Title

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Authors

Hisey, Michael S
Zigler, Jack E
Jackson, Robert
et al.

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Prospective, Randomized Comparison of One-level Mobi-C Cervical Total Disc Replacement vs. Anterior Cervical Discectomy and Fusion: Results at 5-year Follow-up

Michael S. Hisey, MD,[1] Jack E. Zigler, MD,[2] Robert Jackson, MD,[3] Pierce D. Nunley, MD,[4] Hyun W. Bae, MD,[5] Kee D. Kim, MD,[6] Donna D. Ohnmeiss, Dr.Med.[7]

[1]Texas Back Institute, Denton, Texas, [2]Texas Back Institute, Plano, Texas, [3]Saddleback Memorial Medical Center, Laguna Hills, California, [4]Spine Institute of Louisiana, Shreveport, Louisiana, [5]Cedars Sinai Spine Center, Los Angeles, California, [6]Department of Neurological Surgery, University of California, Davis, Sacramento, California, [7]Texas Back Institute Research Foundation, Plano, Texas

Abstract

Introduction

There is increasing interest in the role of cervical total disc replacement (TDR) as an alternative to anterior cervical discectomy and fusion (ACDF). Multiple prospective randomized studies with minimum 2 year follow-up have shown TDR to be at least as safe and effective as ACDF in treating symptomatic degenerative disc disease at a single level. The purpose of this study was to compare outcomes of cervical TDR using the Mobi-C® with ACDF at 5-year follow-up.

Methods

This prospective, randomized, controlled trial was conducted as a Food and Drug Administration regulated Investigational Device Exemption trial across 23 centers with 245 patients randomized (2:1) to receive TDR with Mobi-C® Cervical Disc Prosthesis or ACDF with anterior plate and allograft. Outcome assessments included a composite overall success score, Neck Disability Index (NDI), visual analog scales (VAS) assessing neck and arm pain, Short Form-12 (SF-12) health survey, patient satisfaction, major complications, subsequent surgery, segmental range of motion, and adjacent segment degeneration.

Results

The 60-month follow-up rate was 85.5% for the TDR group and 78.9% for the ACDF group. The composite overall success was 61.9% with TDR vs. 52.2% with ACDF, demonstrating statistical non-inferiority. Improvements in NDI, VAS neck and arm pain, and SF-12 scores were similar between groups and were maintained from earlier follow-up through 60 months. There was no significant difference between TDR and ACDF in adverse events or major complications. Range of motion was maintained with TDR through 60 months. Device-related subsequent surgeries (TDR: 3.0%, ACDF: 11.1%, $p<0.02$) and adjacent segment degeneration at the superior level (TDR: 37.1%, ACDF: 54.7%, $p<0.03$) were significantly lower for TDR patients.

Conclusions

Five-year results demonstrate the safety and efficacy of TDR with the Mobi-C as a viable alternative to ACDF with the potential advantage of lower rates of reoperation and adjacent segment degeneration, in the treatment of one-level symptomatic cervical degenerative disc disease.

Clinical Relevance

This prospective, randomized study with 5-year follow-up adds to the existing literature indicating that cervical TDR is a viable alternative to ACDF in appropriately selected patients.

Level of Evidence

This is a Level I study.

KEYWORDS: TOTAL DISC REPLACEMENT, CERVICAL SPINE, ANTERIOR CERVICAL FUSION, DEGENERATIVE DISC DISEASE, MOBI-C® CERVICAL DISC PROSTHESIS, CERVICAL ARTHROPLASTY, ARTIFICIAL DISC, RANDOMIZED TRIAL, CLINICAL OUTCOME

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Introduction

Pain arising from degenerative changes in the cervical spine can be very debilitating. If nonoperative treatment fails to yield adequate relief, anterior cervical discectomy and fusion (ACDF) is generally the surgical option undertaken. Due to the potential for post-fusion problems such as pseudoarthrosis and adjacent segment degeneration (ASD), an alternative treatment was sought, leading to the development of cervical total disc replacement (TDR). The goal of TDR as a surgical intervention was to reduce pain and restore function, allow motion of the operated segment, avoid the potential problem of pseudoarthrosis, and eliminate or reduce the incidence of adjacent segment degeneration (ASD).

There have been multiple publications reporting the clinical outcome of cervical TDR, including reporting results of prospective, randomized, multicenter trials with 24-month follow-up.[1-8] These studies have consistently found TDR to produce outcomes similar or superior to ACDF. There are a few studies with extended follow-up to five or more years.[9-12] Results of these long-term studies have been consistent in that the favorable outcomes seen at 2 years after surgery were maintained throughout the longer follow-up.

Cervical TDR has been found to be associated with a significantly lower reoperation rate[13-15] as well as reduced occurrence of ASD compared with ACDF.[1,5] However, some authors have reported no significant difference in ASD.[16] More randomized studies with long-term follow-up should be helpful in further evaluating cervical TDR. The purpose of this study was to compare clinical outcomes at 5 years after surgery using TDR with the Mobi-C or ACDF in the treatment of single-level symptomatic disc degeneration based on a prospective, randomized Food and Drug Administration regulated Investigational Device Exemption trial.

Methods

This study was a prospective, randomized, controlled, multicenter clinical trial comparing the safety and efficacy of TDR with the Mobi-C® Cervical Disc Prosthesis (LDR Medical; Troyes, France) to ACDF for the treatment of single-level symptomatic degenerative disc disease (DDD). Patients were randomized in a 2:1 ratio to receive TDR (n=164) or ACDF (n=81, the control treatment). The study was conducted at 23 sites across the United States. The study design, including patient selection criteria, randomization and surgical procedures, has previously been published in detail.[5]

Patient Population

Eligible patients met the primary inclusion criteria of symptomatic DDD with radiculopathy or myeloradiculopathy at one level from C3 to C7, disc height of at least 3 mm, not osteoporotic, no previous cervical fusion, and failure of at least 6 weeks of nonoperative care.

Study Interventions

The TDR investigational device was the Mobi-C® Cervical Artificial Disc. The control treatment was ACDF performed with either the Slim-Loc Anterior Cervical Plate System (Depuy Spine) or the Sofamor Danek Atlantis or Atlantis Vision Anterior Cervical Plate Systems (Medtronic) with corticocancellous allograft in the interbody space.

Study Outcomes

Outcomes were evaluated preoperatively and at 6 weeks, 3, 6, 12, 18, 24, 36, 48 and 60 months postoperatively. The success endpoint used in this analysis was defined with the approval of the FDA within the Post Approval Study (PAS) protocol. This endpoint differs from our previously published definition at earlier follow-up points.[5,17] The primary outcome measure was a composite success criterion requiring patients to meet all of the following to be classified as having a successful outcome: 1) minimum 30/100 point improvement in NDI scores compared to baseline; 2) No device-related subsequent surgery; 3) No adverse events (AEs) classified as possibly or probably device-related by an independent Clinical Events Committee (CEC); 4) No neurologic deterioration; and 5) No intraoperative changes in treatment if randomized to Mobi-C. A device-related subsequent surgery was defined as any device removal, revision,

supplemental fixation, or reoperation at the index level. Adverse events were classified by the CEC composed of 3 independent spine surgeons (two orthopedic surgeons and one neurosurgeon).

Secondary outcome evaluations included visual analog scale (VAS) separately assessing neck and arm pain, quality of life assessed by the Short Form Health Survey (SF-12), and patient satisfaction and recommendation assessed through a patient questionnaire. Neurologic deterioration, adverse events, radiographic failure, subsequent surgery (including those that were not device-related), segmental range of motion (ROM), adjacent segment degeneration, and heterotopic ossification (HO) were evaluated postoperatively through 60 months. For TDR treatment, radiographic failure was defined as spontaneous fusion with radiographic evidence of bridging bone across the disc space and less than 2° of angular motion on flexion/extension. For ACDF treatment, radiographic failure was defined as at least 2° of angular motion on flexion/extension, or radiolucencies at more than 50% of the graft vertebral body interface, or absence of bridging bone across the graft vertebral body interfaces. ASD was assessed using the Kellgren-Lawrence scale of disc degeneration.[18] A patient was classified as having adjacent segment degeneration if there was a deterioration of at least one point on the Kellgren-Lawrence scale compared with the score for the preoperative radiograph. HO was graded using a 0 to 4 scale adapted from the methods described by McAfee et al.[19] and Mehren et al.[20] Since the primary concern with HO is the potential for fusion and restricted motion, the percentage of patients in the TDR group with Grade 4 HO (continuous bridging bone between vertebral bodies resulting in bony ankylosis and resulting in little or no motion at the index level) was calculated. All radiographic assessments were made by an independent evaluator (Medical Metrics, Houston, TX).

Statistical Analysis

This study was designed as a non-inferiority trial with the primary study hypothesis testing the non-inferiority of TDR with Mobi-C against ACDF using a 10% margin with respect to patient success at 60 months. Non-inferiority in the overall success rate was assessed using an exact 95% one-sided confidence bound. Statistical significance in success criteria and incidence rates was determined using Fisher's exact test. Statistical significance of continuous outcome measures was assessed by two-sided t-tests at each time point. Changes from baseline within treatment groups were evaluated by Wilcoxon signed-rank test to determine significance. Statistical significance was indicated by a p-value less than 0.05.

Results

No significant differences were found between the baseline demographics of patients in the two treatment groups.[5] The 60-month follow-up rate was 85.5% for the TDR group and 78.9% for the ACDF group.

Primary Endpoint: Composite Success Criteria

At 60 months, 61.9% of TDR patients and 52.2% of ACDF patients were classified as having achieved overall success. Based on the composite success criteria, TDR was non-inferior to ACDF at all postoperative evaluation points through 60-month follow-up. A higher percentage of TDR patients met the overall success criteria at each time point, although the differences were not statistically significant.

Components of Composite Success

When considering the percentage of patients who met the NDI criterion used to determine composite success, the values were 68.1% in the TDR group and 62.1% for ACDF at the 60 month follow-up. At 60 months, the rate of device-related subsequent surgery was significantly less for the TDR group compared with ACDF (3.0% vs. 11.1%; $p<0.05$; Fisher's exact test). The rate of device-related adverse events as classified by the CEC were statistically similar between treatment groups at 60 months (TDR: 5.5%, ACDF: 3.7%), as was the rate of neurological deterioration (TDR: 4.3%, ACDF: 6.2%). There were no changes in planned surgery in the Mobi-C group.

Secondary Endpoints

NDI Scores

The mean NDI scores improved significantly by 6 weeks after surgery and remained significantly improved throughout 60 month follow-up in both groups (Figure 1). Of note, scores remained very sta-

ble throughout the multi-year study. While the only significant differences between the two groups occurred at early follow-up points, at no time point were the mean scores in the TDR group worse than in the ACDF group.

VAS Pain Scales

VAS neck pain scores improved significantly from baseline at all follow-up points in both treatment groups. Preoperatively, in both groups the mean values were approximately 70, and were less than 20 at 60-month follow-up (Figure 2A). The mean values remained very stable throughout follow-up with no indication of worsening at later follow-up visits.

VAS arm pain scores for the more symptomatic arm followed a pattern very similar to neck pain values. In both treatment groups, the mean arm pain scores improved significantly at all follow-up visits compared with the preoperative values and were stable over 5 years (Figure 2B).

SF-12 Scores

The preoperative SF-12 PCS values were 32.5 and 33.8 in the TDR and ACDF groups, respectively. These scores improved significantly by 6 months after surgery and remained improved throughout 60-month follow-up to values of 47.6 and 48.3 in the two groups. The values were stable throughout annual follow-up with changes of less than 2 points in the TDR scores throughout the long-term follow-up and less than a 3-point change in ACDF scores across all annual visits. The SF-12 MCS followed a similar pattern with significant and sustained improvement in both groups throughout 60-month follow-up.

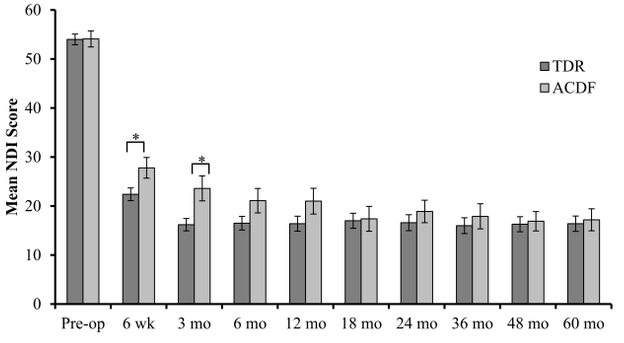

Fig. 1. Mean NDI scores of TDR and ACDF at each follow-up. *Statistical significance determined by Student's t-test, p <0.05.

Subsequent Surgery

In addition to the device-related subsequent surgery criteria used to determine the composite success rate, other surgeries at the index and adjacent levels were also recorded. By 60 month follow-up, 8 patients (4.9%) in the TDR group and 14 patients (17.3%) in the ACDF group underwent subsequent surgery ($p<0.01$; Fisher's exact test). Of the 8 reoperations in the TDR group, one patient underwent laminectomy at the TDR level due to nerve impingement. In 4 cases the TDR was removed and fusion performed. Reasons for disc removal and fusion included oversized implant, development of heterotopic ossification causing pain during flexion/extension movements, and the development of kyphosis due to a malpositioned device. Two of these patients with secondary fusion later required a tertiary surgery to revise the ACDF. The remaining 3 subsequent surgeries in the TDR group were performed to treat symptoms arising from the level adjacent to the TDR level.

Of the 14 ACDF secondary surgeries, 5 were to treat symptomatic pseudoarthrosis, 6 patients had surgery to treat symptoms arising from an adjacent segment,

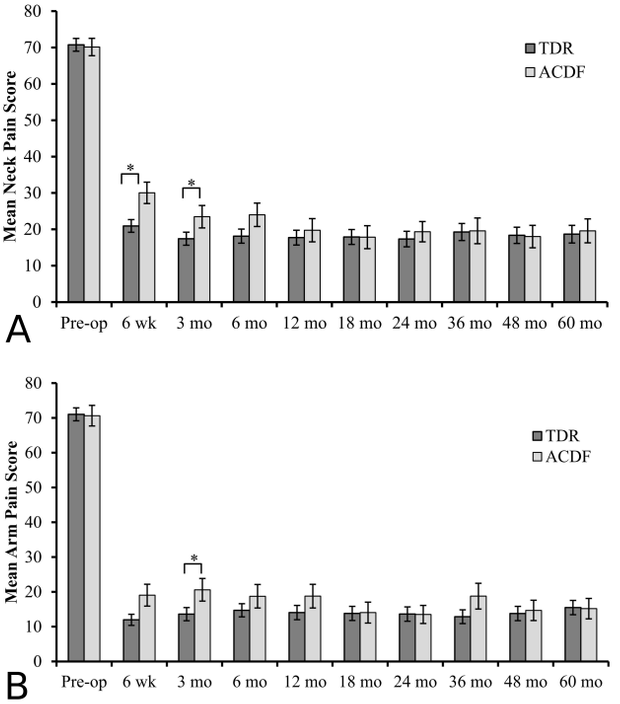

Fig. 2. A. The mean VAS neck pain scores of TDR and ACDF at each follow-up. B. The mean VAS arm pain scores for the more symptomatic arm. *Statistical significance determined by Student's t-test, p<0.05.

one patient underwent surgery to treat stenotic symptoms, one patient required surgery to address a malpositioned screw, and one patient had surgery 5 days after the index procedure to evacuate a hematoma. One tertiary surgery was performed to expand the fusion to adjacent levels. A detailed description of subsequent surgeries in the total safety population (randomized cases and training cases) has been published by Jackson et al.[21]

Patient Satisfaction

Overall, patient satisfaction and recommendation rates were high for both groups at every time point. At 60 months, 92.0% of TDR patients and 83.9% of ACDF patients were very satisfied with their treatment (Figure 3). There was very little change in the distribution in scores across the 4 response categories for satisfaction across multiple follow-up time points. The rate of patients recommending their treatment to a friend was also high in both treatment groups with 97.1% of TDR patients and 91.1% of ACDF patients indicating they would definitely or probably recommend the treatment they received.

Radiographic Assessment

There were no cases of device migration in either treatment group. The occurrence of radiographic failure was similar between TDR (5.5%) and ACDF (3.7%). At 60-month follow-up, 95.2% of TDR subjects and 98.1% of ACDF subjects were classified as having no radiolucency around the implants. In the TDR group, the radiolucencies noted were mild in all cases and in the ACDF group, the one radiolucency noted was severe.

Segmental ROM at the treated level was maintained in the TDR group throughout 60-month follow-up (Figure 4). The greatest value was at the 6-month follow-up with less than 1° difference at any point in the mean values throughout 60-month follow-up. In the fusion group, the mean ROM was less than 2° at 6 week follow-up and remained stable throughout the 60-month period. Left and right side bending was maintained in the TDR group at values slightly greater than the preoperative mean. In the ACDF group, lateral bending was decreased by 6 weeks after surgery and remained less than 2° throughout follow-up.

The percentage of patients with ASD was less in the TDR group at both the superior and inferior adjacent levels compared to the ACDF group at all annual follow-up visits. The values were significantly different at the inferior adjacent segment at all annual visits (Figure 5). At the superior level, the difference was significantly lower in the TDR group at 48 and 60 months.

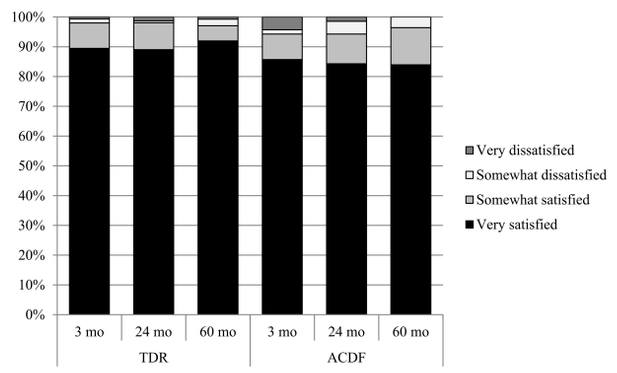

Fig. 3. Distribution of responses to the satisfaction question.

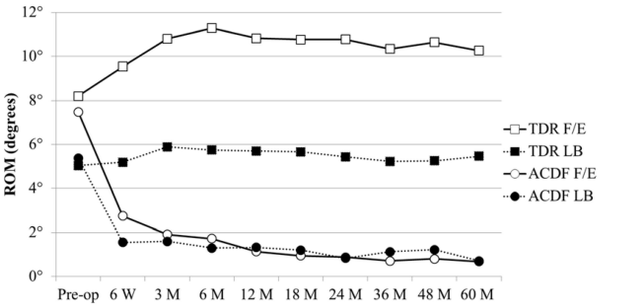

Fig. 4. Mean range of motion of the operated level.

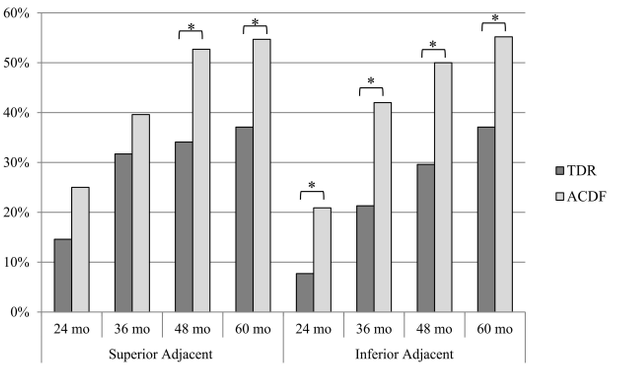

Fig. 5. The percentage of patients with adjacent segment degeneration at the superior or inferior adjacent level. *Statistical significance determined by Mann-Whitney U test, p<0.05.

The rate of Grade 4 HO at the index level at 60-month follow-up was 8.5%.

Discussion

Results of this randomized, controlled, FDA IDE clinical trial with 60-month follow-up found TDR with Mobi-C produced results noninferior to ACDF, and better outcomes on some measures at various time points including NDI and pain scales at early follow-up points, the subsequent surgery rate and adjacent segment degeneration at later follow-up points. These results are consistent with other studies comparing TDR with ACDF with 4 to 8 years follow-up.[10-12] In the current study, as in the others, significant improvement was seen at early follow-up and maintained throughout long-term follow-up.

The flexion/extension mean range of motion at the operated TDR segment increased after surgery and remained stable throughout 5-year follow-up. HO severe enough to measurably limit motion was found in 8.5% of patients 5 years after TDR surgery. Previous studies have shown a variable rate of HO formation with unclear clinical relevance.[22-24] One study with comparable follow-up reported a similar rate of HO.[25] While undesirable, HO does not appear to greatly impact clinical outcomes.[26,27] Considering that severe HO results in essentially a fusion, the clinical results may also be similar to ACDF. The development of HO may be managed with greater attention paid to complete endplate coverage,[28] meticulous surgical technique minimizing uncovered bleeding bone, and prophylactic use of nonsteroidal anti-inflammatory drugs (NSAIDs).

The reoperation rate was significantly lower in the TDR group than in the ACDF group. This has been previously reported in other studies.[13,14,29] In studies specifically addressing reoperation rates, authors found that the primary reason for reoperation in ACDF patients is symptomatic pseudoarthrosis. Symptomatic ASD was also a common reason for subsequent surgery.[13,14] In the current study, a frequent reason for surgery at the index level in the ACDF group was symptomatic pseudoarthrosis, the risk of which is eliminated with TDR. Similar to the studies on reoperations, ASD was a reason for reoperation in both the TDR and ACDF groups, but was the most frequent reason for reoperation in the ACDF group. The relationship of TDR or ACDF and ASD is not fully understood. In the classic study by Hilibrand et al, the rate of ASD was calculated to 2.9% per year.[30] Results of the current study suggest a higher rate. This may be related to several factors such as differences in surgical technique, quality of images available, and/or differences in the assessment methods used to evaluate the adjacent segment. While TDR does not eliminate the risk of ASD, it does appear to be associated with a lower occurrence. Risk factors for developing ASD after cervical TDR have been found to include poor bone quality and the presence of lumbar disc degeneration.[31] In many trials evaluating TDR, including the current study, poor bone quality was an exclusion criterion. The reported association of cervical ASD with lumbar disc degeneration was interesting and may represent patients with genetic and/or systemic risk factors for disc degeneration, which may impact the level adjacent to the index surgery. Luo et al. recently published a meta-analysis of prospective, randomized studies with 24-month follow-up addressing ASD in single-level TDR vs. ACDF.[32] They concluded that TDR was associated with a significantly lower rate of ASD and a significantly lower rate of reoperation for ASD.

Cost can be a deciding factor when considering treatment options. Due to challenges in collecting comprehensive costs data as well as outcome data, costs studies are very difficult to conduct and often have different methods based on data availability. Several studies have compared the cost of single-level cervical TDR to ACDF.[33-37] Most of the studies found lower costs associated with TDR. A large-scale cost analysis of single-level TDR vs. ACDF has been conducted based on data collected from a Blue Health claims database.[34] Over the course of follow-up, the total treatment cost paid by insurers was significantly less for the TDR group. Factors impacting the lower costs were that the TDR group had lower readmission rates and lower cost of the index surgery. Qureshi et al. found that TDR and ACDF were both cost effective treatments, and that TDR would become more cost-effective than ACDF over an extended period.[37] Ament et al. have recently reported

that the cost of 2-level cervical TDR was also less expensive than ACDF.[38] The current study found lower reoperation rate associated with TDR which may be associated with lower cost.

Conclusion

Five-year results showed improvements in pain and function are maintained in both treatment groups. In comparison to ACDF, the TDR group preserved motion and patients exhibited lower rates of adjacent segment degeneration through 60 months. Also, a significantly lower rate of subsequent surgeries was seen in the TDR group, indicating an additional benefit of this treatment option. This study presents Level I evidence demonstrating the safety and efficacy of single-level TDR with Mobi-C as an alternative to ACDF.

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Disclosures

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Corresponding Author

Michael S. Hisey, M.D. Texas Back Institute, 2817 S. Mayhill Rd. #100, Denton, TX 76208. orthoboss@aol.com.

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