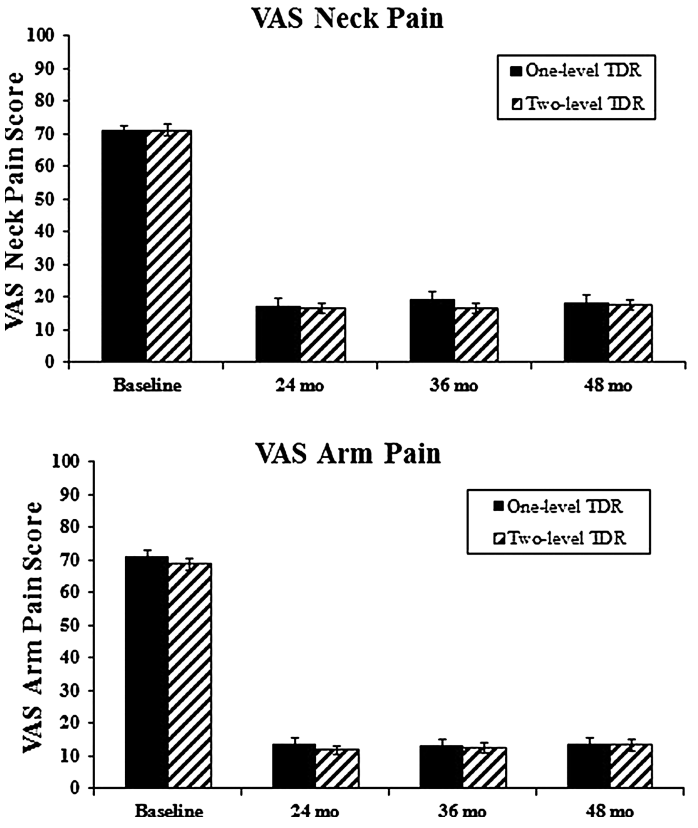

Figure 4. Mean VAS neck pain scores **(A)** and VAS arm pain scores **(B)** of 1- and 2-level cohorts at preoperative, 24, 36, and 48 months. One-level and 2-level TDR groups demonstrated similar improvement. Error bars represent standard error of the mean. VAS indicates visual analogue scale; TDR, total disc replacement.

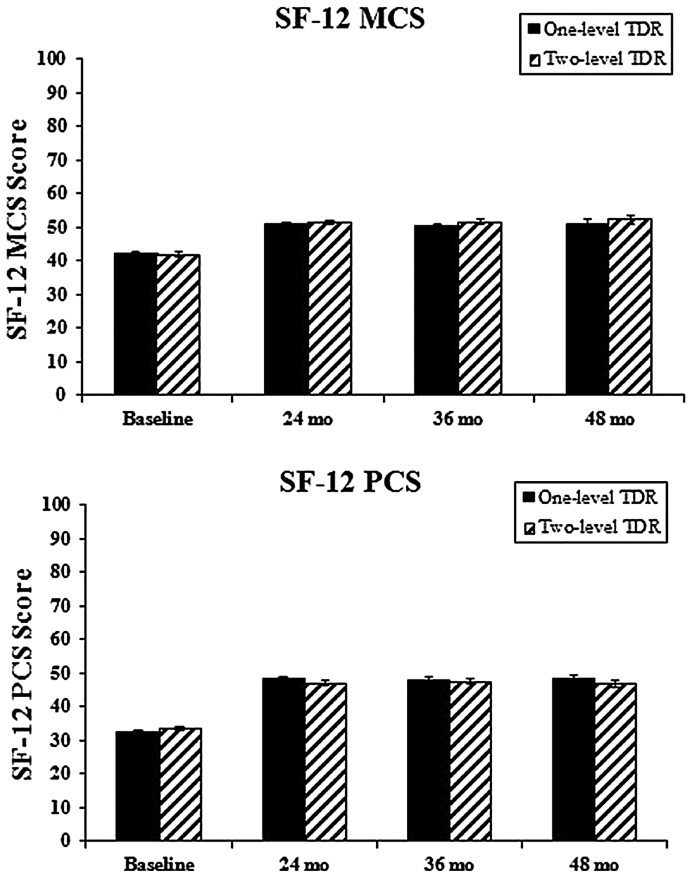

Figure 5. Mean SF-12 MCS **(A)** and SF-12 PCS **(B)** scores of 1- and 2-level patient groups at preoperative, 24, 36, and 48 months. One-level and 2-level TDR groups demonstrated similar improvement. Error bars represent standard error of the mean. SF-12 indicates Short Form 12-item Health Survey; MCS, Mental Composite Score; TDR, total disc replacement; PCS, Physical Composite Score.

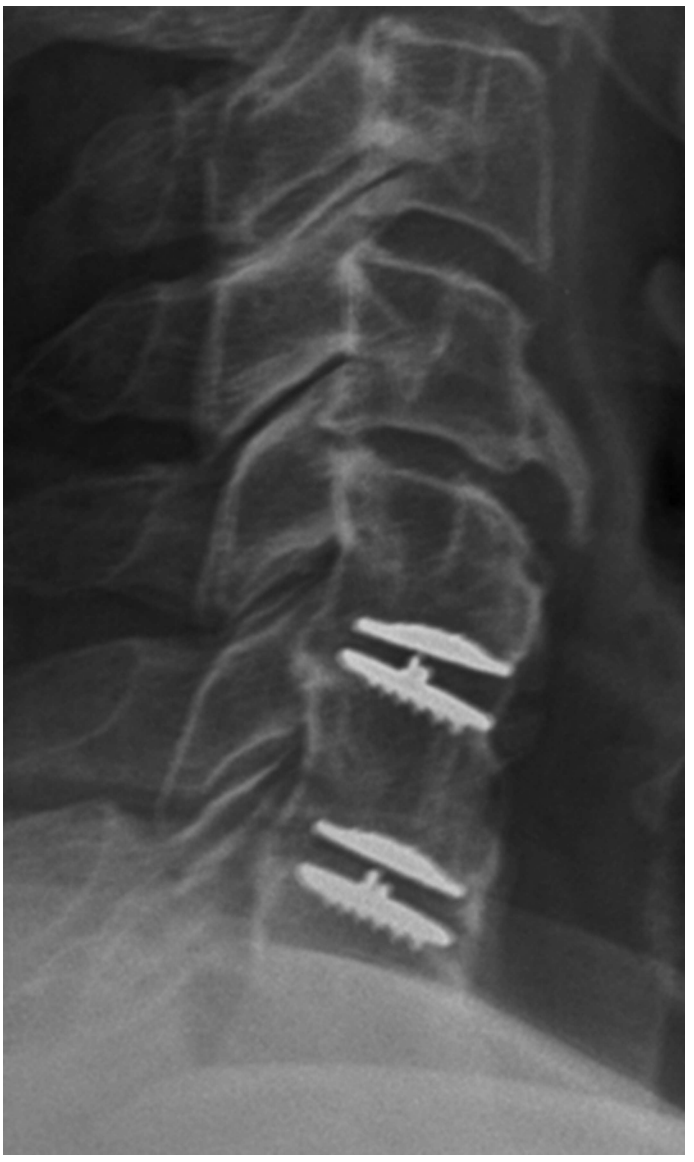

Figure 6. Neutral lateral radiograph of a 2-level TDR patient with clinically relevant heterotopic ossification on the posterior aspect of the superior disc.

Subsequent Surgical Intervention

Subsequent surgical procedures were defined as any surgical procedure at 1 or both treated levels and classified as a removal, revision, supplemental fixation, or reoperation. No significant differences were found between 1 and 2-level TDR patients, with 3.0% of 1-level patients and 4.0% of 2-level patients requiring a secondary surgery through 48 months.

Radiographical Outcomes

On average, both 1- and 2-level TDR patients maintained their preoperative ROM in flexion/extension as well as lateral bending through 48 months.

At 48 months, rates of HO were not significantly different between the 1- and 2-level TDR patients. Clinically relevant HO (grades 3 and 4) was present in 23.8% of 1-level patients and 25.7% of 2-level patients (Figure 6). Of 1-level TDR patients, 15.9% presented with grade 3 and 7.9% with grade 4. For 2-level TDR patients, the HO rates were 15.5% and 10.2% for grades 3 and 4, respectively. The clinically relevant HO rate per segment in the 2-level group was 16.6% (grade 3: 10.7%, grade 4: 5.9%). Combining groups to analyze HO per level treated indicates clinically relevant HO in 18.4% of treated segments (grade 3: 12.0%, grade 4: 6.4%)

For the 1-level arm, RASP was present in 44.3% of patients. RASP was observed in 41.5% of the 2-level population. Between the 1- and 2-level TDR groups, the rate of RASP was not statistically different.

DISCUSSION

The methodology of this IDE study allows for direct comparison of patient outcomes within (longitudinally over time) and across 1 and 2-level treatments with TDR. Although the statistical plan of this trial was not designed to test across

TDR treatment arms (1- *vs*. 2-level), subgroup comparisons allowed for a more thorough characterization of TDR. Few investigations have evaluated such a relationship.

Limited multilevel TDR data are available in the literature, and to the authors' knowledge, no controlled investigations with the size and scope of the one at hand have been conducted. In a 2-year follow-up of a prospective, multicenter study involving 175 single-level and 56 multilevel (51 two levels, 4 three levels, 1 four levels) TDR patients, Huppert *et al*[23] found no significant differences in VAS scores, NDI scores, patient satisfaction, overall complication rate, or postoperative mobility between single- or multilevel TDR patients treated with a Mobi-C Cervical Artificial Disc. Another prospective study conducted using 1- and 2-level Prestige ST (LDR Medical, Troyes, France) with up to 3-year follow-up found significant improvement in all outcome measures when compared with those recorded preoperatively. The single- and 2-level groups performed similarly.[24] Two-year outcomes are available for a prospective large consecutive case series involving both single- and multilevel discs. Among 204 operated patients, cervical TDR was inserted at one level in 119 patients, at two levels in 67 patients, at three levels in 17 patients, and at four levels in 1 patient. The results indicate that all groups experienced significant improvement within group when compared with preoperatively with no significant differences between the treatment groups.[25] In another study with 158 single-level and 53 multilevel patients, Pimenta *et al*[26] investigated single- and multilevel TDR using the PCM Cervical Disc (Nuvasive, Inc., San Diego, CA) with up to 3 years of follow-up. The investigators found statistically greater improvement in NDI scores as well as greater improvement in VAS scores in the multilevel TDR group than in the single-level group. The investigators reported similar subsequent surgery and serious adverse event rates between the 2 TDR groups.

Here, we compared results of 164 one-level and 225 two-level treated patients. Unlike the studies of a heterogeneous mix of 2-, 3-, and 4-level patients by Pimenta *et al*[26] and Huppert *et al*,[23] only 2-level patients were compared with 1-level patients. Like Huppert *et al*, and unlike the study by Pimenta *et al*, which found superiority for multilevel TDR, we found no significant statistical differences between single- and multilevel TDR outcomes with regard to improvement in NDI scores, VAS scores, patient satisfaction, or postoperative ROM through 48 months. We also found no significant differences between patient SF-12 PCS or SF-12 MCS scores. Like both of the aforementioned studies, complication and secondary surgery rates were also similar between TDR groups.

Huppert *et al*[23] did find significant differences between the single- and multilevel TDR patients regarding HO rates and analgesic use, where multilevel patients had significantly higher analgesic use and a significantly lower overall HO rate (grades 1–4).[23] Nonsteroidal anti-inflammatory drugs are known to influence HO rates, but the protocol in our study restricted nonsteroidal anti-inflammatory drug use for the single and multilevel patients. No significant differences were found in clinically relevant HO rates between the single (grade 3:15.9%, grade 4:7.9%) and 2 levels (grade 3:10.7%, grade 4:5.9%) when analyzing HO by segments treated. Patients with grade 4 HO on average maintained good clinical outcomes, including NDI, VAS, and satisfaction scores. The rates of HO are similar to rates published in the literature. A European study investigating HO rates in Prodisc-C (Synthes Spine Company, L.P., West Chester, PA) patients reported that grade 3 HO was present in 45% and grade 4 in 18% of treated levels at 4 years.[27] Another study of 21 patients treated with a BRYAN Cervical Disc (Medtronic Sofamor Danek, Memphis, TN) reported similar results, with 42.9% of patients and 33.3% of segments presenting clinically relevant HO at 8 years.[28] Prodisc-C reported 5-year grade IV HO in 6 of 103 patients; however, grade III was not reported in this article.[16] Comparisons between devices are difficult to assess given the limited amount of data on HO rates for TDR at 4 or more years. HO is still a concern for the TDR procedure, and further long-term investigations are needed to clarify HO incidence rates and the effects of HO on clinical outcomes.

Although multilevel ACDF has been presented as a safe and effective procedure, the current question on whether or not multilevel ACDF is equivalent in efficacy to single-level ACDF has yet to be answered. Studies suggest that multilevel ACDF produces more biomechanical stress and strain on adjacent segments than 1-level ACDF. A computational study conducted by Lopez-Espina *et al*[29] investigated adjacent-level stresses using finite element models of 1- and 2-level fusion. Results showed up to a 96% increase in stresses at adjacent annuli, nuclei, and endplates after fusion, with larger stresses in 2-level fusion than in 1-level fusion. Matsunaga *et al*[30] performed a study with 96 single- and multilevel ACDF patients using dynamic radiography and magnetic resonance imaging to test for shear strain at adjacent levels before and after surgery. The investigators reported no statistical differences in shear strain after ACDF for patients treated at 1 level. However, they did report increases in shear strain from 15% to 23% at adjacent levels for patients treated at 2 and 3 levels at 1 year postsurgery.[30]

RASP is another concern when undergoing surgery for DDD. ACDF has been associated with increased risk of RASP, yet the underlying mechanisms are ill-defined. We report RASP rates of 44.3% and 41.5% for patients treated with TDR at 1 and 2 levels, respectively, at 48 months postsurgery. Given the present data, TDR does not prevent RASP, although the rates are significantly less when compared with ACDF.[18,31–33] It is likely that TDR provides greater biomechanical stability after discectomy that, unlike ACDF, does not create hypermobility at the adjacent level. Furthermore, the results presented assess only radiographical RASP; they do not assess the clinical relevance of degeneration as it relates to pain and function. Like HO, the relationship between RASP and TDR remains vague. Longer-term studies may be needed to answer the question whether TDR, in comparison with ACDF, reduces clinical adjacent segment pathology.[34]

➢ Key Points

- ❑ One- and 2-level TDR patients experience significant improvement in outcomes from the preoperative time point within groups.
- ❑ Patients receiving 1- or 2-level TDR experience similar outcomes and complication rates, with no statistical differences found between groups.
- ❑ Both 1- and 2-level TDRs in this study indicate less and slower progression of radiographical pathology at the adjacent level than traditional fusion procedures.

CONCLUSION

This was a *post hoc* comparison of 1- and 2-level TDR-treated patients concurrently enrolled in a multicenter FDA IDE clinical trial followed through 4 years. There were no statistical differences between 1- and 2-level TDR for all measured outcomes, including NDI, VAS, SF-12 MCS/PCS scores, and patient satisfaction. No differences were found between 1-level and 2-level TDR with regard to overall complication and subsequent surgery rates. This FDA IDE, level 1 evidence clinical trial has shown that 2-level TDR is as safe and effective as 1-level TDR in indicated patients.

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