



ROI-C® Cervical Cage

ABSTRACT
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TITLE

Comparison of a zero-profile anchored spacer (ROI-C) and the polyetheretherketone (PEEK) cages with an anterior plate in anterior cervical discectomy and fusion for multilevel cervical spondylotic myelopathy

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OBJECTIVE: We aimed to analyze the clinical and radiographic efficacy of a new zero-profile anchored spacer called the ROI-C in anterior discectomy and fusion (ACDF) for multilevel cervical spondylotic myelopathy (MCSM).

METHODS: We retrospectively reviewed the clinical, radiological outcomes and complications of multilevel ACDF with the ROI-C or with the polyetheretherketone (PEEK) cages with an anterior plate. From April 2011 to April 2014, 60 patients with MCSM were operated on using ACDF, with the ROI-C in 28 patients and PEEK cages with an anterior plate in 32 patients. The operative time, intraoperative blood loss, and clinical and radiological results were compared between the ROI-C group and the cage-plate group.

RESULTS: The mean follow-up time was 23.8 ± 6.6 months, ranging from 12 to 36 months. At the first month and the last follow-up, the neck disability index (NDI) scores were decreased, and the Japanese Orthopedic Association (JOA) scores were significantly increased, compared with the presurgical measurements in both groups. There were no significant differences in NDI scores or JOA scores between the two groups ($P>0.05$), but there were significant differences in the operation time, blood loss and the presence of dysphagia ($P<0.05$). In addition, the cervical Cobb angle and disk height showed significant corrections, compared to those measured before the operation. There was no adjacent disc degeneration observed in the ROI-C group, and one patient with skip levels showed disc degeneration of the normal level between the skip levels in the cage-plate group. The degeneration rate of the cage-plate group was 3.1 %.

CONCLUSION: The primary clinical and radiographic efficacies of both ROI-C and cages with plates in ACDF for MCSM were satisfactory; both approaches could improve and maintain cervical lordosis and disk height. However, the ROI-C was associated with a simpler operation, a shorter operation time, less blood loss, and a lower risk of postoperative dysphagia compared to the PEEK cage with an anterior plate.

KEYWORDS: Multilevel spondylotic myelopathy – Anterior discectomy and fusion - ROI-C - PEEK cage.

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The ROI-C® implant is a sterile cage intended for an arthrodesis of the cervical vertebrae through anterior approach.

The ROI-C® instruments constitute an instrument set intended to allow the ROI-C® implant implantation.

Before any surgical procedure, read carefully the instructions and the surgical technique.

Anterior Cervical Fusion With Tantalum Implant

A Prospective Randomized Controlled Study

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Study Design. A prospective randomized controlled study was carried out.

Objective. To determine the effectiveness and safety of a tantalum implant in achieving anterior cervical fusion following 1-level discectomy as treatment of degenerative cervical disc disease with radiculopathy.

Summary of Background Data. The gold standard for the treatment of degenerative cervical disc disease could not be already identified. The morbidity of autologous graft and plating, and the doubt about the mechanical efficacy of plate fixation and the clinical benefits in 1-level fusion have promoted the use of other constructs.

Methods. Sixty-one patients were randomized to anterior cervical discectomy and fusion with interbody implant of tantalum ($n = 28$) or by means of autologous iliac bone graft and plating ($n = 33$). Fusion rate and segmental height and alignment were blind assessed by radiographs by 2 independent reviewers. Clinical status was evaluated using pain visual analogue scale, the Neck Disability Index, and the Zung Depression Scale. Patient's subjective satisfaction was recorded. Complications and operative parameters were also taken into account.

Results. With an endpoint of 24 months, radiologic and clinical outcomes were similar for both treatments without significant difference. The safety of fusion with tantalum implant was obvious, based on the analysis of complications. Complication rate was considerably higher for the autologous graft plus plating procedure than for implant tantalum ($P < 0.005$).

Conclusion. The efficacy to achieve fusion after 1-level anterior cervical discectomy, with a good radiologic and clinical outcome, using tantalum implant is equivalent to that of autologous graft and anterior plate, being safer as avoids donor-site graft harvesting and plating complications.

Key words: tantalum, anterior cervical discectomy and fusion, complications. *Spine* 2008;33:465–472

Anterior cervical discectomy and fusion (ACDF) is a widely accepted procedure in the treatment of degenerative cervical disc disease.^{1,2} The stability of cervical segment drops dramatically after discectomy.³ Interbody fusion restores segmental stability, intervertebral height,

cervical lordosis, and painless function.^{2,4–6} The insertion of an interbody graft reduces this instability by 50%.³ The use of internal fixation attempts to improve fusion rate,^{7–11} while reducing the period and extent of postoperative immobilization,³ avoiding graft extrusion, collapse and subsidence.^{9–13} However, there is some doubt about the mechanical efficacy and clinical benefits of plate fixation in 1-level fusion.^{6,14–18} Furthermore, it must be considered the disadvantages of plating.^{19,20}

Among the diverse techniques used, the model graft-type is essential to achieve optimal fusion rate.¹ Small variations in interbody construct yield greater differences in rigidity than does the choice of plate.^{21,22} Commonly, autologous bone is preferred as interbody graft,^{23,24} but the donor-site morbidity^{25–27} has promoted the use of allograft,^{1,2,28–30} or some other osteoconductive materials,³¹ cages,^{32–37} or porous tantalum implants.^{38–41}

Tantalum is of a great interest as constitutive material of this type of spinal implants. It produces slight artifact in magnetic resonance imaging, permitting good imaging of surrounding structures.^{42,43} It has a high compressive strength and a Young's modulus within the range seen for cancellous bone.^{44–47} The primary stability of the interbody construct is very good since the high resistance to shear of this interface, achieving rapidly osteointegration and then definite long-lasting stability,⁴⁸ void of toxicity and with an excellent biocompatibility.⁴⁴

To date, there is scarce literature dealing with clinical use of tantalum cervical implants.^{38–41} The aim of this prospective randomized controlled trial is to evaluate the effectiveness and safety of a porous tantalum implant in achieving anterior cervical 1-level fusion for the treatment of degenerative cervical disc disease with radiculopathy. Our hypothesis is the tantalum interbody implant yields better results than autologous interbody graft associated to anterior plating, following single-level anterior cervical discectomy.

Materials and Methods

From October 2003 to May 2005, consecutive patients with neck pain and arm radiculopathy that had to undergo treatment with ACDF were recruited into this prospective randomized controlled trial:

The criteria of inclusion in this study were as follows:

1. Patients with neck pain, brachalgia and clinical findings of cervical nerve root compression corresponding to a herniated disc and/or spondylosis (cervical disc disease) at 1 single cervical level verified by magnetic resonance imaging.

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The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication.

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2. Unresponsive to conservative, nonoperative treatment for 6 weeks.
3. One single involved segment between C₃ and C₇.
4. No previous surgical intervention at the involved level
5. Age between 18 and 65 years at the time of surgery.
6. Willingness to comply with the study plan and sign the consent form.

Exclusion criteria were as follows:

1. Any cervical spinal condition requiring surgical treatment other than symptomatic cervical disc disease with radiculopathy.
2. Myelopathy.
3. Severe osteopenia, osteoporosis, osteomalacia or metabolic bone disease.
4. Local or systemic infectious or tumoral disease.
5. Smokers, drug- or alcohol abusers.
6. Work-related injuries and/or compensation-related injuries.

All patients fulfilling the inclusion criteria were extensively informed and, after providing informed consent, were blind randomized and assigned to 1 of the 2 groups by means of a computer-generated random list. Group 1 received a standalone interbody porous tantalum cage and Group 2, consisted of controls, and received an interbody autologous tricortical iliac bone graft with an anterior plate.

Before surgery all patients underwent standard clinical and radiologic assessment with AP, lateral neutral, and lateral flexion/extension radiographs, sagittal and axial magnetic resonance imaging scanning, and completed outcome measures as 0 to 10 visual analogue scale (VAS) for neck and radicular "pain right now," the Neck Disability Index (NDI),⁴⁹ and the Zung Depression Scale,⁵⁰ for psychological evaluation.

The same senior surgeon (M.F.-F.) carried out all surgeries. The perioperative regime and surgical technique was identical in both groups. Once the discectomy and endplate preparation was performed, the appropriate graft or tantalum implant height was selected to obtain approximately 2 mm of disc height distraction.⁵¹

The tricortical autograft was harvested from the anterior iliac crest and fashioned in a Smith-Robinson pattern. Anterior plating was performed by means of a straight semiconstrained rotational plate (Alpha Plate; Stryker, Cestas, France). Protruding osteophytes were removed from the anterior cervical aspect at the operative level and the plate was contoured into the desired lordosis and applied centrally maximizing implant-bone contact. The length of the plate was selected to ensure placement of the screws just inferior and superior to the corresponding endplates.

In case of Tantalum interbody implants, Trabecular Metal Cervical Fusion Device TM-100 (Zimmer Spine, Minneapolis, MN) were always used standalone and without bone graft supplement. The tantalum implant or the tricortical bone graft was inserted into the interbody space and countersunk 1 to 2 mm from the anterior vertebral border.

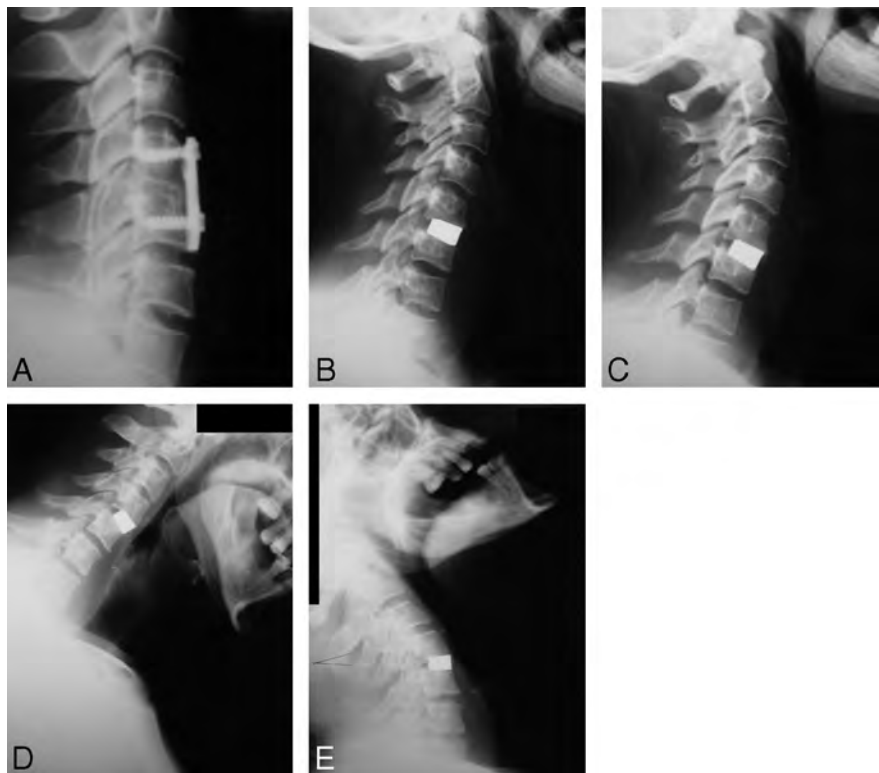
The operation time, blood loss, and duration of hospital stay were recorded.

In both groups, no external immobilization was used. Patients were slowly allowed to resume controlled neck exercises and to return to normal activities as tolerated.

All patients were reviewed at 6 weeks, at 3, 6, 12, and 24 months follow-up.

The primary outcome measure was radiographic evidence of fusion (Figure 1). Segments were deemed fused when there was evidence of bony bridging around the implant and/or $<2^\circ$ of variation of Cobb's angle on F/E radiographs or <2 mm of

Figure 1. The primary outcome measure in this study was radiographic evidence of fusion; (A) easier to evaluate in the case of bone graft and plating than in case of tantalum implant. The radiopaque nature of tantalum makes difficult to judge the presence of bridging trabeculae across the bone-implant interface. (B and C) Case of fusion achieved by means of tantalum device: (B) immediate postoperative view; (C) settling of the implant in the interbody space at 6 months follow-up, with a full contact between the superior and inferior surfaces of tantalum implant and the contiguous dense vertebral endplates, and a longitudinal calcic shadow extending down from the anterior-inferior corner of the superior vertebral body covering the proximal third of the anterior aspect of tantalum implant. (D and E) Case deemed as failure in achieving fusion, showing $>2^\circ$ of variation of Cobb's angle, and >2 mm of variation in the inter-spinal distance, on dynamic lateral radiographs, and radiolucency around the inferior edge of the cage on the extension radiograph (E).



variation in the interspinous distance, in the absence of peri-implant radiolucency.^{32,52} Collapse or subsidence of the graft or the implant were assessed adopting methods described in previous publications.^{28,30,53} Alignment was evaluated measuring the angle between the posterior borders of the 2 vertebral bodies on a lateral radiograph. Adjacent level degeneration was determined by the presence of disc space narrowing, anterior or posterior osteophytes.

All radiographs were evaluated by 2 independent orthopedic surgeons not involved in patient surgeries, with each observer blinded to the results of the other, patient's clinical status and the timing of their follow-up. Agreement among the evaluators was measured by calculating concordance rates and simple Kappa coefficients.

At the 2-year follow-up, an unbiased observer graded the patients' clinical outcome using Odom's criteria.^{6,54}

Patient's subjective perception of overall satisfaction was graded according to the Patient Satisfaction Index.^{5,55}

All complications were recorded and classified as surgery-related or implant-related. A global assessment of favorable or unfavorable outcome was made considering those patients with fusion, maintenance of space height, improvement in all of the clinical outcome measures, a grade "excellent" or "good" in the Odom's scale, positive degree of patient satisfaction, and no complication, to have had a favorable outcome.

Statistical analysis was carried out applying unpaired *t* test for parametric data and crosstabulation tables and χ^2 test with the Yates correction for nominal variables. Person's *r*, λ was obtained to determine the strength of association between variables. Also, for 2×2 constructs that entailed values <5 a 2-tailed Fisher exact test was conducted. Changes in the test results for the 2 groups between the pre- and the postoperative examination were evaluated using the Wilcoxon signed-ranks test for paired samples. To assess the extent of change secondary to the intervention, effect size⁵⁶ was calculated. Differences between those operated with tantalum implants and those with graft and plate fixation were calculated using the Mann-Whitney *U* test. Analysis of variances were conducted for appropriate data sets. Significance for each statistical test was set at $P < 0.05$. Data were analyzed using SPSS statistical software version 11.01.

■ Results

Patient Population

A total of 61 patients have been randomized into this trial: 28 patients received interbody porous tantalum implant (Group 1) and 33 received interbody autologous bone graft plus anterior plate fixation (Group 2).

Group 1 consisted of 18 women and 10 men with a mean age of 47.5 years (range, 27–62), Group 2 was comprised of 21 women and 12 men with a mean age of 49.3 years (range, 22–65). The variables age and gender (Table 1), preoperative pain, function and psychological status, radiologic appearance, pathology, and operated level did not show any statistically significant difference between the groups.

Surgical Parameters

The average duration of surgery was 53 minutes (range, 40–62 minutes) for ACDF with tantalum implant *versus* 98.5 minutes (range, 78–120 minutes) for discectomy

Table 1. Demographic Characteristics, Pathology, and Operated Level by Group

	Group 1	Group 2
N	28	33
Male	10	12
Female	18	21
Average age (range)	47.5 (27–62)	49.3 (22–65)
Herniated disc	10 (35.7%)	10 (30.3%)
Spondylosis	11 (39.2%)	14 (42.4%)
Spondylosis + herniated disc	7 (25.0%)	9 (27.2%)
Operated level		
C ₄ –C ₅	2 (7.1%)	1 (3.0%)
C ₅ –C ₆	17 (60.7%)	21 (63.6%)
C ₆ –C ₇	9 (32.1%)	11 (33.3%)

and fusion with autologous graft and plating ($P < 0.05$). Blood loss was greater for the fusion with graft and plate (average, 289 mL; range, 200–400 mL) than for the tantalum procedure (average, 97 mL; range, 80–130 mL) with a significant difference ($P < 0.05$). No patient stayed in the hospital for more than 1 day in Group 1, but patients of Group 2 were hospitalized for an average of 2.1 days (range, 1–5 days) (Table 2).

Radiologic Results

The fusion rate was 82.1%, at 6 months follow-up and 89.3% at 12- and 24 months follow-up for patients with porous tantalum, and 78.7% and 84.8%, respectively, for the autologous graft and plating, with no significant differences ($P > 0.5$) with respect to rate or time required for incorporation of the implant. Interobserver agreement was excellent (concordance rate = 0.96%; Kappa coefficient = 0.81).

Subsidence of tantalum implant into adjacent vertebrae was seen in 2 cases (7.1%) with 3 mm of subsidence each. Both fused within 6 months after surgery. In the control group, autologous graft subsided 1 to 2 mm in another 2 cases (6%). Graft collapse occurred in 5 patients of this group (7.2%), with an average of 1.6 mm of loss of height (range, 1–2 mm) and a radiolucent line in the upper bone-graft interface in the dynamic radiographs in 3 of these cases.

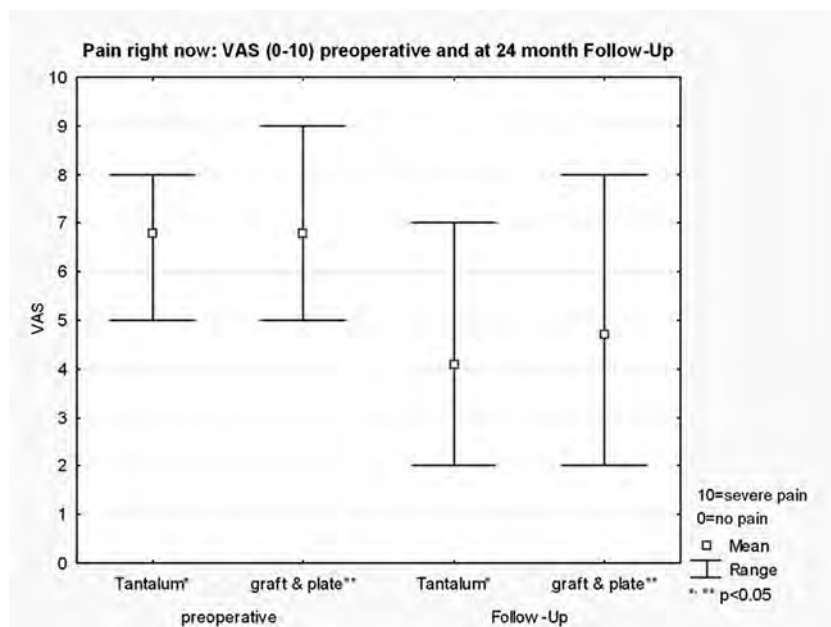
Four patients (14.2%) receiving the tantalum implant developed segmental kyphosis in a range from -3° to -11° (average, 7°), as it was for 3 patients operated by graft and plating (9%) in a range from -2° to -5° (average, 3.6°).

At 2-year follow-up, the onset of degeneration of disc spaces adjacent to the operated level was observed in 4

Table 2. Surgical and Hospital Details by Group

	Group 1	Group 2	Significance
Duration of surgery (min)	53 (range: 40–62)	98.5 (78–120)	$P < 0.05$
Blood loss (mL)	97 (range: 80–130)	289 (200–400)	$P < 0.05$
Hospital stay (days)	<1 each	2.1 (1–5)	

Figure 2. Visual analogue scale (VAS) for neck and radicular "pain right now," with endpoint anchors of 0 "no pain" and 10 "severe pain," preoperative and 24 months postoperative. The improvement in pain is significant ($P < 0.05$) in both treatments but not between groups ($P > 0.1$)



patients of Group 1 (14.2%) and in 6 patients of Group 2 (18.1%).

Neither the difference in subsidence nor in development of kyphosis or degeneration of adjacent disc spaces were statistically significant ($P > 0.1$, $P > 0.5$ and $P > 0.5$, respectively).

No patient required a reoperation.

Clinical Results

Pain on a 0 to 10 VAS improved in both groups from an average of 6.8 for Group 1 (range, 5–8) and 6.8 for Group 2 (range, 5–9), before surgery, to 4.1 (range, 2–7) and 4.7 (range, 2–8) at 24 months after treatment, respectively (Figure 2).

Before surgery, the average NDI score was 46.8% for the tantalum group (range, 38–56), and 48.9% for

the control group (range, 32–66), with no significant difference between groups. Twenty-four months after surgery, the NDI was 19% on average for the tantalum implant group (range, 10–34), and 20.9% for the other group (range, 10–40) (Figure 3). The improvement in pain and NDI is significant for both treatments ($P < 0.05$), but there is no significant difference between the groups ($P > 0.1$). The effect size of treatment was small on pain and moderate on disability for both groups.

Zung score was on average 40 (range, 24–62) for Group 1, and 43 (range, 22–67) for Group 2, before surgery, without changes after treatment in any of both groups (average, 37; range, 30–63, for Group 1; average, 38; range, 26–65, for Group 2) ($P > 0.5$).

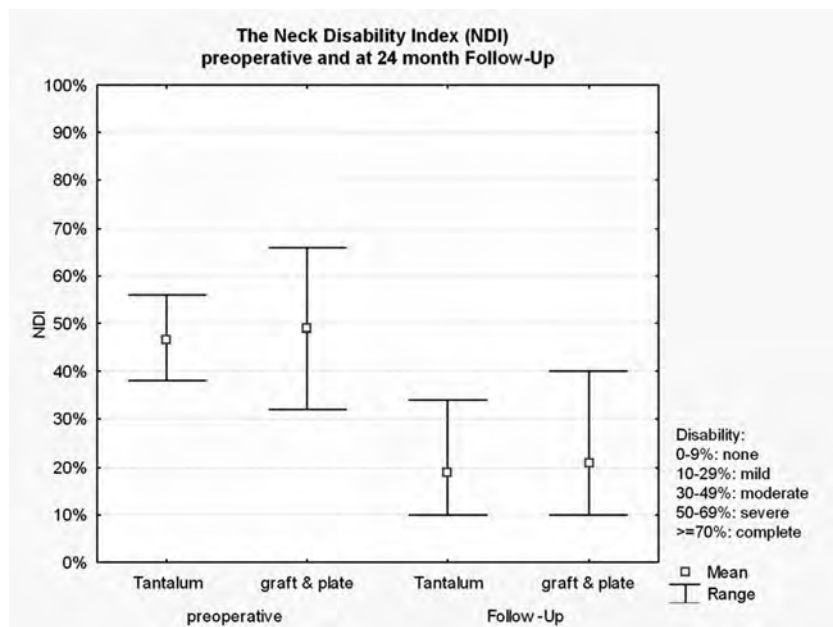


Figure 3. The Neck Disability Index (NDI), preoperative and 24 months postoperative. It is considering a score of 0% to 9% as no disability, 10% to 29% as mild disability, 30% to 49% as moderate, 50% to 69% as severe, and 70% or more as complete.

Table 3. Complication Rate and Details in Group 2

Complications Group 2	No. of Cases	Description
Total	11 (33%)	
Graft donor-site pain	7 (21%)	Prolonged graft donor-site pain at least 4 on the 10-point scale. Graft donor-site hematoma needed to be drained in two cases
Dysphagia	2 (6%)	Two patients experienced early postoperative dysphagia that resolved spontaneously in a few days
Loosened screws	2 (6%)	Loosened screws were seen in two cases in the Rx control 6 mo after surgery, one of them with loosening of the plate. Additional revision surgery was not required

For group 1 there were no cases with complications reported, neither surgery-related nor implant-related.

At 6 months, 85.7% of patients in Group 1 were graded excellent or good after the Odom's criteria. The satisfying outcome was maintained in this group at the 12- and 24-month follow-up. In the control group, 75.7% and 78.7% of patients were scored excellent or good at 6 months and at 12- and 24-month follow-up, respectively. The difference between groups was not significant ($P > 0.5$). All patients who did not achieve fusion reported fair outcomes. No poor results were noted in this series.

Patients showed a good level of satisfaction with the result of the operation in 25 cases in Group 1 (82.2%) and in 23 cases in Group 2 (69.7%), with no significance difference ($P > 0.1$).

Complications

In the Group 1, neither surgery-related nor implant-related complications occurred. In contrast, an overall

complication rate of 33.3% was registered in Group 2 ($P < 0.005$). Seven patients (21.2%) experienced prolonged graft donor-site pain at least 4 on the 10-point scale. Four patients (12.1%) continued to report graft site pain at 12 months after surgery. Graft donor-site hematoma needed to be drained in 2 cases. Two patients (6%) experienced postoperative dysphagia that resolved spontaneously in a few days. Loosened screws were seen in 2 cases (6%) in the radiographic control 6 months after surgery, with loosening of plate in 1 of these 2 cases. The instrumentation failures were inconsequential, without dysphagia and were nonprogressive. Complications necessitating reoperation occurred in none of the patients (Table 3).

Overall Outcome

The outcomes were favorable in 57.5% of patients in the control group, and 78.6% of the tantalum group (Figure 4), with no significant difference ($P > 0.1$).

Discussion

From a systematic literature review,¹⁸ a gold standard for the treatment of degenerative cervical disc disease with radiculopathy could not be identified because of the heterogeneity of methods. To obtain optimal clinical outcome it is essential to achieve fusion,^{35,57-59} which correlates well with our own experience. Thus, the ideal graft and/or implant material is essential to increase the propensity to achieve radiographic fusion. Attending to that, this study has been designed to evaluate the performance of cervical interbody porous tantalum implant compared to fusion with autograft and anterior plating as a classic procedure to treat cervical disc disease.^{1,2}

In our series, fusion rates have been found similar for the standalone tantalum implant and for the control procedure, such as it has been already referred in other stud-

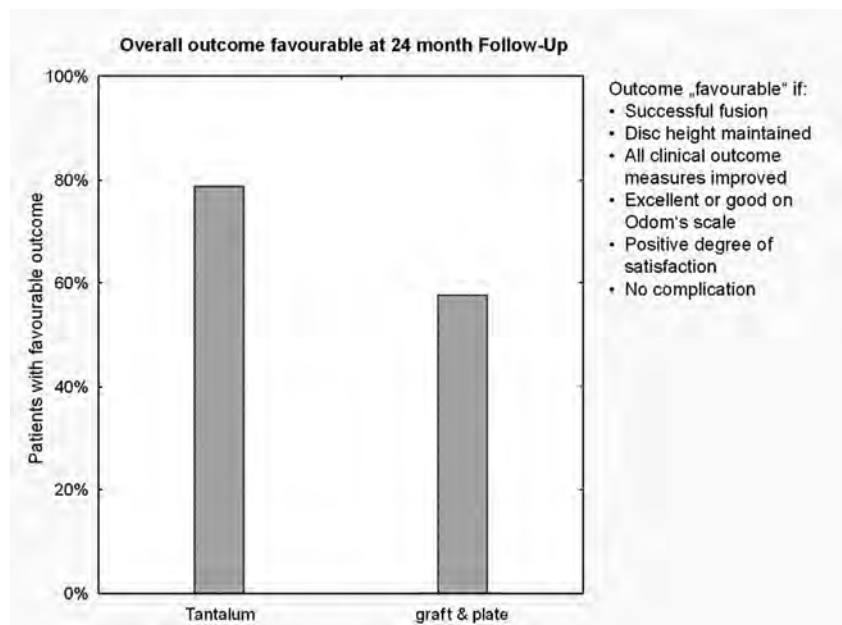


Figure 4. Percentage of patients with favorable outcomes (f, favorable; u, unfavorable). The difference between groups is not significant ($P > 0.1$).

ies comparing tantalum implant and auto- or allograft, with or without anterior plating.^{39,41}

Assessment of fusion has been discussed controversially by a large number of authors.^{2,60–66} We believe that for implants made of tantalum “functional arthrodesis” describing patients with less than 2° of motion on flexion/extension radiographs⁶⁷ is the best available term to be considered as endpoint of fusion.⁶⁸

The presence of radiolucencies seen early in the interface between tantalum implant and the vertebral endplates, becoming more evident in flexion/extension, must be considered a sign of instability and of failure of implant to integrate, as described by other authors.⁴¹

From our results, union when achieved was totally established in the 12 months after surgery, little longer than reported in other series.^{34,35,69} After this time, the possibility to progress to tantalum-to-bone integration, found by other authors,³⁸ should be very low.

Subsidence may influence long-term clinical results,^{1,28,34,69} even if it seems not to affect the development of a solid bone arthrodesis.⁷⁰ High subsidence rates of cages have been reported in the literature⁷¹; however, in our series, the tantalum implant obviously exhibited good distractive properties. The rippled surface of the tantalum block implant offers an excellent support to vertebral endplates and consequently permits reduction of subsidence. In fact, the rate of subsidence of the implant in our cases was equivalent to that reported for a titanium cage with analogous shape.³⁴

Although we found less segmental kyphosis and better preserved “disc height” in the control group than in the tantalum group, both cases with definitive subsidence of the tantalum implant were asymptomatic, which corresponds well to other publications.^{23,36,72,73}

Clinical outcomes are unreliable as indirect measures of fusion,⁴¹ but the subjectivity of defining fusion increases the importance of the clinical outcome for evaluating the surgical techniques and biomechanical properties of implants or instrumentation.^{60,64} Clinical results were similar after the use of an interbody tantalum implant or autologous graft and plating, the same was the case concerning the fusion rate. In the short-term of 2 years, the ACDF with the tantalum implant and the ACDF with autologous graft and anterior plating resulted in improved pain and disability. Nevertheless, the effect size on 1-level ACDF was small as reported in other series,^{6,74} either with the tantalum implant or with autograft and plate.

The operative technique of the tantalum implant is easier and shorter as evidenced by no additional operative time needed for the standard graft technique and plating. The high porosity of this implant enhances bone integration without the necessity of bone grafting, as it was seen in retrieved tantalum 7 months after implantation,⁴¹ avoiding the morbidity of harvesting autogenous bone.

From the results obtained, we think the interbody tantalum implant is stable enough not to require the addition of a plate, as has also been confirmed by other stud-

ies,^{40,41} resolving the controversy existing about the convenience to plate for single-level disease and avoiding morbidity of plating.^{2,14,75,76} The surface roughness of the tantalum implant assures improved initial stability making a postoperative external support unnecessary and avoiding implant dislodgement.

In contrast with other series,³⁸ tantalum device fragmentation was never observed.

In conclusion, the tantalum cervical interbody implant achieved a rate of fusion and patient outcome similar to that of ACDF with autologous graft and plating, avoiding graft requirements/risks and requiring generally fewer hospital resources. The Trabecular Metal porous implant is a good alternative for a cervical spine interbody fusion.

■ Key Points

- The aim of this prospective randomized controlled trial is to evaluate the effectiveness and safety of a porous tantalum implant in achieving anterior cervical 1-level fusion for the treatment of degenerative cervical disc disease with radiculopathy.
- Comparison was made between a standalone tantalum cage, and an interbody autologous tricortical iliac bone graft with an anterior plate, as a classic procedure to treat degenerative cervical disc disease.
- The tantalum cervical interbody implant achieved a rate of fusion and patient outcome similar to that of ACDF with autologous graft and plating, avoiding graft requirements/risks and requiring generally fewer hospital resources.
- The tantalum porous implant is a good alternative for a cervical spine interbody fusion.

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Cervical Disc Arthroplasty vs Anterior Cervical Discectomy and Fusion at 10 Years: Results From a Prospective, Randomized Clinical Trial at 3 Sites

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ABSTRACT

Background: Over the past 20 years, multiple randomized controlled trials have shown cervical disc arthroplasty (CDA) to be safe and effective for treating 1- and 2-level degenerative disc disease (DDD). The purpose of this postmarket study is to compare 10-year outcomes between CDA and anterior cervical discectomy and fusion (ACDF) from a randomized study at 3 centers.

Methods: This study was a continuation of a randomized, prospective, multicenter clinical trial comparing CDA with the Mobi-C cervical disc (Zimmer Biomet) vs ACDF. Following completion of the 7-year US Food and Drug Administration study, 10-year follow-up was obtained from consenting patients at 3 high-enrolling centers. The clinical and radiographic endpoints collected at 10 years included composite success, Neck Disability Index, neck and arm pain, short form-12, patient satisfaction, adjacent-segment pathology, major complications, and subsequent surgery.

Results: A total of 155 patients were enrolled (105 CDA; 50 ACDF). Follow-up was obtained from 78.1% of patients eligible after 7 years. At 10 years, CDA demonstrated superiority to ACDF. Composite success was 62.4% in CDA and 22.2% in ACDF ($P < 0.0001$). The cumulative risk of subsequent surgery at 10 years was 7.2% vs 25.5% ($P = .001$), and the risk of adjacent-level surgery was 3.1% vs 20.5% ($P = .0005$) in CDA vs ACDF, respectively. The progression to radiographically significant adjacent-segment pathology at 10 years was lower in CDA vs ACDF (12.9% vs 39.3%; $P = 0.006$). At 10 years, patient-reported outcomes and change from baseline were generally better in CDA patients. A higher percentage of CDA patients reported they were “very satisfied” at 10 years (98.7% vs 88.9%; $P = 0.05$).

Conclusions: In this postmarket study, CDA was superior to ACDF for treating symptomatic cervical DDD. CDA was statistically superior to ACDF for clinical success, subsequent surgery, and neurologic success. Results through 10 years demonstrate that CDA continues to be a safe and effective surgical alternative to fusion.

Clinical Relevance: The results of this study support the long-term safety and effectiveness of cervical disc arthroplasty with the Mobi-C.

Level of Evidence: 1.

Cervical Spine

Keywords: cervical disc arthroplasty, Mobi-C, degenerative disc disease, adjacent-segment pathology, anterior cervical discectomy and fusion

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) has been the standard surgical treatment for symptomatic cervical spondylosis since the mid-20th century. In the past 20 years, multiple randomized controlled trials (RCTs) have shown cervical disc arthroplasty (CDA) to be safe and effective for the treatment of both 1- and 2-level cervical degenerative disc disease (DDD). ACDF is known to alter segmental motion at adjacent vertebrae, which places additional stress on adjacent discs that may accelerate degeneration.^{1–3} By preserving spinal motion, CDA may reduce degeneration at the adjacent segments compared with ACDF.^{3–8}

The US Food and Drug Administration (FDA) approved the Mobi-C cervical disc (Zimmer Biomet [now ZimVie], Westminster, CO) in 2013 for treatment of 1- or 2-level cervical DDD with radiculopathy and/or myelopathy. Upon approval, the FDA required a postapproval study to collect data out to 7 years. The Mobi-C was shown statistically superior to ACDF in terms of composite measures of overall success through 7 years.^{9–13} The safety and effectiveness have recently been reported out to 10 years in a cohort from the FDA study.¹⁴ The purpose of this postmarket study is to compare 10-year outcomes between CDA and ACDF from a randomized study at 3 centers.

METHODS

Study Design

This was a prospective, randomized study of patients treated with CDA or ACDF at 3 centers. Patients were enrolled in the prospective, randomized multicenter investigational device exemption (IDE) clinical trial (ClinicalTrials.gov registration no. NCT00389597). Institutional review board approval and patient informed consent were obtained at each investigational site. The study was divided into separate arms of 1- and 2-level treatment, conducted in tandem. Enrollment criteria included a diagnosis of DDD with radiculopathy or myeloradiculopathy at either 1 or 2 contiguous levels from C3 to C7, with no prior cervical operations. The details of the study protocol, inclusion and exclusion criteria, and patient characteristics have been reported previously.¹³

Patient Selection

Surgeries occurred between May 2006 and March 2008. The investigational group was treated with 1- or 2-level CDA. The control group received 1- or 2-level ACDF with allograft and anterior cervical plate. Patients were randomized in a 2:1 ratio (CDA:ACDF). Upon completion of the 7-year FDA postapproval study, 3 high-enrolling centers committed to continue

follow-up beyond the 7-year follow-up required by the FDA. These centers collaborated to obtain follow-up at 10 years for consenting CDA and ACDF patients. The patients from the 3 centers accounted for more than 25% of the original IDE cohort.

Study Device

The Mobi-C is a 3-component, mobile-bearing device comprised of an ultra-high-molecular-weight polyethylene mobile insert between 2 titanium plasma-sprayed and hydroxyapatite-coated cobalt-chromium-alloy endplates. The superior endplate incorporates a convex shape to match the natural cervical anatomy, and both the superior and inferior endplates feature low profile, inclined teeth along the lateral edges to provide initial stability. The shape of the device and inclined teeth were designed to facilitate a bone-sparing surgical technique. The device is available in several footprints and a range of heights, including 5 mm, to accommodate individual anatomical requirements. The device allows 5 independent degrees of freedom: 2 translational and 3 rotational (Figure 1).

Outcomes

The outcome measures were defined in the original IDE study and included secondary surgical procedures

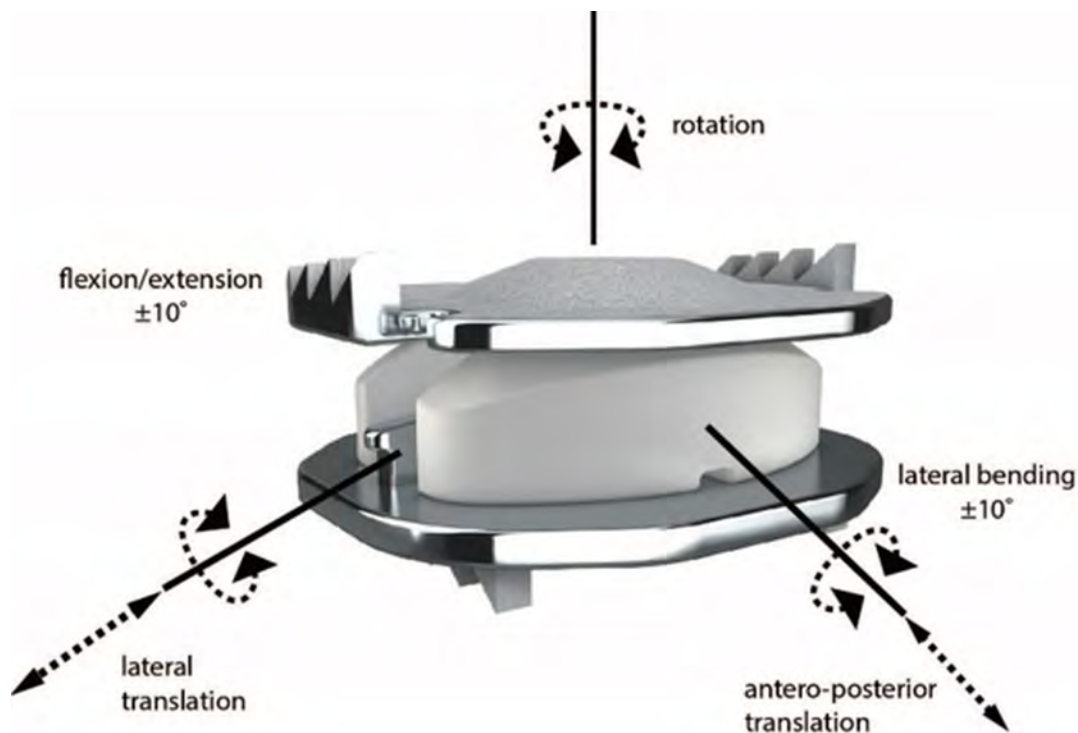


Figure 1. The Mobi-C cervical disc.

(removals, revisions, reoperations, or additional fixation), adverse events (AEs), the Neck Disability Index (NDI), visual analog scale neck and arm pain, short form-12 (SF-12) physical component score (PCS) and mental component score (MCS), patient satisfaction, and neurologic function. The neurologic function was assessed with tests of sensory, reflex, and motor function. Neurologic success was defined as maintained or improved motor, sensory, and reflex assessment compared with preoperative baseline. Radiographic adjacent segment pathology (RASP) was defined with the Kellgren-Lawrence Scale.¹⁵ Grade 3/4 RASP was considered radiographically significant. Independent radiologists (Medical Metrics, Inc., Houston, TX) conducted radiographic evaluations.

Similar to the IDE study, a composite endpoint was used to define clinical success. A patient was considered to have a successful outcome at 10 years if each of the following criteria were met:

- The NDI score improved by at least 15/100 points for a patient with a preoperative NDI score of 30 or greater or improved by at least 50% of a preoperative NDI score of less than 30.
- No subsequent surgical intervention occurred at the index or adjacent level(s).
- No serious treatment-related AEs occurred.
- Neurologic function was not worse than the preoperative function.

Patients with a subsequent surgery or treatment-related AE at any timepoint were carried forward as a failure in the 10-year success endpoint.

Statistical Analysis

All patients and follow-up from 3 sites were included in the analysis. All 1- and 2-level patients were pooled for this analysis due to the low number available at 10 years, especially in the ACDF cohort. The baseline characteristics between the cohort from the 3 centers and the remaining patients from the IDE trial were compared to show that this subset was representative of the original FDA study cohort.

The composite success endpoint was assessed under the hypothesis of noninferiority of CDA vs ACDF using the Farrington-Manning test with a 10% noninferiority margin. Noninferiority was defined using a 95% 1-sided lower confidence bound of -10% for the difference between CDA and ACDF, and superiority was tested using a lower confidence bound of 0%. Repeated measures mixed effects analysis of variance was used to compare postoperative outcomes between CDA and

ACDF patients, as well as to compare 10-year results with preoperative and 7-year outcomes within the CDA and ACDF groups. *P* values and confidence limits were adjusted for multiplicity using a Monte Carlo simulation-based method. Survival function estimates for secondary surgery and device-related AEs were calculated using the Kaplan-Meier method, with the log-rank test to compare survival functions. All patients who were withdrawn or lost to follow-up were censored at their last visit prior to study withdrawal. Categorical proportions were compared using Fisher's exact test for independent samples. Confidence intervals for proportions were calculated with the Clopper-Pearson exact binomial method. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

The sensitivity analysis was performed to investigate the potential impact of dropouts on overall study success and rate of subsequent surgery at 10 years. Each dropout was considered a hypothetical success or failure to investigate the effects of all possible combinations of the values of missing data in the CDA (treatment) vs the ACDF (control) group. The sensitivity analysis was run against all combinations of success and failure to determine the tipping point of the study (ie, the combinations of success and failure among dropouts that would change the study conclusions).

RESULTS

Study Cohort

The original enrollment at 3 sites was 155 patients (105 CDA; 50 ACDF). There were no significant differences in preoperative and operative characteristics between the CDA and ACDF treatment groups (Table 1). The comparison of baseline characteristics between patients from the 3 centers and the remaining patients from the IDE trial found no significant differences in preoperative characteristics between these patients and the original FDA cohort. Outcomes at 7 years for the 3-center cohort were also similar to those reported for the IDE study.

Follow-up was obtained from 107 patients at 10 years, representing 69% (107/155) of all patients enrolled at these sites, and 78.1% (107/137) of patients available after 7 years, after excluding 1 patient who died prior to 10 years (Figure 2). Five patients who did not return for in-person follow-up did not have 10-year radiographs, but patient-reported outcomes (NDI, pain, and SF-12), AEs, and reoperation were collected via phone interview and review of medical records. The longest follow-up was 13.1 years.

Table 1. Preoperative and operative characteristics of CDA and ACDF patients at 3 centers.

Characteristic	CDA (n = 105)	ACDF (n = 50)	P Value ^a
Age, y, mean \pm SD (range)	44.2 \pm 8.0 (28–66)	43.9 \pm 8.2 (27–66)	0.79
Gender, n (%)			
Men	52 (49.5%)	25 (50.0%)	0.96
Women	53 (50.5%)	25 (50.0%)	
BMI, mean \pm SD	27.5 \pm 4.5	27.2 \pm 3.8	0.66
Obese (BMI >30)	30 (28.6%)	14 (28.0%)	0.94
Caucasian	100 (95.2%)	48 (96.0%)	0.83
Preoperative scores, mean \pm SD			
Neck Disability Index	50.7 \pm 13.9	50.9 \pm 14.4	0.92
Neck pain (VAS)	72.1 \pm 20.8	73.1 \pm 19.8	0.77
Left arm pain (VAS)	47.9 \pm 35.1	45.4 \pm 37.3	0.69
Right arm pain (VAS)	41.4 \pm 36.3	36.6 \pm 35.5	0.44
Procedure, n (%)			
1 Level	49 (46.7%)	22 (44.0%)	0.86
2 Level	56 (53.3%)	28 (56.0%)	
Treated segment(s), n (%)			
1 Level			0.27
C3-C4	0 (0.0%)	1 (4.5%)	
C4-C5	1 (2.0%)	1 (4.5%)	
C5-C6	27 (55.1%)	9 (40.9%)	
C6-C7	21 (42.9%)	11 (50.0%)	
2 Level			0.18
C3-C5	0 (0.0%)	1 (3.6%)	
C4-C6	17 (30.4%)	5 (17.9%)	
C5-C7	39 (69.6%)	22 (78.6%)	

Abbreviations: ACDF, anterior cervical discectomy and fusion; BMI, body mass index; CDA, cervical disc arthroplasty; VAS, visual analog scale.

^aComparisons via *t* test for continuous variables. Fisher's exact test for categorical variables.

Composite Success

At 10 years, CDA demonstrated superiority compared with ACDF (Table 2). The rate of success was 62.4% (53/85) in the CDA group and 22.2% (8/36) in the ACDF group, with a difference of 40.1% and a lower 95% confidence bound of 23.9%. Analyzing the individual components of success showed that the primary drivers of CDA superiority were a significantly lower incidence of subsequent surgery and a higher incidence of neurologic success.

Sensitivity Analysis

At 10 years, there were 20 CDA and 14 ACDF dropouts for whom composite success and subsequent surgery were unknown. The sensitivity analysis evaluated all 315 combinations of success and failure. For composite success, the sensitivity analysis supported the study conclusion of superiority of CDA vs ACDF in 93.3% of the scenarios (Figure 3). Therefore, when we consider all possible outcomes among dropouts, we conclude there is only a 6.7% chance of obtaining a different conclusion. The tipping point for study success occurred if at least 79% (11 of 14) of ACDF dropouts were a study success, combined with study failure in

95% (19 of 20) of CDA dropouts. Although CDA was not statistically superior to ACDF in those cases, the observed treatment effect was always positive, and no scenario resulted in the superiority of ACDF over CDA. Under the worst-case scenario (all ACDF dropouts = success; all CDA dropouts = failures), CDA was shown to be noninferior to ADCF (50.5% vs 44%; Δ = 6.5%; P = 0.027).

For subsequent surgery, 81.3% of the scenarios in the sensitivity analysis supported the conclusion of superiority of CDA vs ACDF (Figure 4). Therefore, the chance of obtaining a different conclusion for subsequent surgery is 18.7%. The tipping point for study success occurred if at least 50% of ACDF dropouts were a study success, combined with study failure in 100% of CDA dropouts. In those cases, CDA was not superior to ACDF, but no scenario resulted in superiority of ACDF over CDA.

Safety

After 7 years, 1 CDA patient underwent supplemental fixation at the index level, 9.5 years after surgery. One ACDF patient had nonadjacent fusion 10.6 years after surgery, followed by an adjacent-level fusion 11.7 years after surgery. There were no adjacent-level surgeries reported in CDA patients after 7 years. The cumulative risk of any subsequent surgery at 10 years was 7.2% vs 25.5% (P = 0.001) in CDA vs ACDF (Table 3; Figure 5). The cumulative risk of an adjacent-level surgery was 3.1% vs 20.5% (P = 0.0005) in CDA vs ACDF, respectively (Table 3; Figure 6). All cases of adjacent-level surgery in this series were due to symptomatic adjacent-level disease. The risk of adjacent surgery in the CDA cohort was unchanged after 6 years.

Between 7 and 10 years, 3 treatment-related AEs were reported in 3 CDA patients (subsidence—2; radiculopathy—1). The patient with radiculopathy underwent posterior fusion 9.5 years post-CDA surgery. One patient with subsidence received facet joint injections; the remaining CDA patient did not require an intervention. In the ACDF cohort, 4 AEs related to treatment were reported in 2 patients (kyphosis—1; decreased range of motion—1; diminished reflexes—1; muscle spasms—1), with none requiring an intervention. The cumulative risk of a treatment-related AE at 10 years was 18.6% in CDA vs 32.2% in ACDF (P = 0.024; Table 3).

Adjacent-Segment Pathology

Similar to earlier periods, the progression to grade 3/4 RASP from baseline to 10 years was significantly

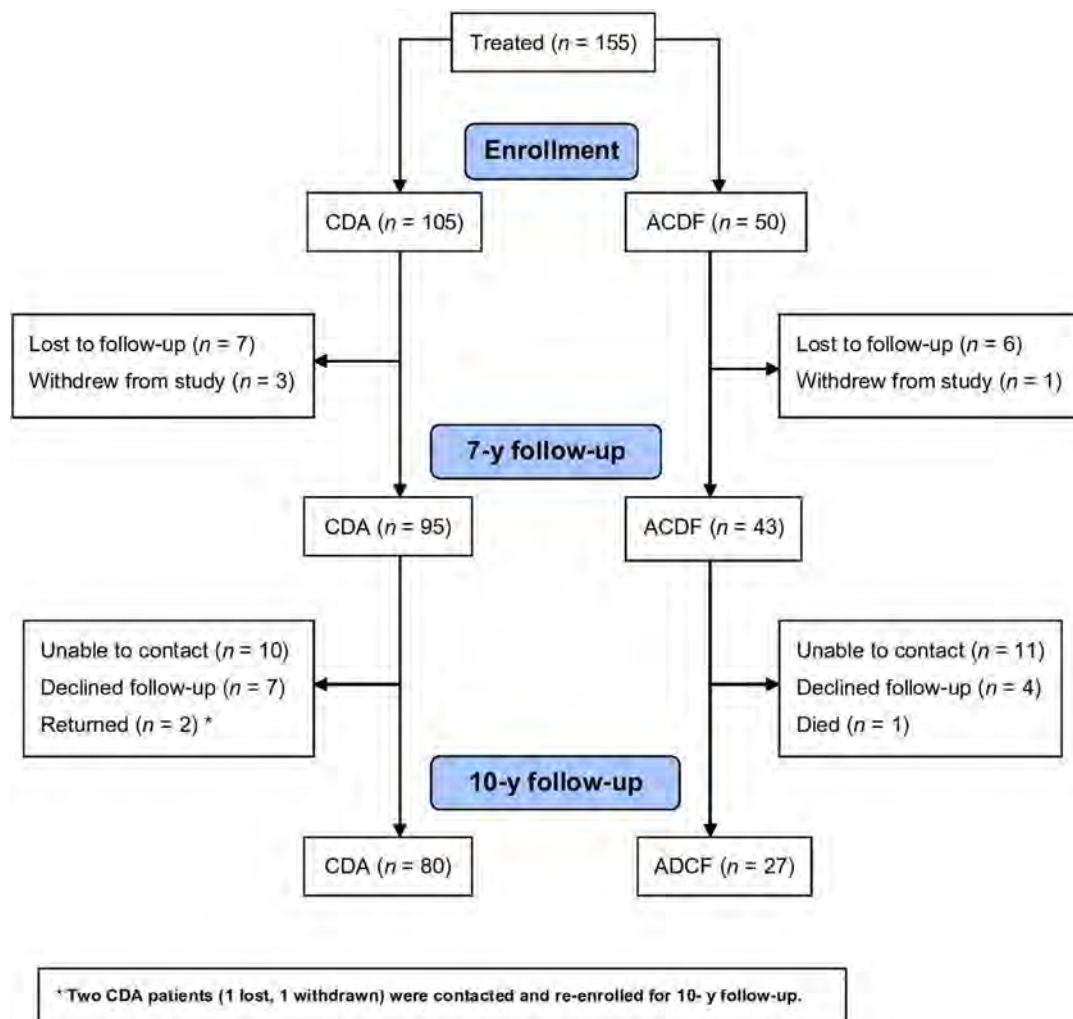


Figure 2. Flow diagram of patient enrollment and follow-up. ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

lower in CDA vs ACDF (12.9% vs 39.3%, respectively; $P = 0.006$; Figure 7).

Clinical Outcomes

CDA and ACDF patients had similar preoperative NDI, pain, and SF-12 scores, and all patient-reported outcomes remained significantly improved

from baseline for both treatments through 10 years ($P < 0.05$). At 10 years, patient-reported outcomes and change from baseline were generally better in CDA patients (Table 4). Specifically, the CDA group had greater improvement in SF-12 PCS than the ACDF group (15.7 vs 9.5; $P = 0.004$) at 10 years. Other differences between CDA and ACDF at 10 years were less

Table 2. Overall success and components of success for CDA and ACDF at 10 years.

Outcome	CDA	ACDF	<i>P</i> Value ^a	Difference
Composite success	62.4% (51.2%, 72.6%)	22.2% (10.1%, 39.2%)	<0.0001	40.1% ^b (23.9%, 56.4%)
Neurologic success	87.8% (78.2%, 94.3%)	55.6% (35.3%, 74.5%)	0.0015	32.3% ^b (17.8%, 46.8%)
Subsequent surgery	8.2% (3.4%, 16.2%)	33.3% (18.6%, 51.0%)	0.0017	25.1% ^b (12.5%, 37.7%)
Treatment-related serious adverse event	2.4% (0.3%, 8.2%)	11.1% (3.1%, 26.1%)	0.06	8.8% ^c (−0.1%, 18.1%)
Neck Disability Index success	84.8% (75.0%, 91.9%)	74.1% (53.7%, 88.9%)	0.25	10.7% ^c (−2.3%, 23.8%)

Abbreviations: ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

Note: Data presented as overall success rate (95% CI).

Significant *P* values indicated in bold.

^aFisher's exact test comparing CDA vs ACDF at 10 y.

^bSuperiority of CDA vs ACDF with 95% lower confidence bound of difference >0%.

^cNoninferiority of CDA vs ACDF with 95% lower confidence bound of difference >−10%.

Number of successes among dropouts in the CDA cohort	20	0.535	0.515	0.495	0.475	0.455	0.435	0.415	0.395	0.375	0.355	0.335	0.315	0.295	0.275	0.255
	19	0.526	0.506	0.486	0.466	0.446	0.426	0.406	0.386	0.366	0.346	0.326	0.306	0.286	0.266	0.246
	18	0.516	0.496	0.476	0.456	0.436	0.416	0.396	0.376	0.356	0.336	0.316	0.296	0.276	0.256	0.236
	17	0.507	0.487	0.467	0.447	0.427	0.407	0.387	0.367	0.347	0.327	0.307	0.287	0.267	0.247	0.227
	16	0.497	0.477	0.457	0.437	0.417	0.397	0.377	0.357	0.337	0.317	0.297	0.277	0.257	0.237	0.217
	15	0.488	0.468	0.448	0.428	0.408	0.388	0.368	0.348	0.328	0.308	0.288	0.268	0.248	0.228	0.208
	14	0.478	0.458	0.438	0.418	0.398	0.378	0.358	0.338	0.318	0.298	0.278	0.258	0.238	0.218	0.198
	13	0.469	0.449	0.429	0.409	0.389	0.369	0.349	0.329	0.309	0.289	0.269	0.249	0.229	0.209	0.189
	12	0.459	0.439	0.419	0.399	0.379	0.359	0.339	0.319	0.299	0.279	0.259	0.239	0.219	0.199	0.179
	11	0.450	0.430	0.410	0.390	0.370	0.350	0.330	0.310	0.290	0.270	0.250	0.230	0.210	0.190	0.170
	10	0.440	0.420	0.400	0.380	0.360	0.340	0.320	0.300	0.280	0.260	0.240	0.220	0.200	0.180	0.160
	9	0.431	0.411	0.391	0.371	0.351	0.331	0.311	0.291	0.271	0.251	0.231	0.211	0.191	0.171	0.151
	8	0.421	0.401	0.381	0.361	0.341	0.321	0.301	0.281	0.261	0.241	0.221	0.201	0.181	0.161	0.141
	7	0.411	0.391	0.371	0.351	0.331	0.311	0.291	0.271	0.251	0.231	0.211	0.191	0.171	0.151	0.131
	6	0.402	0.382	0.362	0.342	0.322	0.302	0.282	0.262	0.242	0.222	0.202	0.182	0.162	0.142	0.122
	5	0.392	0.372	0.352	0.332	0.312	0.292	0.272	0.252	0.232	0.212	0.192	0.172	0.152	0.132	0.112
	4	0.383	0.363	0.343	0.323	0.303	0.283	0.263	0.243	0.223	0.203	0.183	0.163	0.143	0.123	0.103
	3	0.373	0.353	0.333	0.313	0.293	0.273	0.253	0.233	0.213	0.193	0.173	0.153	0.133	0.113	0.093
	2	0.364	0.344	0.324	0.304	0.284	0.264	0.244	0.224	0.204	0.184	0.164	0.144	0.124	0.104	0.084
	1	0.354	0.334	0.314	0.294	0.274	0.254	0.234	0.214	0.194	0.174	0.154	0.134	0.114	0.094	0.074
	0	0.345	0.325	0.305	0.285	0.265	0.245	0.225	0.205	0.185	0.165	0.145	0.125	0.105	0.085	0.065
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number of successes among dropouts in the ACDF cohort																

Figure 3. Tipping point analysis for composite success showing estimated treatment effect (difference between cervical disc arthroplasty [CDA] success and anterior cervical discectomy and fusion [ACDF] success). Axes represent the number of successes that could be observed among dropouts in the CDA group and the ACDF control group. White cells indicate superiority of CDA vs ACDF, and gray indicates noninferiority for each combination of successes. The lower right corner represents the worst-case scenario (all ACDF missing = success; all CDA missing = failures).

Number of successes among dropouts in the CDA cohort	20	0.453	0.433	0.413	0.393	0.373	0.353	0.333	0.313	0.293	0.273	0.253	0.233	0.213	0.193	0.173
	19	0.444	0.424	0.404	0.384	0.364	0.344	0.324	0.304	0.284	0.264	0.244	0.224	0.204	0.184	0.164
	18	0.434	0.414	0.394	0.374	0.354	0.334	0.314	0.294	0.274	0.254	0.234	0.214	0.194	0.174	0.154
	17	0.425	0.405	0.385	0.365	0.345	0.325	0.305	0.285	0.265	0.245	0.225	0.205	0.185	0.165	0.145
	16	0.415	0.395	0.375	0.355	0.335	0.315	0.295	0.275	0.255	0.235	0.215	0.195	0.175	0.155	0.135
	15	0.406	0.386	0.366	0.346	0.326	0.306	0.286	0.266	0.246	0.226	0.206	0.186	0.166	0.146	0.126
	14	0.396	0.376	0.356	0.336	0.316	0.296	0.276	0.256	0.236	0.216	0.196	0.176	0.156	0.136	0.116
	13	0.387	0.367	0.347	0.327	0.307	0.287	0.267	0.247	0.227	0.207	0.187	0.167	0.147	0.127	0.107
	12	0.377	0.357	0.337	0.317	0.297	0.277	0.257	0.237	0.217	0.197	0.177	0.157	0.137	0.117	0.097
	11	0.368	0.348	0.328	0.308	0.288	0.268	0.248	0.228	0.208	0.188	0.168	0.148	0.128	0.108	0.088
	10	0.358	0.338	0.318	0.298	0.278	0.258	0.238	0.218	0.198	0.178	0.158	0.138	0.118	0.098	0.078
	9	0.349	0.329	0.309	0.289	0.269	0.249	0.229	0.209	0.189	0.169	0.149	0.129	0.109	0.089	0.069
	8	0.339	0.319	0.299	0.279	0.259	0.239	0.219	0.199	0.179	0.159	0.139	0.119	0.099	0.079	0.059
	7	0.330	0.310	0.290	0.270	0.250	0.230	0.210	0.190	0.170	0.150	0.130	0.110	0.090	0.070	0.050
	6	0.320	0.300	0.280	0.260	0.240	0.220	0.200	0.180	0.160	0.140	0.120	0.100	0.080	0.060	0.040
	5	0.311	0.291	0.271	0.251	0.231	0.211	0.191	0.171	0.151	0.131	0.111	0.091	0.071	0.051	0.031
	4	0.301	0.281	0.261	0.241	0.221	0.201	0.181	0.161	0.141	0.121	0.101	0.081	0.061	0.041	0.021
	3	0.291	0.271	0.251	0.231	0.211	0.191	0.171	0.151	0.131	0.111	0.091	0.071	0.051	0.031	0.011
	2	0.282	0.262	0.242	0.222	0.202	0.182	0.162	0.142	0.122	0.102	0.082	0.062	0.042	0.022	0.002
	1	0.272	0.252	0.232	0.212	0.192	0.172	0.152	0.132	0.112	0.092	0.072	0.052	0.032	0.012	-0.008
	0	0.263	0.243	0.223	0.203	0.183	0.163	0.143	0.123	0.103	0.083	0.063	0.043	0.023	0.003	-0.017
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Number of successes among dropouts in the ACDF cohort																

Figure 4. Tipping point analysis for subsequent surgery showing estimated treatment effect (difference between cervical disc arthroplasty [CDA] surgery and anterior cervical discectomy and fusion [ACDF] surgery). Axes represent the number of successes that could be observed among dropouts in the CDA group and the ACDF control group. White cells indicate superiority of CDA vs ACDF, and gray cells show where CDA was not superior to ACDF. The lower right corner represents the worst-case scenario (all ACDF missing = no surgery; all CDA missing = surgery).

Table 3. Cumulative risk of subsequent surgery and treatment-related adverse events at 10 y after CDA or ACDF.

Outcome	CDA (N = 105)		ACDF (N = 50)		P Value ^b
	% (n) ^a	95% CI	% (n) ^a	95% CI	
Any subsequent surgery	7.2% (7)	2.7%–13.3%	25.5% (13)	14.6%–40.3%	0.001
Adjacent-level surgery	3.1% (3)	0.6%–7.5%	20.5% (9)	10.0%–33.6%	0.0005
Index-level surgery	5.2% (5)	1.7%–10.6%	10.5% (7)	3.5%–20.7%	0.18
Treatment-related adverse events	18.6% (18)	11.4%–27.1%	32.2% (15)	19.4%–46.5%	0.024

Abbreviations: ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

Significant P values indicated in bold.

^aNumber of patients with event through 10 y.^bLog-rank test comparing survival functions.

than the minimal clinically important difference for NDI (15/100) and pain (10/100) and were not statistically significant. There was a trend toward higher NDI success in CDA, with rates of 85% vs 74.1% at 10 years ($P = 0.25$).

Patient satisfaction was high in both groups (CDA: 89.9% [78/79] vs ACDF: 85.2% [24/27]; $P = 0.50$). However, of those who were satisfied, a higher percentage of CDA patients reported they were “very satisfied” at 10 years (98.7% vs 88.9%; $P = 0.05$). Neurologic success was significantly higher in CDA (88%) vs ACDF (55.6%) at 10 years ($P = 0.004$), due primarily to diminished reflexes observed in ACDF patients at 5 years and beyond.

DISCUSSION

This postmarket study compares the safety and effectiveness of CDA with ACDF at 10 years. CDA continues to show superiority compared with ACDF for symptomatic cervical DDD at 10-year follow-up. The CDA group was statistically superior to ACDF in overall success rate (62.4% vs 22.2%), subsequent surgery

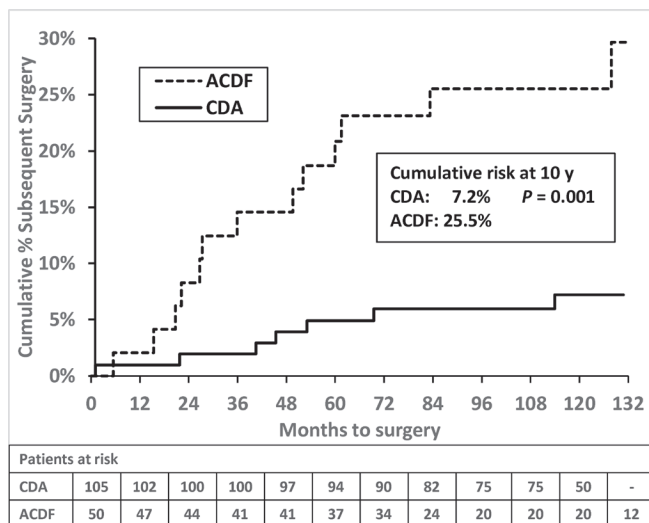
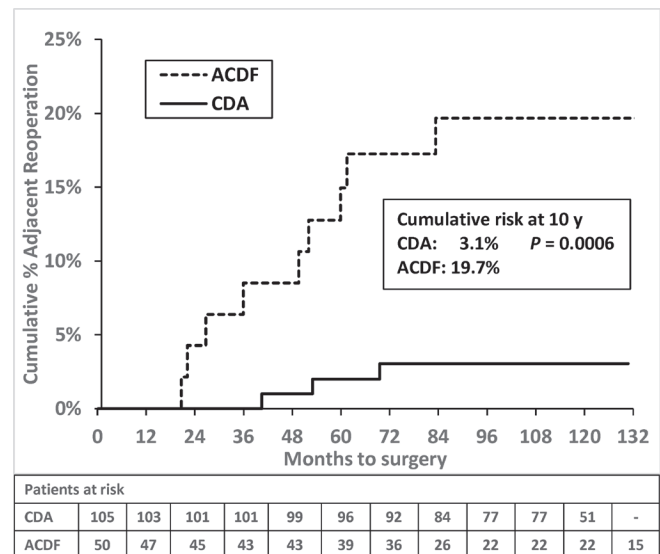
(8.2% vs 33.3%), and neurologic success (87.8% vs 55.6%). At 10 years, CDA was noninferior to ACDF on all measures of clinical success.

Adjacent-Segment Pathology

The rates of secondary surgery at an adjacent level remained significantly lower in CDA patients up to 10 years after treatment. CDA had less progression of RASP from 7 to 10 years than in ACDF. In this study, grade 3/4 RASP occurred in 12.9% of CDA patients (1 and 2 levels combined) compared with 39.3% in ACDF.

One of the major concerns after ACDF is degeneration of the adjacent segments that can lead to reoperation to relieve associated symptoms.¹⁶ CDA has been shown to have lower rates of adjacent-segment degeneration^{13,17–19} and lower rates of subsequent surgery at adjacent levels^{13,20–26} compared with ACDF.

CDA can reduce the incidence of adjacent-segment pathology by preserving segmental motion and natural spinal kinematics. In vitro studies have shown that adjacent-segment motion, intradiscal pressure, and facet

**Figure 5.** Cumulative risk of subsequent surgery after cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF).**Figure 6.** Cumulative risk of adjacent-level subsequent surgery after cervical disc arthroplasty (CDA) and anterior cervical discectomy and fusion (ACDF).

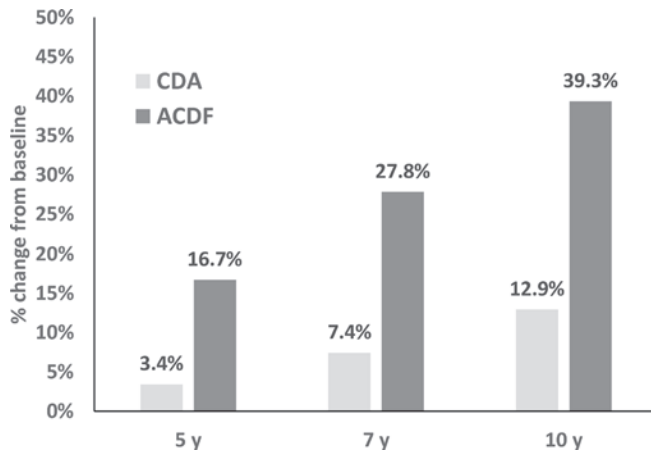


Figure 7. Percent of patients who progressed to grade 3/4 adjacent-segment pathology in cervical disc arthroplasty (CDA) vs anterior cervical discectomy and fusion (ACDF) ($P = 0.006$ at 10 y).

joint loading do not change after CDA.^{2,27} On the other hand, when motion in treated segments is eliminated by fusion, the adjacent discs may experience increased loads and stresses, resulting in hypermobility.^{4,6–8} These kinematic changes may initiate or accelerate degeneration in the untreated adjacent segments.²⁸ The Mobi-C has shown maintenance of motion out to 10 years and minimal progression of RASP after 5 years.¹⁴

Whereas the progression of RASP is a radiographic finding that may not be directly associated with clinical outcomes, other studies have reported adjacent-level subsequent surgery as a proxy for clinically symptomatic adjacent-segment pathology. In this study, the rate of adjacent-level surgery at 10 years was 3.1% in CDA vs 20.5% in ACDF. The rate of adjacent-level surgery for ACDF in this study is consistent with the 2.4% to 2.7% per year reported in the literature.^{29,30} Long-term

studies of CDA have reported adjacent-level surgery occurring in 4.5% to 13.8% of patients, compared with rates of 16% to 24% in ACDF controls.^{31–34} Hilibrand et al⁵ estimated that 25.6% of ACDF patients develop significant adjacent-level disease within 10 years of ACDF; remarkably similar to rates of adjacent-level surgery reported in the current study. Other studies have reported a cumulative incidence of adjacent-level surgery ranging from 21% to 37% at 10 years after ACDF.^{29,35–37} Recent RCTs have identified ACDF as the primary factor contributing to adjacent-segment pathology and adjacent-level surgeries compared with CDA.^{26,30,38}

Several meta-analyses have confirmed that CDA has lower rates of clinical adjacent-segment pathology (CASP) leading to adjacent surgery. Chang et al²⁵ included the data from RCTs for a robust review of 1864 patients treated with CDA and 1572 treated with ACDF. They reported combined CASP of 3.1% (range, 0.0%–7.1%) for CDA and 6.0% (range, 1.0%–11.9%) for ACDF.²⁵ Luo et al showed CASP was 2.6% after CDA vs 6.0% in ACDF, with a significant difference in favor of CDA ($P < 0.0001$; OR = 0.43; 95% CI = 0.29, 0.64).¹⁸ In a separate meta-analysis, Xu et al³⁹ showed CASP was 2.4% after CDA vs 4.5% in ACDF (OR = 0.52; 95% CI = 0.30, 0.87; $P = 0.01$). Most recently, Deng et al performed meta-analysis on 8 RCTs with follow-up of >48 months.⁴⁰ Their analysis included 1334 patients with CDA and 1061 patients treated with ACDF. They reported overall CASP of 3.6% for CDA and 9.5% for ACDF (OR = 0.38; 95% CI = 0.27, 0.53; $P < 0.0001$).

Table 4. Patient-reported outcomes by treatment.

Outcome and Treatment Group	Score, Mean				<i>P</i> Value ^b
	Baseline	7 y	10 y	Δ at 10 y ^a	
Neck Disability Index					
CDA	50.6	19.1	16.2	34.1	0.30
ACDF	50.6	20.8	20.4	30.0	
VAS neck					
CDA	72.1	18.5	12.5	59.4	0.25
ACDF	73.3	25.3	20.3	53.4	
VAS arm					
CDA	69.9	15.0	12.2	56.5	0.13
ACDF	64.4	19.1	16.6	47.4	
SF-12 physical component score					
CDA	33.9	46.6	49.5	15.7	0.004
ACDF	34.3	44.1	43.7	9.5	
SF-12 mental component score					
CDA	43.6	51.1	52.8	9.1	0.44
ACDF	44.1	51.0	51.5	7.2	

Abbreviations: ACDF, anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty; SF-12, short form-12; VAS, visual analog scale.

^aLeast-square means and mean change from baseline to 10 y.

^bComparing mean change at 10 y in CDA vs ACDF. Significant *P* values bolded.

Long-Term Safety and Effectiveness of CDA

Both CDA and ACDF demonstrated sustained improvement of NDI, pain scores, and SF-12 from preoperative to 10 years. CDA and ACDF patients had similar preoperative NDI, pain, and SF-12 scores, and all patient-reported outcomes remained significantly improved from baseline for both treatments through 10 years ($P < 0.05$). The percentage of patients who maintained their neurological function also remained stable.

At 10 years, patient-reported outcomes and change from baseline were generally better in CDA patients. Specifically, the CDA group had greater improvement in SF-12 PCS than the ACDF group (15.7 vs 9.5; $P = 0.004$) at 10 years. Other differences between CDA and ACDF at 10 years were less than the minimal clinically important difference for NDI (15/100) and pain (10/100) and were not statistically significant. These results suggest that CDA continues to be a clinically sound alternative to cervical fusion. The Mobi-C has been compared with ACDF for 1- and 2-level cervical disc disease out to 7 years after surgery in a multicenter, prospective, randomized IDE trial. Postoperative outcomes demonstrate statistically significant improvement in NDI, arm and neck pain, and SF-12 at 24 to 84 months in CDA compared with ACDF, especially after 2-level treatment.⁹⁻¹³

Limitations

The inclusion and exclusion criteria of the IDE trial may be considered a limitation of this study. For example, our study patients had no substantial pathology or degeneration adjacent to the treated levels, and patients with a prior fusion or other spinal surgery were not included. As with all IDE studies of CDA, the purpose of standardized inclusion criteria was to enroll patients without significant conditions that could confound the comparison with ACDF.

This study was based on a subset of the Mobi-C IDE trial; therefore, the patients and results from these sites may not represent the larger IDE trial. The randomization plan was applied independently at each center; therefore, treatment assignment at each center was independent and unbiased. This was verified by comparing the preoperative characteristics between CDA and ACDF, which showed a uniform distribution of patients between treatments at the 3 sites. We also compared baseline characteristics between the 3 centers and the remaining patients from the IDE trial who were not included in this subgroup to show that this subset was representative of the original FDA study cohort. The comparison of baseline characteristics between the 3 centers and the remaining patients from the IDE trial found no significant differences in preoperative characteristics between these patients and the original FDA cohort.

Additionally, the 7-year outcomes in this cohort were consistent with outcomes reported for the entire IDE cohort at 7 years.

The attrition between 7 and 10 years could have affected the outcome of the study. Follow-up at 10 years was not obtained from 32 (23%) patients who were considered eligible for this postmarket study. The rate of attrition was higher in the ACDF control group. Eleven patients were alive and successfully contacted but declined to participate, although some who opted out may have done so because they were doing well and did not want to return for follow-up. However, the sensitivity analysis supported the results of the original analysis in over 93% and 81% of scenarios for study success and subsequent surgery, respectively. Those scenarios, where the study conclusions changed, represent extreme departures from data missing at random. Though plausible, these scenarios are very unlikely. With these considerations, the sensitivity analysis results support the validity of the treatment effect found in the original analysis.

This study was not designed to conclude that the results of our ACDF control group are representative of all ACDF techniques. Like many published RCTs of cervical arthroplasty, this study was undertaken to demonstrate noninferiority and, if appropriate, superiority of the Mobi-C disc when compared with ACDF. Although various ACDF techniques with a variety of graft options exist, studies designed to evaluate new cervical discs for FDA acceptance were required to use a single ACDF control that was an on-label application of current technology and generally accepted as the “gold standard” available at the time the study was designed and enrollment begun, in this case, 2004.

CONCLUSIONS

Ten years after surgery, CDA has significantly lower rates of subsequent surgery and adjacent-segment pathology. Our results through 10 years demonstrate that CDA continues to be a safe and effective surgical alternative to fusion. The significantly lower risk of subsequent surgery after CDA has the potential to greatly reduce the overall burden to the patient and health care system.

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a) Cervical Interbody Fusion is Enhanced by Allogeneic Mesenchymal Precursor Cells in an Ovine Model

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STUDY DESIGN: An experimental study using a sheep cervical spine interbody fusion model.

OBJECTIVES: To compare allogeneic mesenchymal precursor cells combined with hydroxyapatite and tricalcium phosphate (HA/TCP) with HA/TCP alone or iliac crest autograft (AG) for cervical interbody fusion.

SUMMARY OF BACKGROUND DATA: We investigated the effect of mesenchymal precursor cells on cervical fusion because of the shortcomings of using iliac crest (donor site morbidity), bone substitute (poor osteoinductive properties) and bone morphogenic proteins (serious complications).

METHODS: Thirty ewes were divided randomly into four groups of six having C3/4 anterior cervical discectomy and fusion using a Fidji™ cage packed with, AG, HA/TCP, HA/TCP containing 5 million MPCs, and HA/TCP containing 10 million MPCs. MPCs were derived from a single batch of immuno-selected and culture-expanded MPCs isolated from bone

marrow of out-bred sheep. The fifth group were non-operated controls. Safety, fusion parameters and biomechanics were assessed.

RESULTS: No cell related adverse events were observed. No significant differences were found between the 5 or 10 million MPC groups. Evaluation of fusion by CT scan at 3 months showed that 9/12 (75%) MPC-treated animals had continuous bony bridging compared with only 1/6 AG and 2/6 HA/TCP ($p = 0.019$ and $p = 0.044$ respectively). By quantitative CT, density of new bone in MPC-treated animals was 121% higher than in HA/TCP ($p = 0.017$) and 128% higher than in AG ($p < 0.0001$). Functional radiology at 3 months revealed that MPC-treated animals had significantly reduced macro-motion at C3/4 compared with AG and HA/TCP groups combined ($p=0.007$).

CONCLUSION: Implantation of allogeneic MPCs when combined with HA/TCP and an interbody spacer facilitates new bone formation following discectomy without any cell related complications. The earlier and dense new bone formation observed with MPCs relative to autograft and HA/TCP alone suggest that this approach may offer therapeutic benefit.

KEY WORDS: Cervical Spine, Stem Cells, Mesenchymal Stem Cells, Interbody Fusion, Osteoinductive graft, Animal Model, Sheep

MINI ABSTRACT

This preclinical study demonstrates that anterior cervical implantation of allogeneic Mesenchymal Precursor Cells when combined with hydroxyapatite and tricalcium phosphate (HA/TCP) in an interbody spacer, safely and effectively facilitate new bone formation following discectomy in an ovine model relative to autograft or HA/TCP alone. This approach may offer a clinical benefit in selected patients.

KEY POINTS:

- Mesenchymal Precursor Cells (MPCs) are a pure population of stem cells derived by

monoclonal antibody immunoselection.

- Together with a tricalcium phosphate and hydroxyapatite carrier MPCs enhance cervical fusion.
- MPCs may have a therapeutic role for certain patients requiring cervical interbody fusion.

INTRODUCTION

Anterior cervical discectomy and fusion accounts for up to forty percent of all spinal fusion procedures and is the most common surgical approach employed for treating cervical spondylosis or discopathies^{1,2}. While iliac crest autograft bone has traditionally been the gold standard source material for cervical fusion, it is associated with the potential for donor site morbidity³. Alternatives, such as bone graft substitutes^{4,5} and allograft, have limited osteo-inductive properties and, whilst they eliminate donor site morbidity, they are considered to result in fusion rates inferior to autograft^{6,7}. Use of allograft has also been associated with resorption, infection and collapse⁷⁻⁹. Bone substitutes are osteoconductive as they provide a matrix into which local cells, including endogenous mesenchymal stem cells (MSC), blood borne cells and osteoblasts can engraft and produce new bone. Levels and bioactivity of endogenous MSCs decline with age, an issue that can reduce bone fusion¹⁰. Multilevel surgery, rheumatoid arthritis¹¹, smoking^{12,13} the use of anti-inflammatory medications¹⁴ can all independently decrease fusion rates. Non union or pseudoarthrosis following anterior cervical discectomy generally results in recurrent radiculopathy and neck pain which may require reoperation¹⁵. Recombinant human bone morphogenetic proteins (rhBMPs) have been used as osteo-inductive agents aimed at increasing cervical interbody fusion rates, but have been reported to result in life threatening complications, including airway and neurological compression¹⁶. Allogeneic mesenchymal precursor stem cells (MPCs) have recently been shown to increase bone fusion rates in clinical¹⁷ and pre-clinical indications^{18,19}. In the present

study we evaluated the capacity of allogeneic MPCs to promote fusion in the cervical interbody space in an ovine model.

METHODS

Study Design

Thirty, two-year-old, Boarder-Leicester/Merino ewes were divided randomly into five groups of 6 animals. Four groups were subjected to C3/4 anterior cervical discectomy and prepared for fusion with a Fidji™ interbody cage (Abbott Spine, Austin, USA). The C3/4 segment was used due to its similarities to the human cervical spine²⁰. The interbody cage was packed with either: (A) Iliac crest autograft (AG) alone; (B) Hydroxyapatite-tricalcium phosphate, containing 15% hydroxapatite and 85% tricalcium phosphate, (HA/TCP, Mastergraft™ Granules, MG, Medtronic, Minneapolis, USA) alone; (C) HA/TCP containing 5 million MPCs group; (D) HA/TCP containing 10 million MPCs group. The fifth group were aged match non-operated controls.

Mesenchymal Precursor Cells

Allogeneic ovine MPCs (Mesoblast Limited, Melbourne, Australia) were isolated from bone marrow of out bred sheep using immunoselection with monoclonal antibodies²¹ to STRO-3+ and manufactured by Lonza Incorporated (Walkersville, MD, USA) under good manufacturing practice (GMP) guidelines. The MPCs were derived from a single batch and culture-expanded to passage 4. The MPC surface marker characteristics have been previously reported²².

The cells were frozen and maintained in the vapour phase of a liquid nitrogen tank until thawed and used within 30 minutes. Cellular viability was greater than 85% using trypan blue exclusion.

Interbody Cage and Carrier

The interbody cage (7.7mm x 12mm x 15mm) was made from polyetheretherketone (PEEK). It was packed with iliac crest autograft cancellous bone in the AG control group (Group A). The HA/TCP carrier was mixed with autologous blood and then packed into the cage in the HA/TCP alone group (Group B). In the cell treated groups, the MPCs were added to the carrier, which was already mixed with autologous blood and packed into the cage (Groups C and D). The MPCs then soaked into the granules avoiding spillage (see figure 1).

Surgical Technique and Post Operative Care

All procedures were carried out with institutional ethics approval (School of Biomedical Sciences, Monash University). Animals were fasted 12 – 24 hours before surgery and were allowed water ad libitum. Sheep were anaesthetised by intravenous injection of Thiopentone 20mg/kg and anaesthesia maintained by Isoflurane (1-3%) inhalation and were positioned supine. Local anaesthetic (0.5% Bupivacaine with 1:200,000 adrenaline) was injected prior to a right anterolateral approach thorough a longitudinal neck incision. The longus coli muscle was elevated bilaterally with diathermy and the position of C3/4 level was confirmed with fluoroscopy. Distraction was achieved with 16mm Caspar pins followed by a total discectomy and removal of the cartilaginous end plates with a high-speed drill to reveal bleeding bone. The posterior longitudinal ligament was opened until the dura was visualised to directly simulate the clinical procedure and to investigate any effects of the MPCs around the neural elements. In sheep receiving autograft, the left iliac crest cortical bone was elevated and cancellous bone curetted and packed into the cage. All cages were inserted and countersunk by approximately 3mm. The longus colli muscle was then approximated by suture, followed by layered closure and subcuticular suture to skin²³.

A Fentanyl Patch was administered postoperatively. Following extubation, the sheep were

transferred to a metabolic cage for observation. After 3 days, the sheep were transferred to open pastures, for the duration of the study where regular observations were made. The sheep were allowed to graze ad-libitum and supplemented with Lucerne chaff. Clinical pathology was performed on Day 0, 1 and 3 months following surgery for standard haematological, comprehensive biochemical and coagulation assays.

Radiographic Analysis

Fusion was assessed by plain and functional radiography, multislice thin cut (0.6mm) CT and quantitative CT. Fusion was defined by continuous bridging of trabecular bone and the absence of radiolucent lines at 3 months on CT^{24,25}. Continuous bridging of trabecular bone was further subdivided into less than or more than 30 percent of the interbody cage area as assessed by three blinded observers using a semi-quantitative score (see table 1 and figure 2). All animals had plain lateral and selected antero-posterior digital radiographs (Radlink, Atomscope HF 200A, Redondo Beach, USA) taken of the cervical spine preoperatively, within 24 hours following surgery and at 1, 2 and 3 months postoperatively. This was performed under sedation (using metomidine (0.025mg/kg intravenously) and reversal using atipamezole (0.125mg/kg intravenously).

Functional radiography was conducted by the method of Kandziora²⁰. After sacrifice the superficial musculature of the explanted fresh spine was removed, carefully sparing all ligaments. T1 was rigidly fixated and a 60-Newton load was applied through C1. Lateral flexion and extension radiographs were taken and the Intervertebral Angle (IVA) and Lordosis Angle (LA) measured²⁰ (see figure 3) and calculated as the difference between flexion and extension by three blinded assessments.

Mutliplanar images were acquired with 0.6mm collimation on a 64-slice-scanner (Siemens

Sensation-64) and reconstructed in the sagittal, axial and coronal planes. Fusion was assessed for evidence of bridging of trabecular bone as described above. Quantitative CT was performed based on the methods of Kandziora^{26,27} and Burkuss²⁴. Specifically, the coronal slice 3.6mm (6 slices) anterior to the cage's posterior radiolucent marker was identified to ensure that an identical location was analysed for each sample. A standardised elliptical Region of Interest (ROI), with an area of 183mm², was selected at this point (see figure 4). The ROI was used to measure the Bone Mineral Density (BMD) of the callus formation in Hounsfield Units. To account for the BMD contribution from the HA/TCP or autograft implanted within the cage, these BMD values were ascertained from control animals and subtracted from the mean BMD to give the BMD of the callus formation alone, referred to as Bone Callus Density (BCD). The control animals were implanted with either autograft alone or HA/TCP alone and sacrificed at one week to allow time for artefacts such as intra-operative air to be reabsorbed but at a time-point before fusion would occur, thus establishing the background density of the autograft and HA/TCP alone, respectively.

Biomechanical Analysis

Biomechanical testing was performed in a similar manner to the non-constrained method described by Gal²⁸. As we have previously described²⁹, pure bending moments were applied to the cervical spine using a custom made rig. Four degrees of movement, namely flexion, extension and left and right lateral bending, were tested at incremental forces of 0.75 Nm to a maximum of 12 Nm after a 15 Nm preload.

Coloured markers, placed into the corpora of C1 to C7 inclusively, were detected with bi-planar digital photography. A computerized motion analysis system (Track Eye Motion Analysis 3.0 (TEMA), Qualysis Inc) was used to track and measure marker positions across the total range of motion. Load-displacement curves were generated to determine stiffness

of the C3/4 segments for each degree of movement. Total displacement of the C3/4 joint was calculated from these curves.

Post Mortem Analysis

Clinical veterinarians performed comprehensive autopsies in a blinded fashion. Samples from all organs and tissues from the peri-surgical site were reviewed by a blinded, board certified veterinary pathologist.

Histomorphological, Histomorphometric and Fluorochrome Analysis

Fluorochromes, Calcein Green 10 mg/kg, Oxytetracycline 50 mg/kg and Alizarin Complexone 30 mg/kg, were administered intravenously at 3, 6, and 9 weeks, respectively. Undecalcified bone histology was performed as previously described³⁰. Following sacrifice, the C3/4 segment was excised and fixed in 10% normal buffered formalin, followed by dehydration in ascending concentrations of ethanol under agitation. The blocks were cleared in butanol prior to embedding in glycolmethacrylate (Technovit 7100, Kulzer, Wehrheim, Germany) using a slow embedding and hardening protocol.

For fluorochrome analysis, the mid sagittal section, was ground to approximately 40µm thickness, using a diamond blade Macrotome (MR Limited, Cambridge, United Kingdom). For light microscopy, the 10 µm sections were cut with a sledge microtome (Leitz, Wetzlar, Germany). Histological sections were stained with Haematoxylin and Eosin, Safranin-O/lightgreen, Von Kossa, Alcian Blue, and Masson-Goldner the later being used for histomorphometric analysis (figure 10). Masson Goldner's Trichrome staining was found to be superior to Von Kossa for this application as it allowed differentiation of new bone from the ceramic which is also stained by the Von Kossa dyes.

Slides were scanned with the Olympus dot slide System (with BX51 Microscope), at x2 magnification for each fluorescent label, using U-MNIBA3, U-WIG3, U-MWU2 filters and a Peltier-cooled high sensitivity camera, at consistent exposure. The images were then uploaded into the Metamorph quantitative analysis software program (version 7.6, Molecular Devices, MDS Inc. California, USA) and the area within the cage marked out on the program. The intensity of each fluorescent label within the cage was measured and expressed as intensity per unit area (square microns). This gave a quantitative assessment of the amount of bone deposition at each time point.

A certified veterinary pathologist performed a semi-quantitative analysis of the histological sections in a blinded fashion. A score, using the criteria of Zdeblick³¹ to assess fusion was assigned separately to the Cage – Vertebral Interface (CVI) and the tissue inside the Cage (CI) using the system: empty (score 0), fibrous tissue (score 1) and bone (score 2). Four points indicate a successful fusion and three points represents a developing fusion.

Histomorphometric analysis was performed using quantitative image analysis for percentage of osteoid formation relative to mineralised bone within the cage area. This was conducted on the midsagittal slice stained with Masson-Goldner in a blinded fashion. Consistent inclusive threshold mapping was then used to measure the threshold percentage within the total cage area containing red staining regions representing osteoid volume (OV), and green staining regions representing mineralised bone volume (Md.V), respectively³²

Statistical Analysis

Comparison of non-parametric data was evaluated by the Kruskal Wallis test on the median values followed by Dunn's Multiple Comparison test, where significant differences were

observed. Parametric data were analysed using one-way Anova followed by Dunnett's Multiple Comparison test where significant differences were observed. The two-tailed Student's t test was used for comparison of parametric data and the Fisher's exact test was used for contingency data when comparing cell treated animals with controls. Prism 5.0 (Graph Pad Software) was used for analysis. Inter-observer reliability was assessed using the Kappa score calculated by a custom made algorithm in Excel (2008, Microsoft Corporation, California, USA) based on the method of Landis and Koch³³. Values were expressed as means and range unless otherwise stated. Graphs show means with standard deviation. A p value of < 0.05 was considered statistically significant.

RESULTS:

Adverse Events

No procedural or cell related adverse events were observed during the study or at post mortem. One ewe developed pneumonia and hypoproteinaemia that resolved under close veterinary treatment. Two ewes, both from the autograft group, lost significant weight during the study period. Veterinary assessment, clinical pathology, gross-pathological and histo-pathological analysis showed no differences between groups.

All outcomes for low and high dose MPC treated ewes (Groups C & D) were not significantly different and were subsequently treated as a single group.

Radiographic Results

The three blinded observers, overall, had inter-observer reliability with Kappa scores ranging from 0.59 - 0.87 being moderate to almost perfect according to the classification of Landis and Koch³³. A consistent observation by all observers was that a score of 3 was never awarded to a non-cell treated animal. By CT scan at 3 months, 9/12 (75%) MPC-treated animals had

continuous bony bridging compared with only 1/6 AG and 2/6 HA/TCP ($p=0.019$ and $p=0.043$ respectively) (see figures 5 and 9). This was confirmed by objective quantitative CT revealing that cell treated animals had significantly higher BCD compared with HA/TCP ($p < 0.017$) and Autograft ($p < 0.0001$) (see figure 6, table 2).

Functional radiography scores obtained for intervertebral angle (IVA) had an inter-observer discrepancy of less than 1 degree, whereas the scores obtained for Lordosis angle (IVA) had an inter-observer discrepancy of 2.8 degrees. There was a reduction in the intervertebral angle in all operated groups compared with non-operated controls ($p < 0.0001$). Cell treated animals had a significant reduction in IVA compared with HA/TCP ($p < 0.001$) and Autograft ($p < 0.012$) treated animals (see figure 7 and table 3). Lordosis angle was not significantly reduced in operated animals compared with non-operated controls. Cell treated animals however, had a significantly reduced LA compared with Autograft ($p < 0.05$) but not compared with HA/TCP ($p < 0.08$).

There was no radiological evidence of ectopic bone formation posteriorly around the spinal canal or at the neural exit foramina in any animals. In controls that received HA/TCP alone, bone callus formation was noted at the anterior of the interbody space at a mean maximal distance of 6.67mm anterior to the cage. Similar reactive bone formation was seen in all of the cell treated groups at a mean maximal distance of 5.94 mm anterior to the cage (see table 4). There was no significant difference in the maximal distance of new bone formation anterior to the cage between any of the groups. There was no evidence of calcification within the muscles or ligaments anterior to the spine.

Biomechanical Results

Significantly more stiffness at the C3/4 level was observed in operated groups compared

with non-operated controls in flexion ($p < 0.015$), however this did not achieve significance in extension or in lateral bending. No significant difference between operated groups was observed in any of the four degrees of motion.

Histological Results

There was no evidence of inflammatory or neoplastic changes in any specimen within the fusion area as reviewed by the Veterinary Pathologist. The semi quantitative histological scoring system revealed that 11 out of 12 (92%) cell treated animals had either developing or complete fusion as compared to 3 out of 6 (50%) treated with HA/TCP alone ($p = 0.02$) and 1 out of 6 (17%) Autograft animals ($p = 0.0007$). Significantly however, the percentage of cell treated animals with complete fusion was 5/12 (42%) compared with 0/6 in either control group ($p = 0.03$). (see table 5) This finding was supported by the histomorphometric analysis which demonstrated significantly more mineralised bone in the cell treated groups versus HA/TCP ($p < 0.008$) and Autograft ($p < 0.0001$) (see figures 8 and 11).

At three weeks postoperatively, the fluorochrome showed more prominent deposition of mineralised bone in cell treated groups compared with Autograft ($p < 0.004$) and HA/TCP ($p < 0.03$). While there were no significant differences between the groups at 6 weeks, by 9 weeks significant differences were observed for the cell treated groups versus Autograft ($p < 0.02$) and a trend observed versus HA/TCP ($p < 0.06$).

DISCUSSION:

These results show that anterior cervical implantation of allogeneic MPCs together with HA/TCP and an interbody spacer safely and effectively facilitate new bone formation following discectomy. Significantly, these MPC mediated osteogenic activities were not accompanied by cell related adverse events.

The bone formation seen anterior to the cage was similar to that shown in previous preclinical studies^{26,31,34}. It has been suggested that the countersinking of the cages results in exposed reamed bone lacking cartilaginous endplates which acts as a source for new bone formation³¹. In the current study, the cages were countersunk by approximately 3mm and the thick periosteum in sheep, along with significant neck mobility, may act as a potent osteogenic stimulus. As this occurred equally in both control and cell treated animals, we postulate that this is a phenomenon related to the animal model or procedure and was not specifically related to the use of MPCs.

The multiple modalities of assessment used in this study showed that MPCs resulted in increased fusion compared to controls representing the current standard of care. It has been said that the ideal graft should be osteogenic, osteoconductive, and osteoinductive, as well as mechanically stable and disease free^{10,35}. Autograft can fulfil these criteria but has the potential for donor site morbidity, as well as prolonged operation time and increased blood loss^{3,35}. Allograft has the potential for collapse and, like autograft, can undergo resorption^{7,9} which does not occur with carriers such as tricalcium phosphate and hydroxyapatite³⁶. Currently, it is unclear from the literature if these osteoconductive carriers result in fusions rates equivalent to autograft³⁷⁻³⁹. Recombinant bone morphogenetic proteins have been used as an additive osteoinductive agent to promote fusion^{40,41}. There are, however, reports of adverse effects of their use in the cervical spine^{7,16,41,42}. Biologically there is an interplay between the 14 naturally occurring BMPs involved in osteogenesis⁴³ and MPCs secrete many of these growth factors (Zannettino personal communication). This paracrine effect of MPCs, in addition to a direct effect of osteogenic differentiation at the fusion site, could account for the beneficial effects mediated by the MPCs in the current study⁴⁴. In combination with the HA/TCP, MPCs are likely osteogenic, osteoconductive and osteoinductive.

Mesenchymal stem cells have been defined by the International Society of Cellular Therapy by their characteristic plastic adherence, fibroblastic morphology and by cell marker expression of CD105, CD73, CD90 and lack of lacking expression of CD45, CD34, CD14, CD11b, CD79a, CD19, HLA-DR⁴⁵. It should be emphasised that the term MSCs refers to a heterogeneous population of cells with variable characteristics^{46 47,48}. The issue of heterogeneity, in cell characterisation and differentiation, becomes significant if these cells are to be used clinically⁴⁹.

The stromal stem cells used in this study have been designated as Mesenchymal Precursor Cells (MPCs) which are a purified monoclonal population of cells derived by immunoselection⁵⁰. These MPC have a greater potential for differentiation into the tissues of the mesenchymal lineage and are more potent with respect to ability for self-renewal⁵¹. The homogeneity and low immunogenicity of the MPCs make them an attractive prospect for clinical use in spinal surgery. They exhibit low levels of cell surface markers such as the MHC class and lack surface expression of immune co-stimulatory molecules⁵². MPCs also lack the ability to induce an allogeneic Mixed Lymphocyte Reaction (MLR)^{53,54} and secrete multiple anti-inflammatory and immunosuppressive cytokines, e.g. IL-10⁵³. These anti-inflammatory properties possibly have a beneficial effect on radiculopathy or myelopathy, which are the common underlying problems necessitating cervical fusion. The potential beneficial properties of MPCs reported in this animal study require evaluation in a human clinical setting.

Conclusion

The more robust bone formation observed with MPCs, relative to autograft and HA/TCP bone substitute in this study suggest that this biological approach may offer a therapeutic benefit when rapid fusion of the cervical interbody space is indicated. This would obviate the donor

site morbidity associated with autograft harvest and the potential life-threatening complications associated with the use of bone morphogenetic proteins. The potential mechanisms by which MPC mediated spinal fusion could include promotion of osteoblast differentiation and their secretion of trophic factors, such as multiple BMPs and other growth factors, which are known to up-regulate osteogenesis.

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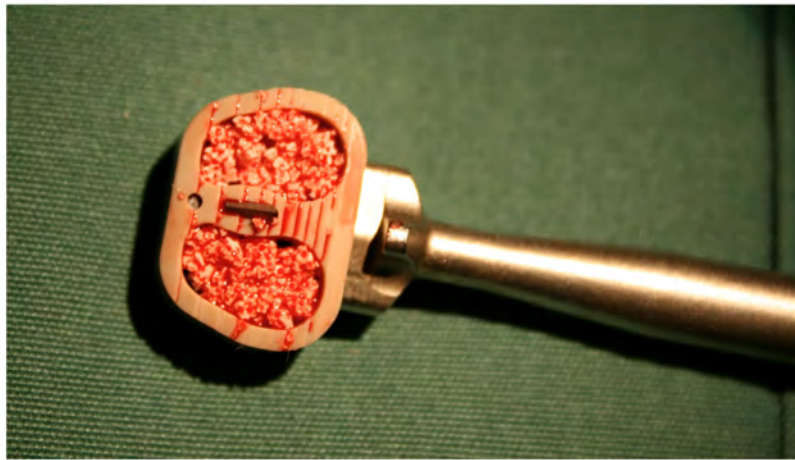


Figure 1. Fidji™ cervical PEEK interbody cage packed with Mastergraft™ granules and Mesenchymal Precursor Cells

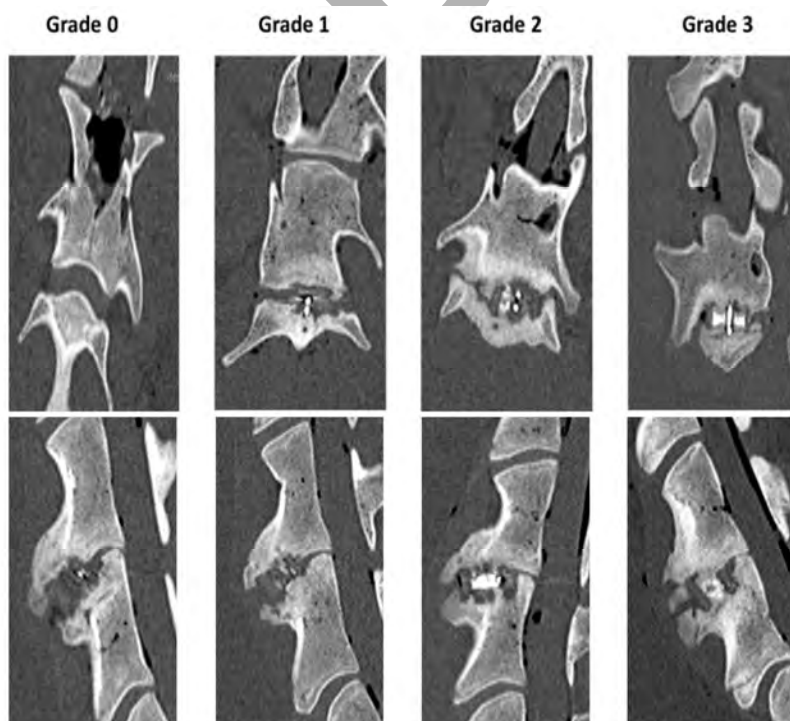


Figure 2. Computed Tomography, in the coronal plane above and sagittal plane below, giving an example of each scoring grade see table 1.



Figure 3. Functional radiography demonstrating the measurement of the Intervertebral and Lordosis angles in flexion and extension



Figure 4. Quantitative computed tomography in the coronal plane, showing the region of interest (ROI) measuring bone mineral density (BMD)

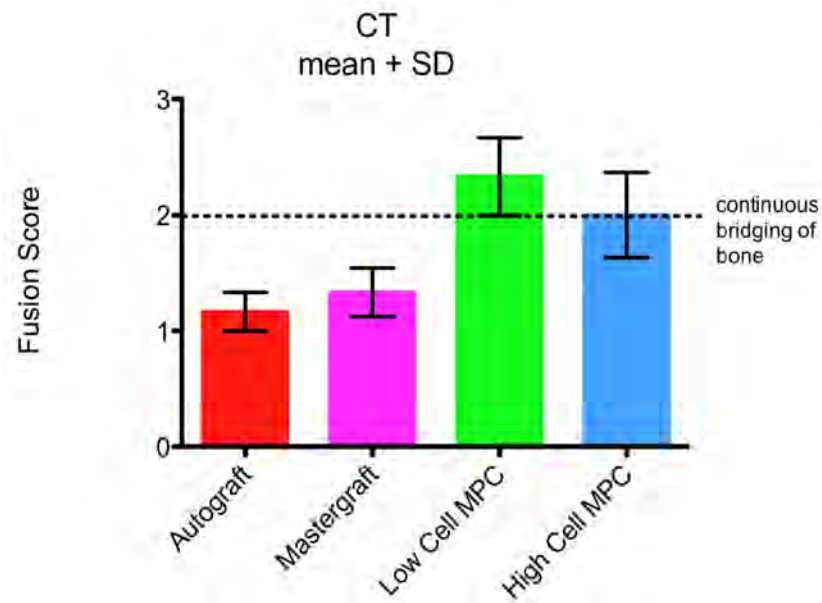


Figure 5. Graph of Computed Tomography (CT) results at 3 months

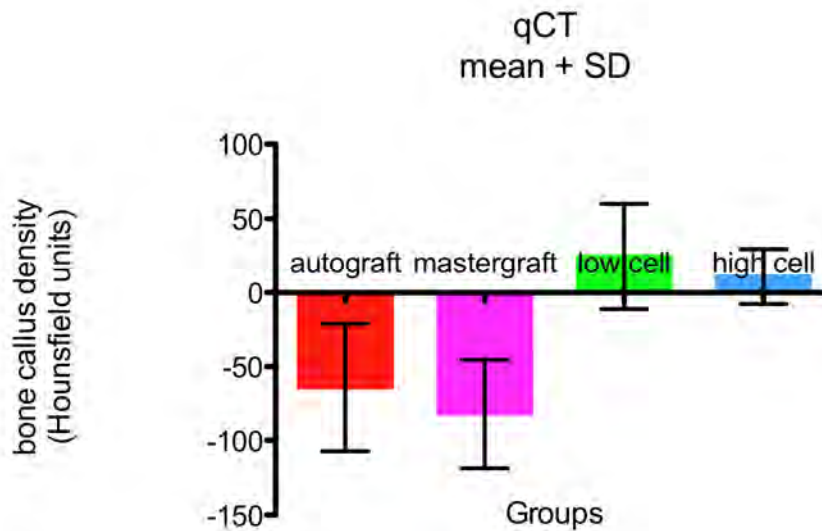


Figure 6: Graph of quantitative Computed Tomography (qCT) results at 3 months

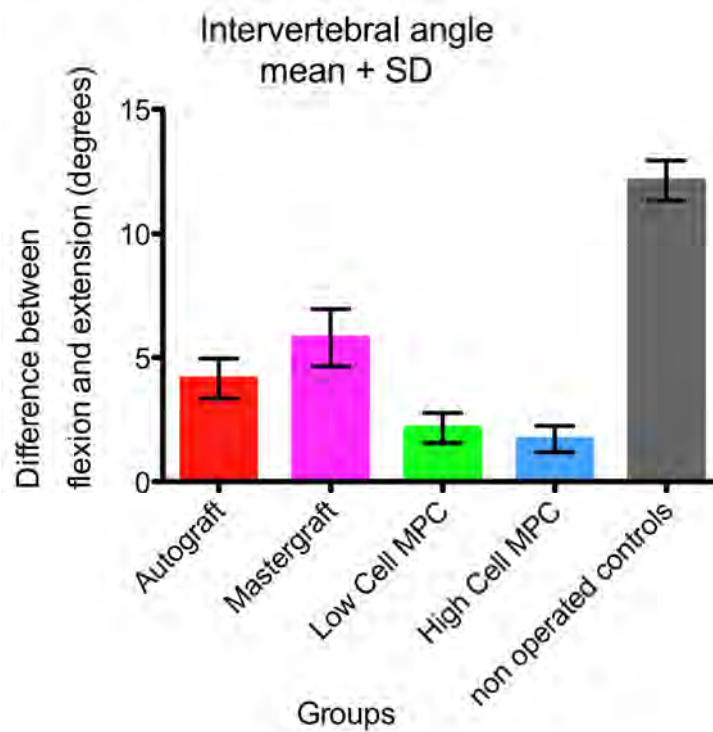


Figure 7: Difference between flexion and extension of Intervertebral angle (degrees)

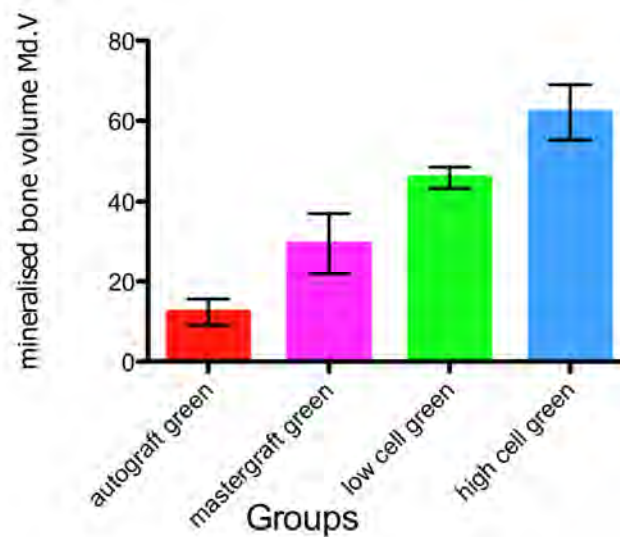


Figure 8: Graph of histomorphometric results of mineralized bone volume within the cage on mid sagittal section stained with Mason Goldner's Trichrome

Table 1: Scoring system for computed tomography evidence of fusion

Grade	Description
Grade 0	No new bone formation
Grade 1	New bone formation but not continuous between C3 and C4 (clef of discontinuity)
Grade 2	Continuous bridging new bone but comprises less than 30% of fusion area
Grade 3	Continuous bridging new bone formation of more than 30% of fusion area

Table 2: Quantitative CT results mean Hounsfield units (range)

Group	Autograft	Mastergraft	Low cell	High cell
Bone Mineral Density (BMD)	591.8 (459 to 704)	758.2 (621to 882)	864.5 (801 to 1032)	851.0 (784 to 917)
Control BMD	656	840	840	840
Bone Callus Density	-64.17 (-197 to 47)	-81.83 (-219 to 42)	24.50 (-39 to 192)	11.00 (-56 to 77)

Table 3: Functional radiography at 3 months. Difference between flexion and extension in degrees. Mean (range)

Group	Autograft	Mastergraft	Low cell	High cell	Non operated control
IVA	4.16 (2.71 to 8.09)	5.79 (2.84 to 10.6)	2.17 (0.54 to 4.92)	1.71 (0.56 to 3.99)	12.14 (10.10 to 15.17)
LA	6.83 (2.45 to 11.99)	5.78 (2.01 to 8.48)	4.23 (2.04 to 5.50)	4.15 (2.58 to 5.38)	7.248 (4.42 to 9.25)

IVA= Intervertebral Angle; LA= Lordosis Angle

Table 4: Mean of maximal bone distance anterior to the cage millimetres (range)

Group	Autograft	Mastergraft	Low cell	High cell
Bone Anterior to the cage	6.11 (4.79 to 6.7)	6.67 (3.94 to 8.70)	4.90 (2.53 to 8.16)	5.94 (2.74 to 8.76)

Table 5: Histopathology results, number with developing or complete fusion based on Zdeblick⁵³ scoring system

Group	Autograft (n=6)	Mastergraft (n=6)	Low Cell (n=6)	High Cell (n=6)
Developing fusion	1	3	3	3
Complete fusion	0	0	2	3



ROI-C® Cervical Cage with VerteBRIDGE® Plating : Clinical and Radiological Outcomes

LDR Medical part of the ZIMMER BIOMET Group
Clinical Affairs Department - Europe



ROI-C® Cleared Indications for Use

The LDR Medical ROI-C® Cervical Cage System is indicated for use in skeletally mature patients to perform a cervical arthrodesis (limited to three levels), in the context of disk(s) treatment Between C2 and T1 vertebra with intractable symptomatic cervical disc disease (SCDD). SDDD is defined as radiculopathy and/or myeloradiculopathy (neck pain, arm pain, and/or a functional neurological deficit in a specific nerve root situated between C2 and T1 vertebra), and refractory to nonoperative treatment conducted during at least six weeks. Herniated nucleus pulposus and/or Discarthrosis should be confirmed by imaging (CT, MRI, or X-rays). The ROI-C® cage is implanted via an open anterior approach following partial discectomy. Following the implantation of the ROI-C® cage, and in order to ensure its stability in the intervertebral space, the ROI-C® cage have to be used with its ROI-C® anchoring plate (VerteBRIDGE®) so as to fix the cage on the two proximal vertebral plates. Note: The ROI-C® Spinal System Surgical Techniques should be followed carefully. These documents are distributed by LDR Medical.

Key Takeaways

- In a multi-center, prospective study of 90 ROI-C patients, fusion rate was 92.2%.
- The follow-up rate at one year was 80%.
- NDI, Vas arm and neck pain and SF-36 scores were improved.
- Disc space height and curvature were restored.

Introduction

Anterior cervical discectomy and fusion (ACDF) can be a therapeutic option for cervical degenerative disc disease (DDD) in order to achieve decompression of neural structures, maintain disc space height and provide long-term stabilization of index level. Supplementary fixation using anterior cervical plate may be added to increase cage stability and stiffness of the cervical segment, thus improving fusion rates. However, this system requires some further handling and has a significant spinal congestion.

There are several options for surgeons when performing an ACDF procedure including use of allograft bone and anterior plating, PEEK cages with anterior plating, and stand-alone interbody fusion devices. The ROI-C cervical cage with VerteBRIDGE plating is designed to be a stand-alone interbody fusion device that requires no external plates anterior to the bone and no posterior fixation.

This study assessed clinical and radiological performances of the ROI-C cervical interbody cage with integrated fixation system.

Study Design

In this prospective study, seven centers treated 90 patients for degenerative disc disease and/or moderate intervertebral instability. All subjects were treated with the ROI-C device. Each patient was evaluated pre-operatively, at 2, 6, and 12 months. Fusion was evaluated from CT-images by independent lab at 1 year. VAS for neck and arm pain, NDI and SF-36 quality of life scales were determined via self-administered questionnaire. All clinical complications were reported. Radiological outcomes included functional spinal unit (FSU) mobility at implanted level (range of movement = ROM flexion/extension), cervical lordosis, FSU lordosis, disc height and adjacent levels mobility. Measurement of disc height as the sum of anterior disc height, central height and posterior height divided by sagittal disc width.

Inclusion criteria: Patients aged at least 18 years (no upper age limit), no previous spinal surgery, degenerative disc disease, moderate intervertebral instability, Kyphosis.

Exclusion criteria: No compliance with the study protocol, multi-level surgery with an other device, dislocation, hyper-mobility in flexion/extension, rheumatoid polyarthritis, osteopenia, osteoporosis, infection, tumor, narrowing of the spinal canal.

Learning curve: 3 surgeries of ROI-C cage before inclusion for each investigator.

Ethics Approval

According to the French regulation, each patient was appropriately informed of his freely participation to a study and of his rights towards medical data collection. Observational study does not modify the surgeon-patient relationship or the usual care of patients. No act or particular examination being requested which are not used in current practice. No visit is imposed. Graft choice is determined by investigator.

Data Collection

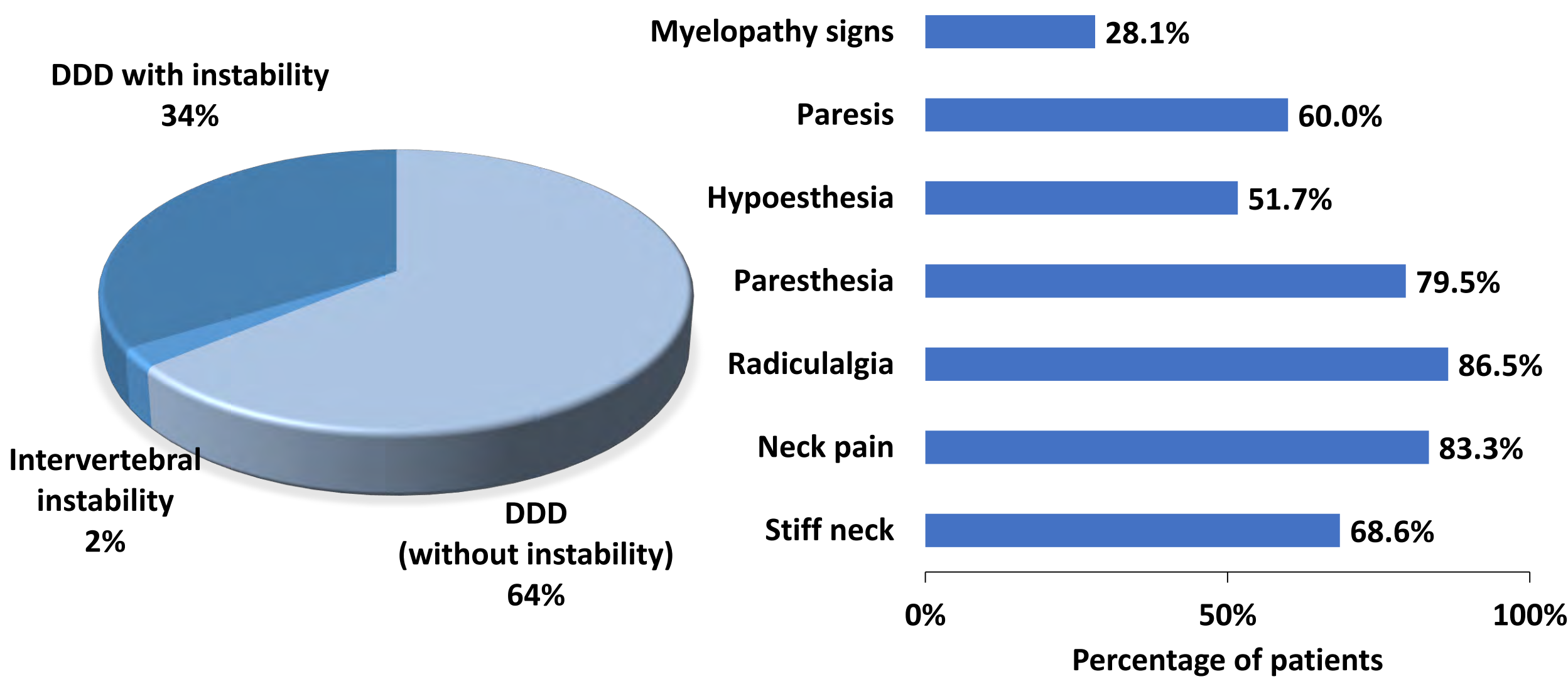
Data were collected from electronic case report forms (e-CRFs) by investigators. Statistical analyses were performed by Clinical Affairs Department of LDR Medical. Descriptive statistics compared score at each follow-up (FU) to pre-op baseline score. Parametric or non parametric tests were used (Wilcoxon or t-test), depending on whether the data were normally distributed or not. For categorical variables McNemar test is used. P-value<0.05 was considered as statistically significant. All available data were taken into account. There was no strategy of missing value replacement.

Patient Sample & Follow-up

Ninety patients were included in the study; 45 females and 45 males. The average age of the patients was 48.8 years and 31% of the patients were smokers. The average time since the onset of symptoms was 13.5 months.

At one year the FU rate was 80%.

Indication & Symptoms



Summary Results

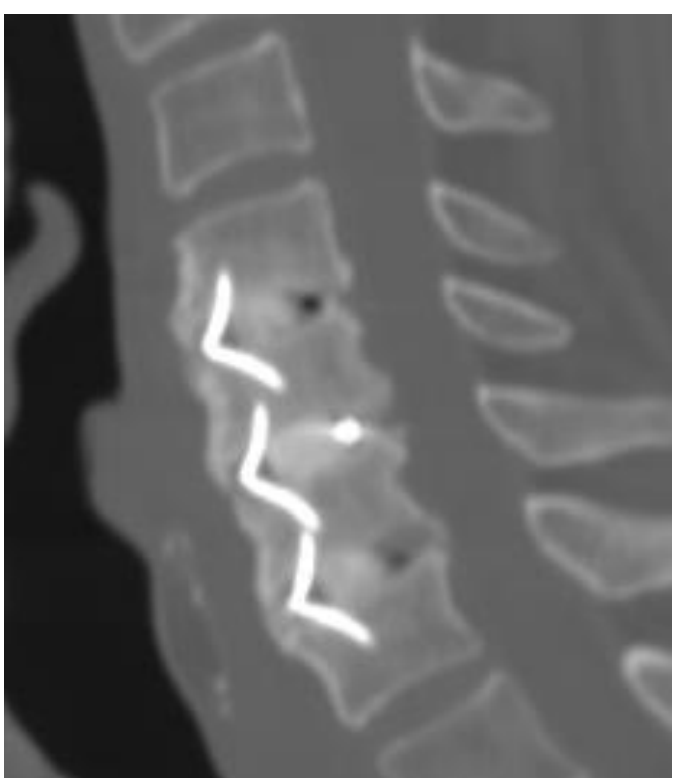
At 12-months, the fusion rate was 92.2%. All clinical outcomes were significantly improved at 1 year FU compared to baseline : NDI 44.4% vs 17.7% , VAS for arm pain 61.9mm vs 14.4mm, VAS for neck pain 55.6mm vs 20.4mm. SF-36 scores were significantly improved at 1 year FU compared to baseline with stability over time. Striking increase of working part of the patients after surgery was observed (from 27.6% preoperatively to 54.7% at 1 year). Only one case of Dysphagia, resolved under 12 months, and one case of neuro-motor sequelae were reported. No implant revision was performed. 5/125 (4%) implanted cages were reported with subsidence without clinical consequences or reoperation. Range of motion (ROM) of the functional spine unit (FSU) decreased significantly from 10.1° preoperatively to 2.4° after 1 year. Superior and inferior adjacent discs showed no significant change of motion at 1 year-FU compared to baseline. Disc height and lordosis were restored.

Fusion Rate

Fusion rate at 12 months : 92.2% (IC 95% : 81.5% ; 96.9%)



1-level fusion (C6-C7)

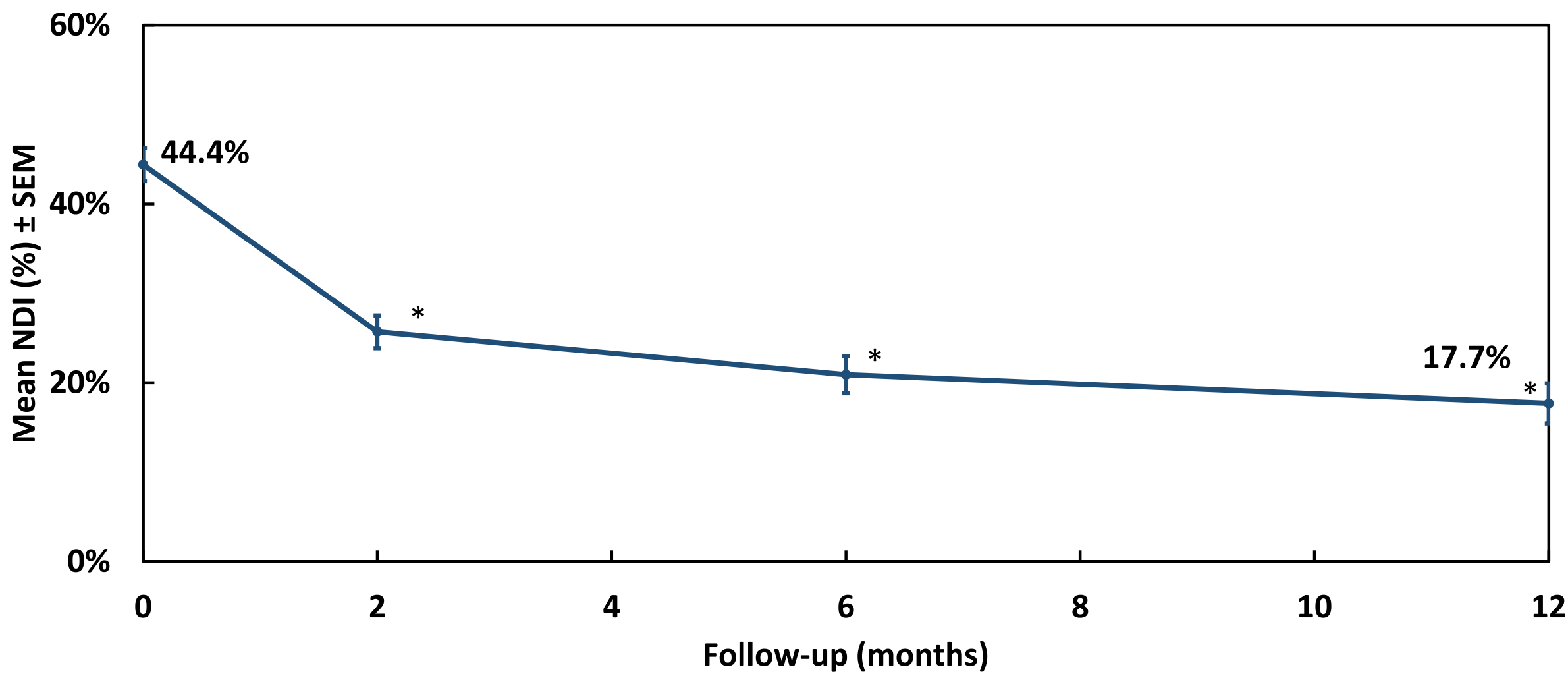


3-levels fusion (C4-C5-C6-C7)

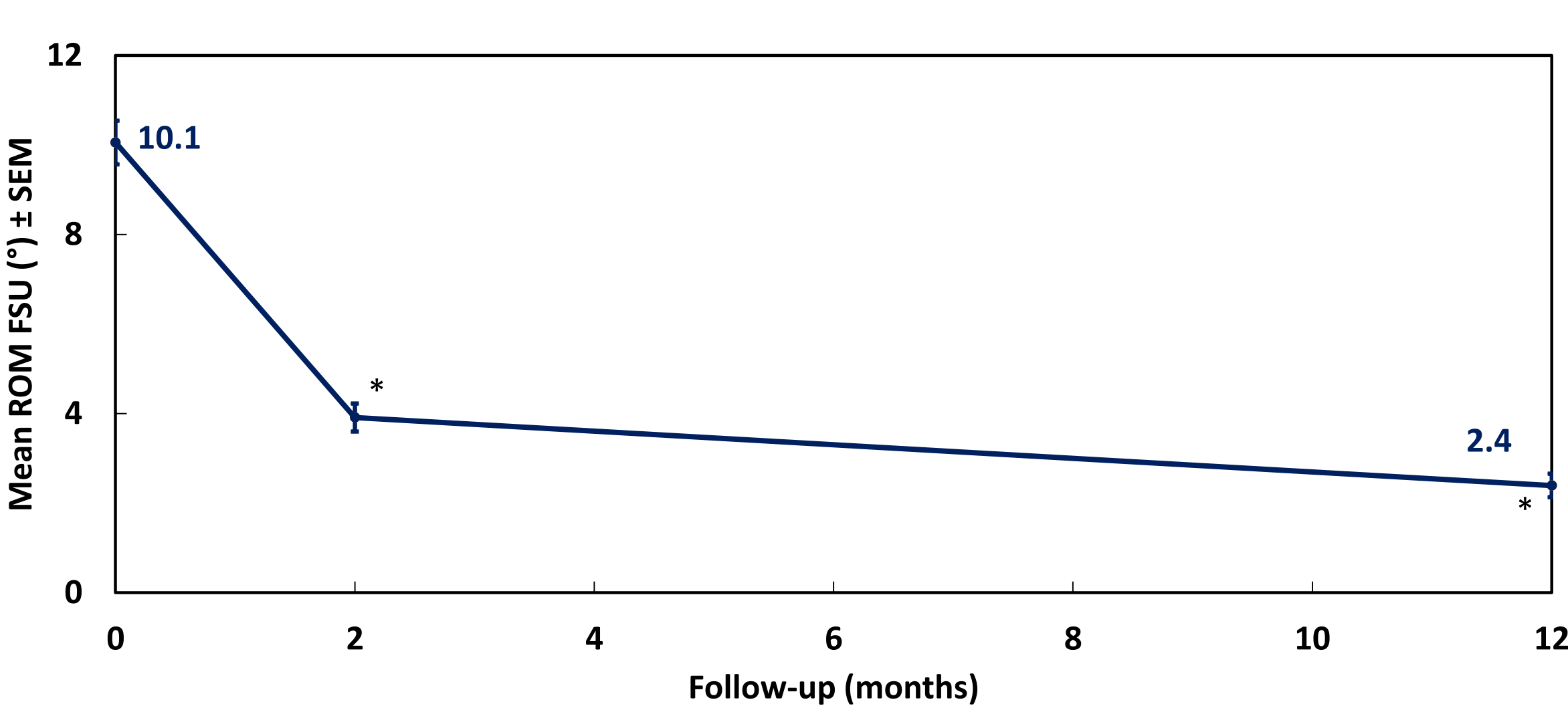
Surgical Procedures

A total of 90 patients included in this study received 125 ROI-C devices. Of all implanted level, 68.9% treated 1-level and 31.1% treated multi-levels. The mean surgery duration was 84.5 min (range 35-180). The mean hospital duration was 3.3 days (range 0-9). Graft used : autograft : 1 patient (1.1%), allograft : 28 patients (31.5%) and substitut (BF+) : 60 patients (67.4%).

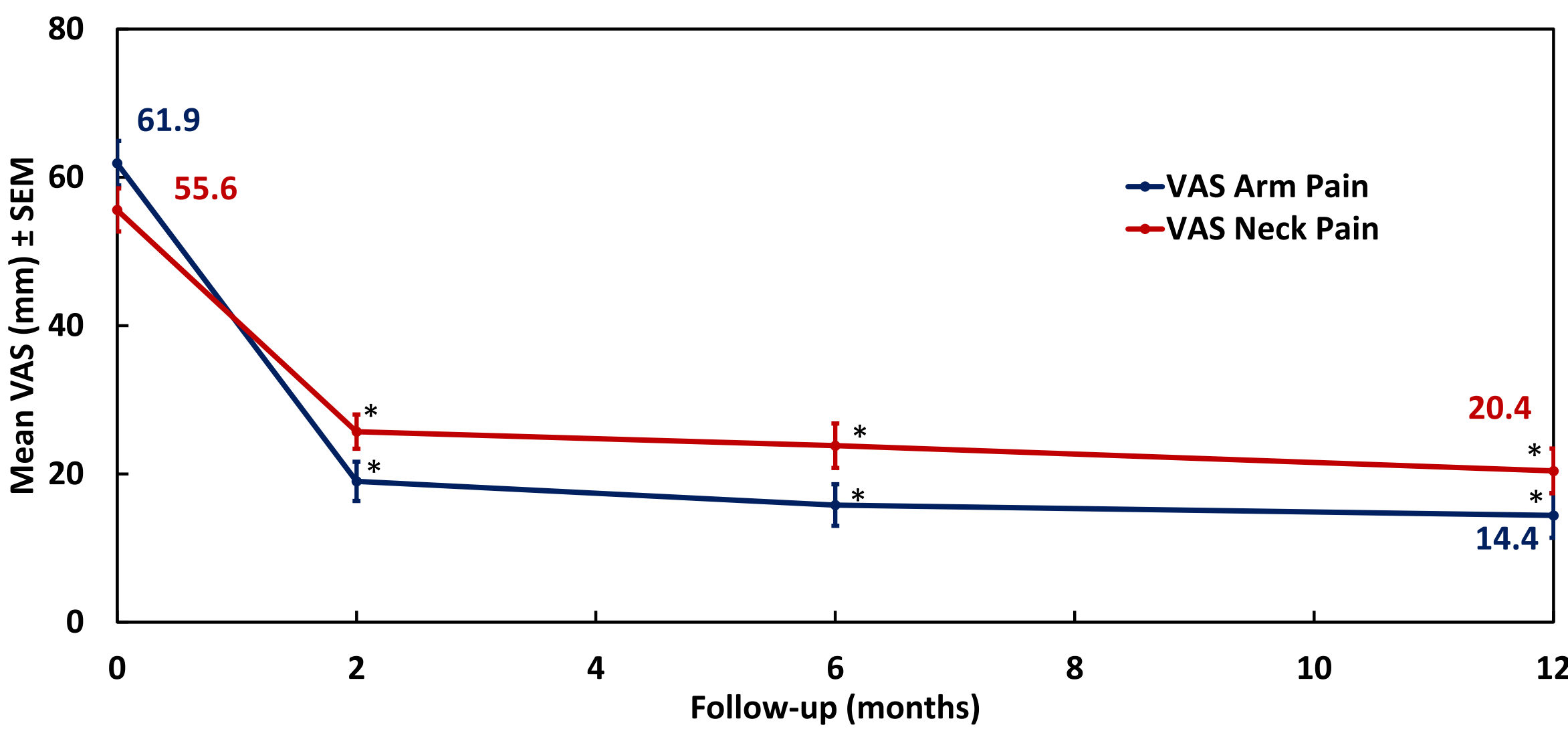
Neck Disability Index (0-100%)



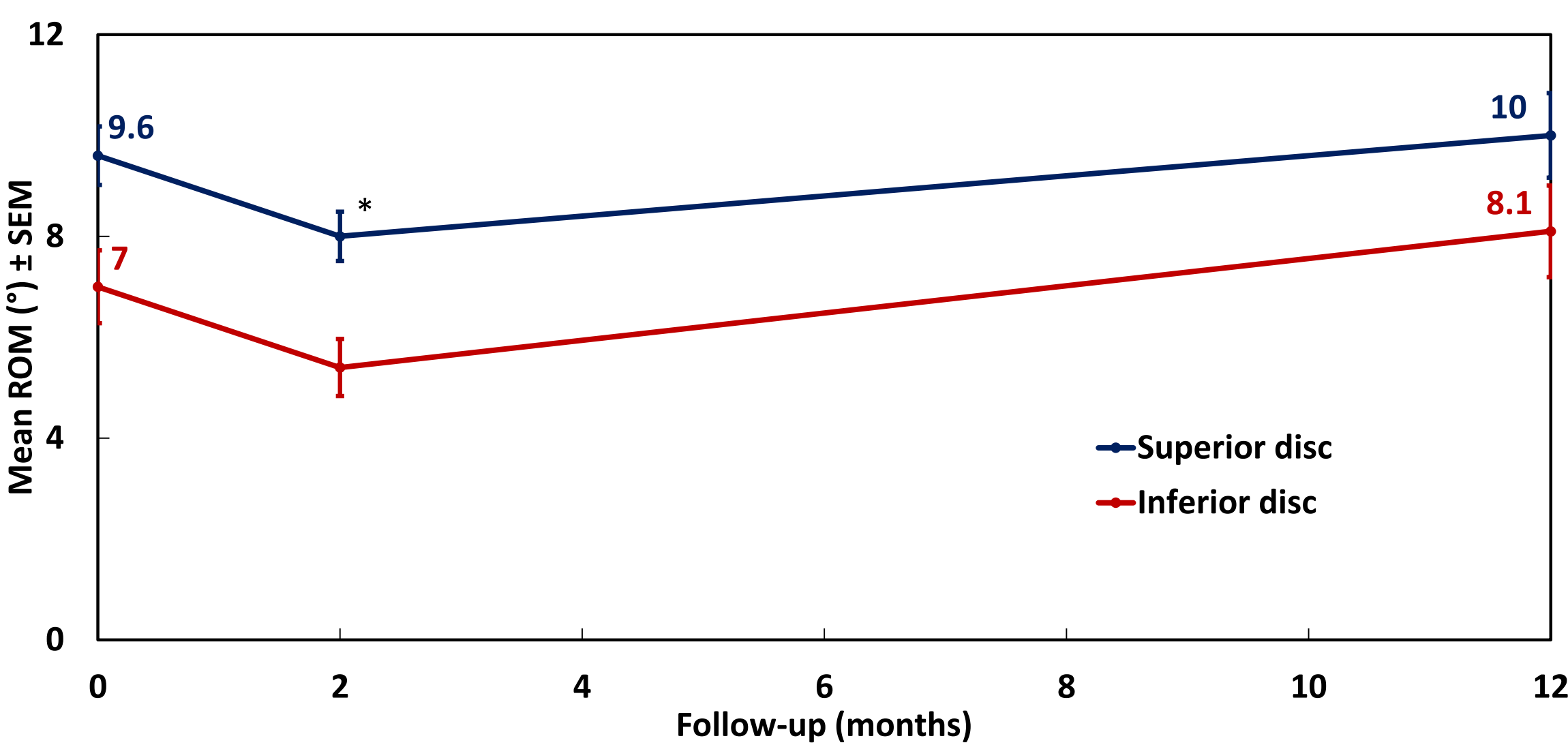
Mobility of Implanted FSU



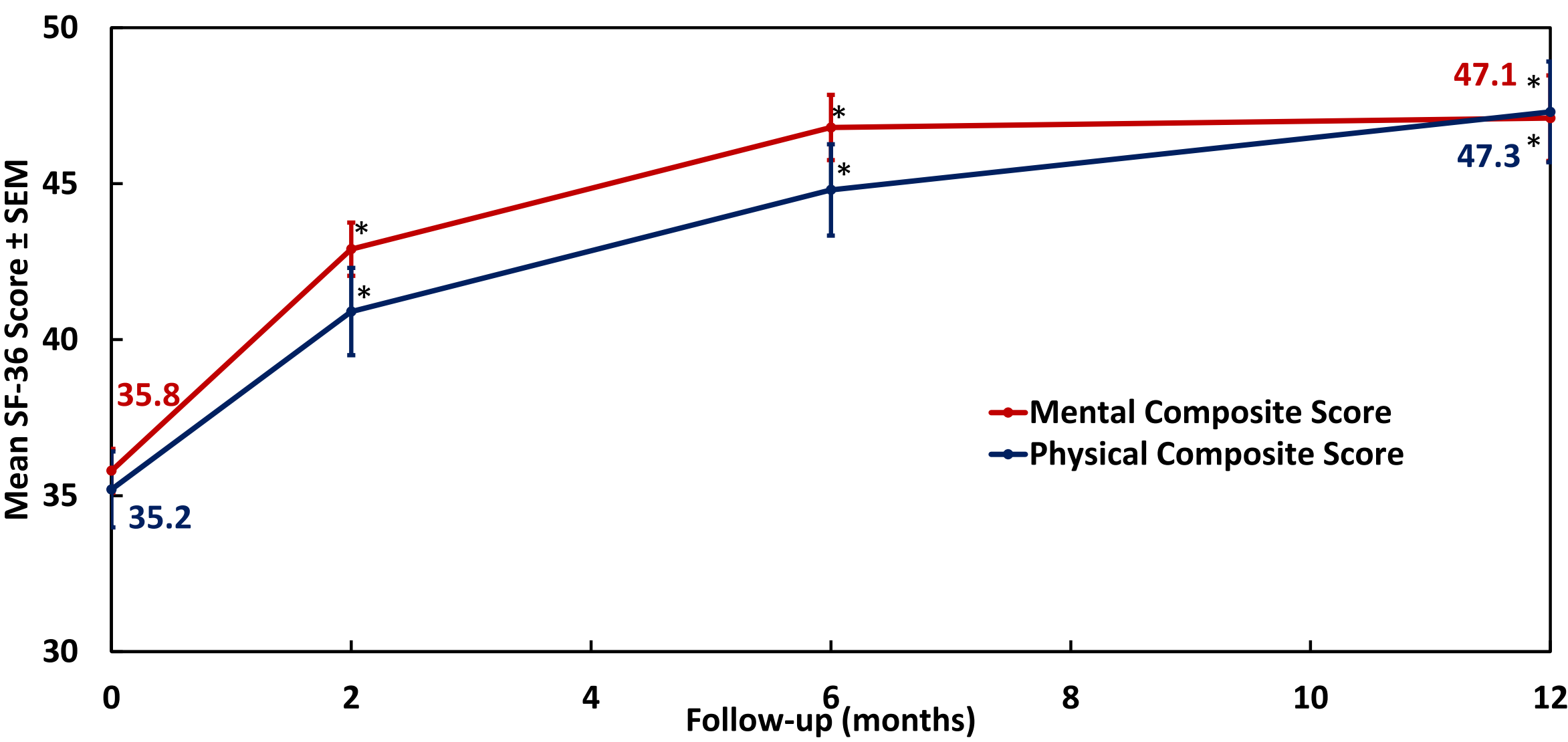
VAS for Arm and Neck Pain (0-100 mm)



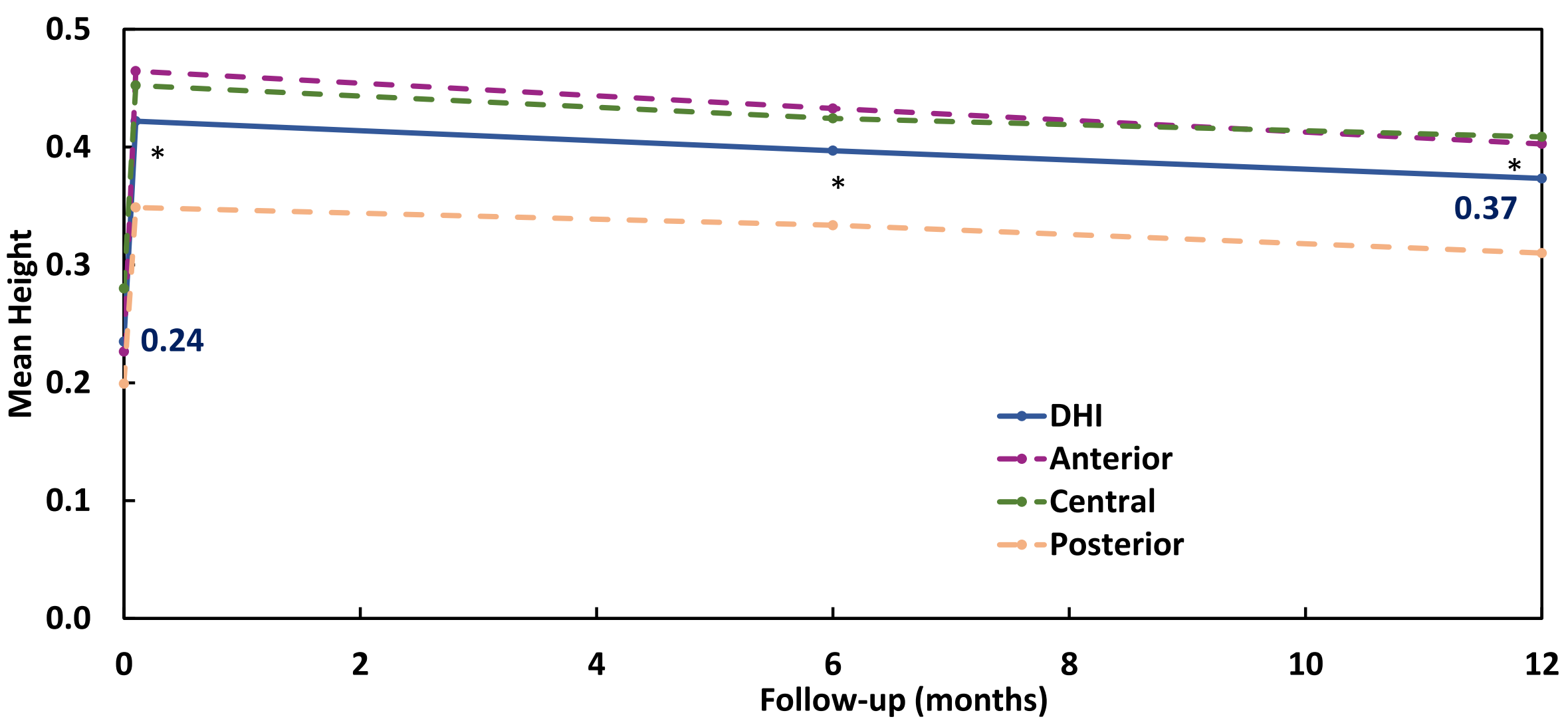
Mobility at Adjacent Levels



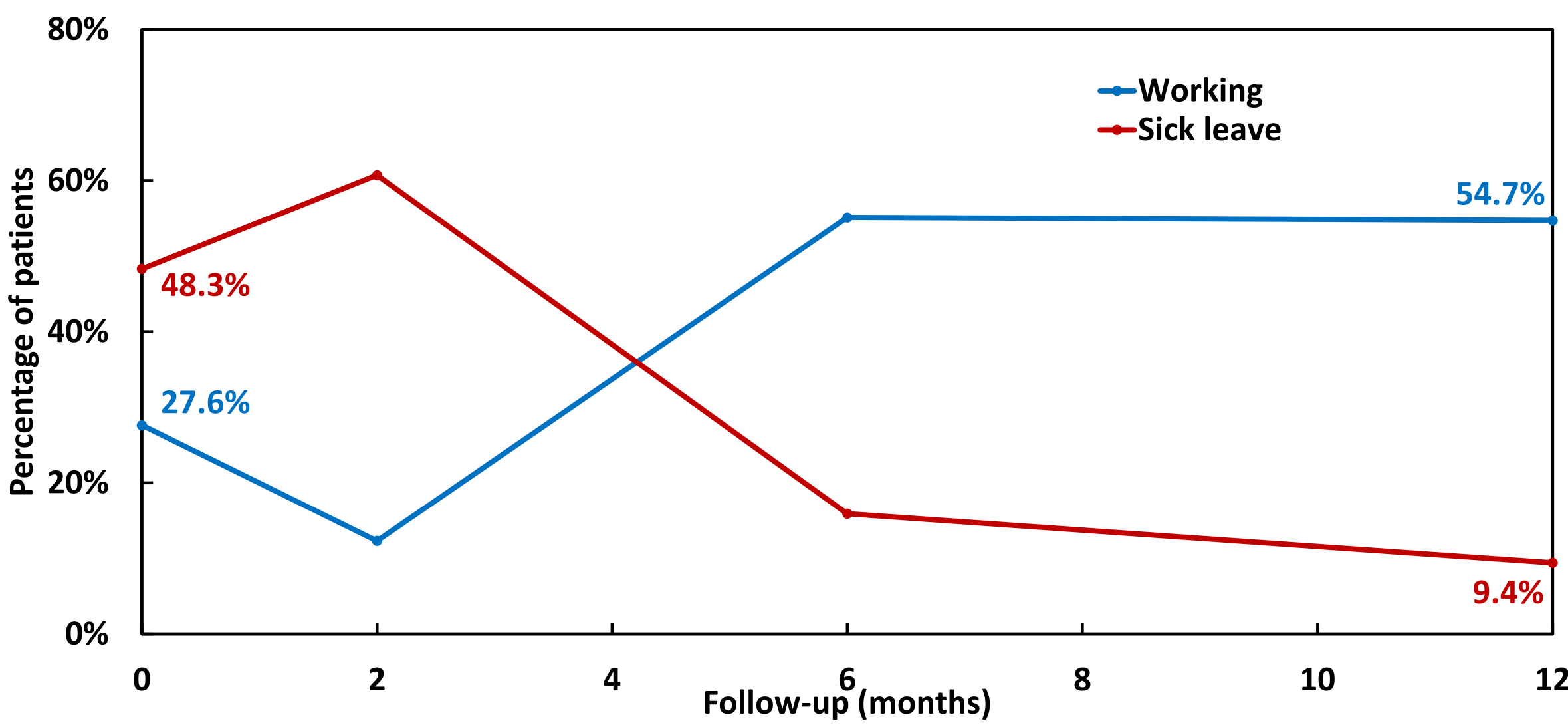
Quality of Life SF-36



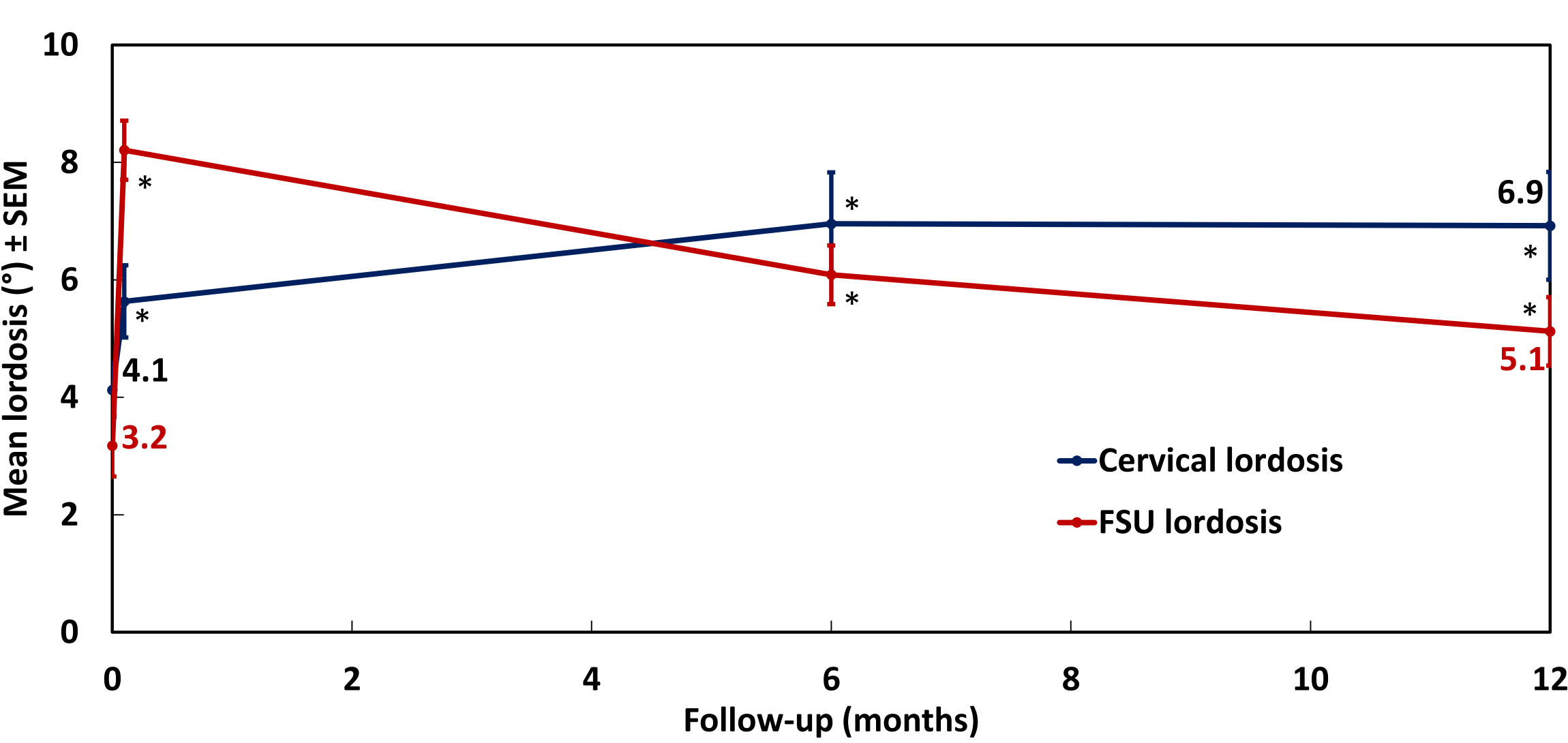
Disc Height



Professional Status Evolution



Curvature



*Difference statistically significant compared to preoperative baseline, using Wilcoxon matched pairs signed rank test.

Clinical Complications

Complications	n	Evolution
Dysphagia	1 patient (1/90)	Resolved under 12 months
Nerve root trouble	1 patient (1/90)	Persistent neur-motor sequelae
Revision surgery	none	
Adjacent level surgery	3 patients (3/90)	Adjacent DDD

Security & Stability

Radiological events	n
Subsidence of cage	4% (5/125)
Migration of cage	0
Fracture of cage	0
Fracture of vertebral body (peroperatively)	1% (1/125)
Migration of anchoring plate	0
Fracture of anchoring plate	2% (5/249)

Conclusions

Anterior cervical discectomy and fusion using a zero profile ROI-C stand-alone interbody fusion PEEK cage demonstrated a high interbody fusion rate, with a lower rate of complication due to the low-profile design of this cage with no hardware protruding anterior of the vertebral bodies. Outcomes showed reducing the symptoms (arm and neck pain, functional disability) and improving the quality of life. Professional status was upgraded with an increase of working patients and decrease of sick leave group up to 1 year after surgery. Radiographic evidence supports restoration of disc space height and curvature and no significant difference of mobility at adjacent levels. This study is still ongoing in order to confirm these results.

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Flexibility and fatigue evaluation of oblique as compared with anterior lumbar interbody cages with integrated endplate fixation

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³Pinnacle Orthopaedics, Marietta, Georgia

OBJECTIVE This study was undertaken to quantify the in vitro range of motion (ROM) of oblique as compared with anterior lumbar interbody devices, pullout resistance, and subsidence in fatigue.

METHODS Anterior and oblique cages with integrated plate fixation (IPF) were tested using lumbar motion segments. Flexibility tests were conducted on the intact segments, cage, cage + IPF, and cage + IPF + pedicle screws (6 anterior, 7 oblique). Pullout tests were then performed on the cage + IPF. Fatigue testing was conducted on the cage + IPF specimens for 30,000 cycles.

RESULTS No ROM differences were observed in any test group between anterior and oblique cage constructs. The greatest reduction in ROM was with supplemental pedicle screw fixation. Peak pullout forces were 637 ± 192 N and 651 ± 127 N for the anterior and oblique implants, respectively. The median cage subsidence was 0.8 mm and 1.4 mm for the anterior and oblique cages, respectively.

CONCLUSIONS Anterior and oblique cages similarly reduced ROM in flexibility testing, and the integrated fixation prevented device displacement. Subsidence was minimal during fatigue testing, most of which occurred in the first 2500 cycles.

<http://thejns.org/doi/abs/10.3171/2015.4.SPINE14948>

KEY WORDS fatigue; interbody cage; interbody device; lumbar spine biomechanics; pullout testing; subsidence

LUMBAR spinal fusion may be achieved using anterior or posterior devices to stabilize the spine during the bone fusion period. Posterior lumbar surgery has been shown to adversely affect the paraspinal muscles.^{5,12–14,19,21,22,24} Anterior interbody techniques that use structural bone graft or cage devices have the advantage of reliably increasing disc height with indirect foraminal decompression, restoring lordosis, and avoiding epidural scarring and radiculitis related to posterior interbody techniques.^{11,15}

“Standalone” interbody fusion devices are appealing because they avoid supplemental posterior fixation and spinal muscle injury related to the fusion. These devices may also reduce implant costs related to the posterior procedure and operative time. Standalone fusion devices require adequate fixation to the anterior vertebral column, either by supplemental plates or screws or by integrated

fixation intended to prevent device dislodgment and enhance motion segment rigidity. Devices with integrated fixation typically have a lower profile and require less exposure to implant as compared with cages supplemented with independent plates. Furthermore, cages with integrated plates require less exposure than cages with integrated bone screws, which necessitate high-angle trajectories for insertion.

One challenge of interbody device implantation is device design: most are designed for a direct anterior approach, which may be difficult at L4–5 due to the vascular anatomy, thereby increasing surgical risk.^{3,7,26} Furthermore, standalone anterior interbody devices with multipoint screw fixation require greater exposure, which again may be difficult at L4–5. To overcome this concern, oblique and extreme lateral interbody fusion devices have been developed that are placed by an anterolateral or transpoas lat-

ABBREVIATIONS DEXA = dual-energy x-ray absorptiometry; IPF = integrated plate fixation; ROM = range of motion.

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eral approach, respectively. Thus, a cage that has the same biomechanical support as an anterior device but is safer to implant would be preferable to use clinically. Yet another concern is the lack of dynamic performance data for cages. Although prior flexibility studies suggest that the ability of standalone devices to produce a rigid motion segment is sufficient,^{1,4,6} the construct rigidity of standalone devices over time in vivo is not well understood.

The purposes of this study were to determine whether an anterolateral oblique interbody cage would perform as well as a conventional anteriorly placed device and to assess the effects of supplemental fixation. Additionally, because flexibility testing may represent only the immediate postoperative period, cyclic loading (30,000 cycles) was performed to assess device subsidence in the early in vivo state.

Methods

Specimen Preparation

Fourteen L1–S1 cadaver lumbar spine specimens (cadaver age range 40–67 years, 9 men and 5 women) were scanned using dual-energy x-ray absorptiometry (DEXA; GE Lunar, iDXA) to quantify bone density. The specimens were dissected, preserving all ligamentous structures, into a total of 26 L2–3 and L4–5 motion segments. The motion segments were divided into a flexibility and pullout testing group and a fatigue testing group, with 6 anterior and 7 oblique devices in each group. Specimens were potted as previously described.¹

For both the anterior and oblique interbody cages, flexibility testing was performed on the following configurations: 1) intact spinal motion segments; 2) isolated cage; 3) cage + integrated plate fixation (IPF); and 4) cage + IPF + pedicle screws and rods (Fig. 1). Following the intact tests, discectomies were performed by an experienced spine surgeon (G.R.B. and J.R.M.). For the anterior implants, the midline was identified and an annulotomy was performed laterally for 1.5–2 cm bilaterally. For the oblique implant, the midline was identified and the annulotomy was made to the left of midline for approximately 3.5 cm. Complete cleaning of the disc space was performed to accommodate the cages. The cages were sized using trial instruments to slightly distract the disc space and to provide a snug fit for the device. Correctly sized anterior (ROI-A, LDR Spine; footprint size: 5 cages measuring 27 × 36 mm and 1 cage measuring 30 × 39 mm) or oblique polyetheretherketone (PEEK) cages (ROI-A Oblique, LDR Spine; footprint size: 4 cages measuring 27 × 30 mm and 3 measuring 30 × 33 mm) were inserted into each specimen. Flexibility tests were conducted after cage implantation. Two integrated fixation plates were then deployed and flexibility testing was repeated. Final flexibility tests were conducted after supplementation with pedicle screws. Fluoroscopic images were acquired for each instrumented condition to confirm implant position and sizing.

Flexibility Testing

Flexibility tests were conducted by applying pure moments of ± 6 Nm at 0.5 Nm/sec with a 50-N compressive preload to the superior vertebral body using a hydraulically actuated spinal loading fixture (MTS 858 Mini

Bionix, MTS Systems).⁶ The inferior vertebral body was mounted to a passive XY slide table, and a load cell with 6 degrees of freedom mounted directly above the specimen was used to control the application of loads and moments. Data were collected only on the third cycle. A noncontact motion measurement system was used to track 3D spinal motion, as described previously.^{9,10,25} Range of motion (ROM) was calculated as the difference between the peak positive and peak negative rotations, while neutral zone was calculated as the amount of motion in the low-load region, between -0.25 Nm and $+0.25$ Nm.

Pullout Testing

After flexibility testing was completed, the pedicle screws and rods were removed from each specimen, and pullout testing was performed on the cages with fixation plates. An aluminum block was directly screwed to the exposed face of the cage and connected to the machine actuator with a swaged steel cable (Fig. 2). The implant was pulled out of the motion segment in a direction perpendicular to the face of the device. A 400-N axial compressive force was applied during pullout using a fixture previously described.¹ Pullout tests were conducted at 10 mm/min with data acquisition at 20 Hz. The peak pullout load was calculated as the maximum load sustained by the device. The mechanism of failure (i.e., device or vertebral body failure) was recorded for each pullout test.

Fatigue Testing

Motion segments implanted with either anterior or oblique interbody cages with IPF were wrapped in saline-soaked gauze and tested in flexion-extension and lateral bending by applying pure moments of ± 5 Nm at 1 Hz with a 400 N follower load (Fig. 3). A custom-designed pneumatic follower load system was used to apply a 200-N load to each side of the spine for a cumulative load of 400 N. Load cells were placed in-line with the follower load cables to continuously monitor the applied load. The follower load cables were placed at the approximate center of the vertebral bodies in the sagittal plane and adjusted such that follower load-induced rotations were less than 0.25° . Fatigue testing was alternated between 2500 cycles of flexion-extension and 2500 cycles of lateral bending until 30,000 cumulative cycles were performed.

Implant subsidence was quantified by lateral fluoroscopy (OEC 9900 C-arm, GE Healthcare) at 10, 100, 1000, and 2500 cycles and at each 2500-cycle increment thereafter. Specimens were carefully positioned on a rigid table by placing the potting material against physical “stops” with index lines for specimen alignment. The mobile fluoroscopy unit was not disturbed following the initial setup of lateral and anteroposterior images of the specimen, and all images were acquired and saved using the detached monitor and control unit. The techniques used for fluoroscopic image acquisition resulted in nearly perfect image overlays for each cyclic time point and allowed for accurate disc height measurements. Disc height measurements were performed in Adobe Illustrator. Images were placed into individual layers for each cyclic time point, magnified by approximately 1200% to allow precise visualiza-

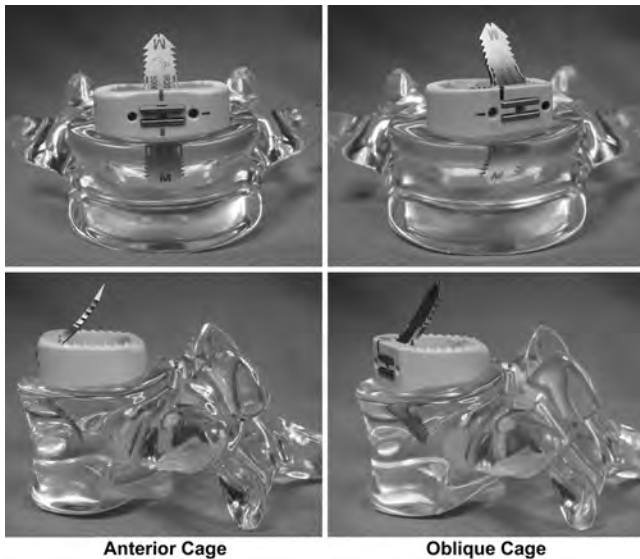


FIG. 1. The anterior (left) and oblique (right) interbody cages with anchor plates.

tion of the endplate/disc interface, and vertical lines were measured at the middle of the disc to quantify disc height. A machined 20-mm reference was placed in each fluoroscopic image for proper scaling. At the completion of fatigue testing, each specimen was disarticulated to perform a visual and photographic examination of the vertebral body endplates and failure mode.

Statistical Analysis

A 1-way repeated-measures ANOVA was performed to examine statistical differences in ROM data for each test direction. Nonnormal ROM data were analyzed using a repeated-measures ANOVA on ranks. A t-test was performed to examine statistical differences in flexion-extension and axial torsion ROM between the oblique cage + IPF and the anterior cage + IPF. Due to unequal variances, a rank-sum test was performed on the lateral bending ROM data for the oblique versus anterior device comparison. Linear regression was used to evaluate the relationship between pullout load and bone mineral density. A t-test was performed on the subsidence data at 30,000 cycles to analyze differences between the 2 test groups. Statistical significance was declared at $p < 0.05$.

Results

Flexibility Testing

The average (\pm SD) DEXA T-scores were -0.1 ± 1.2 , and the difference between the anterior and oblique groups was not significant ($p = 0.64$). The ROM of the intact motion segments was similar for the anterior and oblique groups (Table 1). Implantation of the isolated oblique cage reduced ROM by 33% in flexion-extension and 27% in lateral bending, but differences from intact motion segments were not significant. In axial torsion, the isolated oblique cage resulted in an average increase in ROM of 84% due to excision of the annulus for device placement. Implantation of the anterior interbody cage significantly reduced motion in flexion-extension by 42% and in lateral bending

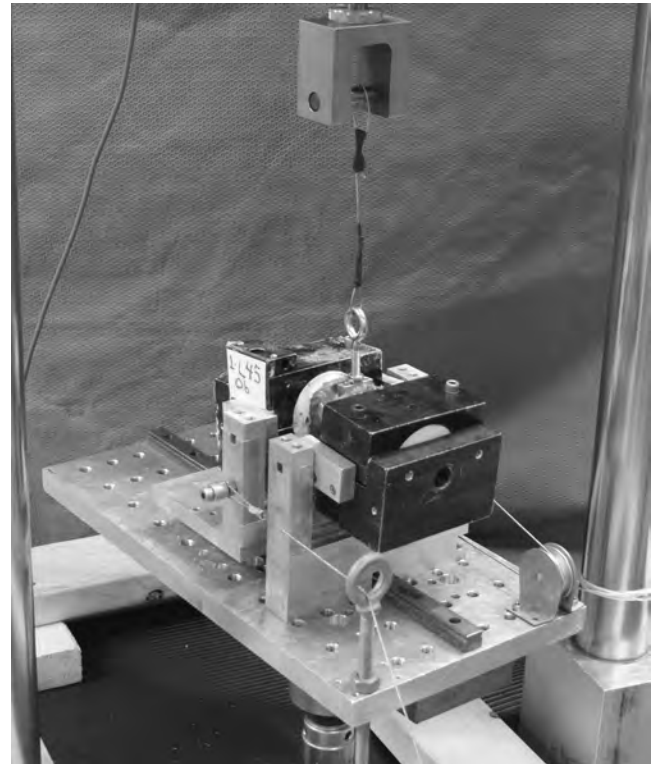


FIG. 2. The interbody spacers were pulled out of each motion segment in a direction perpendicular to the exposed face of the device (anterior or oblique). A 400-N compressive load was applied to the motion segment during pullout testing using a system of cables, pulleys, and dead weights.

by 61% ($p \leq 0.02$ vs intact). The anterior interbody cage increased ROM in axial torsion by 19%. There were no significant differences between the anterior and oblique cages in flexion-extension, lateral bending, or torsion.

Both the anterior and oblique cage groups experienced little difference in ROM when the IPFs were deployed. The IPFs were most effective in torsion, where ROM was reduced by 1.8° with IPF deployment as compared with the oblique isolated cage, and by 1.5° for the anterior cage.

Pedicle screws and rods were the most effective at reducing ROM in both the anterior and oblique groups, with overall reductions from intact ROM of $85\% \pm 10\%$ in flexion-extension, $88\% \pm 7\%$ in lateral bending, and $63\% \pm 23\%$ in axial torsion. There was no significant difference in ROM between cage types with the addition of supplemental fixation.

Pullout Testing

The peak pullout loads were similar between the two groups, with an average of 651 ± 127 N for the oblique group and 637 ± 192 N for the anterior group. There was no relationship between bone mineral density and pullout load for either group. The failure mechanism for all specimens was anterior (anterior group) or anterolateral (oblique group) vertebral body fracture resulting from pulling the plates through the bone. No cage fractures occurred.

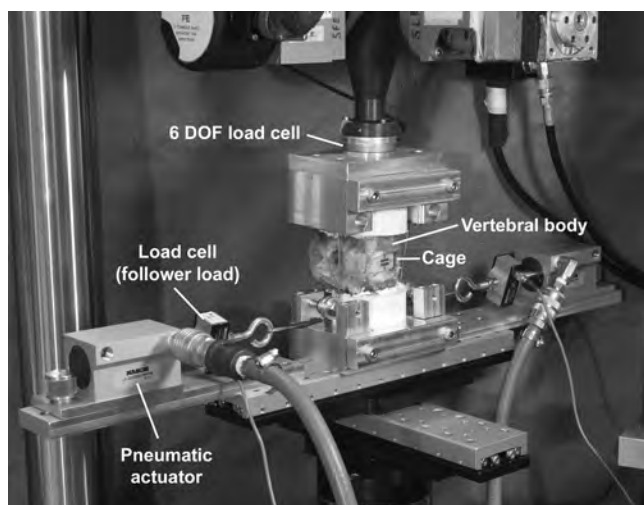


FIG. 3. Fatigue testing was conducted using a follower load system consisting of bilateral pneumatic actuators that applied a constant 200-N load to the cables. Load cells were positioned in line with the cables to monitor the applied loads. DOF = degrees of freedom.

Fatigue Testing

All specimens successfully completed fatigue testing without any damage to the interbody cage. No instances of vertebral body fractures were noted, and on average, the devices experienced very little anterior migration as measured from the posterior implant marker (< 1 mm). After 30,000 cycles of loading, no significant differences in subsidence were noted between the anterior and oblique implants, with median values of 0.8 mm and 1.4 mm, respectively ($p = 0.096$; Fig. 4). The oblique group had two outliers, with 3–5 mm of subsidence noted in spacers with below-average footprint size. For both groups, most implant displacement occurred during the first 2500 cycles, with a median subsidence of 0.4 mm for the anterior group and 1.0 mm for the oblique group.

Discussion

The present study provides a comprehensive biomechanical characterization of both oblique and anterior cages with IPF, in terms of flexibility, pullout resistance, and fatigue loading subsidence. While flexibility and pullout testing are commonly performed on interbody spacers with integrated fixation, this study also conducted fatigue testing at physiological loads.

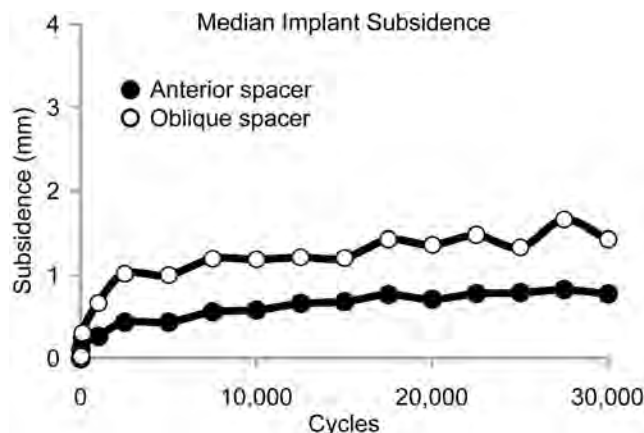


FIG. 4. Graph of the median subsidence of the anterior and oblique cages + IPF as measured from fluoroscopic images. All interbody height changes were due to bone endplate subsidence, and no cage failures were observed.

Specifically, the study demonstrated that an interbody spacer reduced ROM in bending and, with integrated fixation plates, also reduced ROM in torsion; thus, the devices impart increased rigidity to the motion segment. The greatest reduction in ROM in all axes of rotation resulted from the addition of pedicle screw fixation. The degree of motion reduction for the devices of this study is essentially identical to what has been previously reported for interbody cages with and without supplemental fixation (Fig. 5).^{1,4,6} As previously shown, anterior supplemental instrumentation decreased torsion ROM. The present study also found that a cage that is designed to be inserted obliquely (using the anterolateral approach) rather than by direct anterior insertion gives the same degree of rigidity. The cages used in this study, with their integrated fixation plates, were able to resist migration; the pullout test results were similar to a previous study of a device with multiple bone screws.¹

Flexibility testing has limitations and it has been recommended that cyclic or fatigue testing may better mimic the in vivo state. Subsidence of interbody devices by 1–4 mm is common and has been previously described.^{5,8,23} Clinically, fusion may still occur despite mild subsidence if the biological environment is sufficiently healthy. However, in some instances, subsidence can lead to instability and secondary pseudarthrosis.^{2,17,20} Assuming that fatigue testing may be a better predictor of in vivo performance during the early fusion period, this test was

TABLE 1. Average ROM for the anterior and oblique interbody cages*

Direction	Intact		Isolated Cage		Cage + IPF		Cage + IPF + Pedicle Screws	
	Anterior	Oblique	Anterior	Oblique	Anterior	Oblique	Anterior	Oblique
Flexion-extension (°)	10.1 ± 4.7	8.8 ± 1.9	5.9 ± 3.7†‡	5.9 ± 3.4	5.9 ± 4.3†‡	6.5 ± 3.9†	1.2 ± 0.5‡	1.4 ± 0.9‡
Lateral bending (°)	9.4 ± 2.0	8.8 ± 2.5	3.7 ± 1.5†‡	6.4 ± 4.0†	3.1 ± 1.3†‡	5.7 ± 3.1†	0.9 ± 0.4‡	1.2 ± 0.5‡
Axial torsion (°)	3.6 ± 2.1	3.2 ± 3.7	3.9 ± 2.2†	5.3 ± 5.4†	2.5 ± 1.7†	3.5 ± 3.2	0.9 ± 0.5‡	1.0 ± 0.5

* All data given as means ± SDs.

† $p < 0.05$ versus pedicle screws.

‡ $p < 0.05$ versus intact screws.

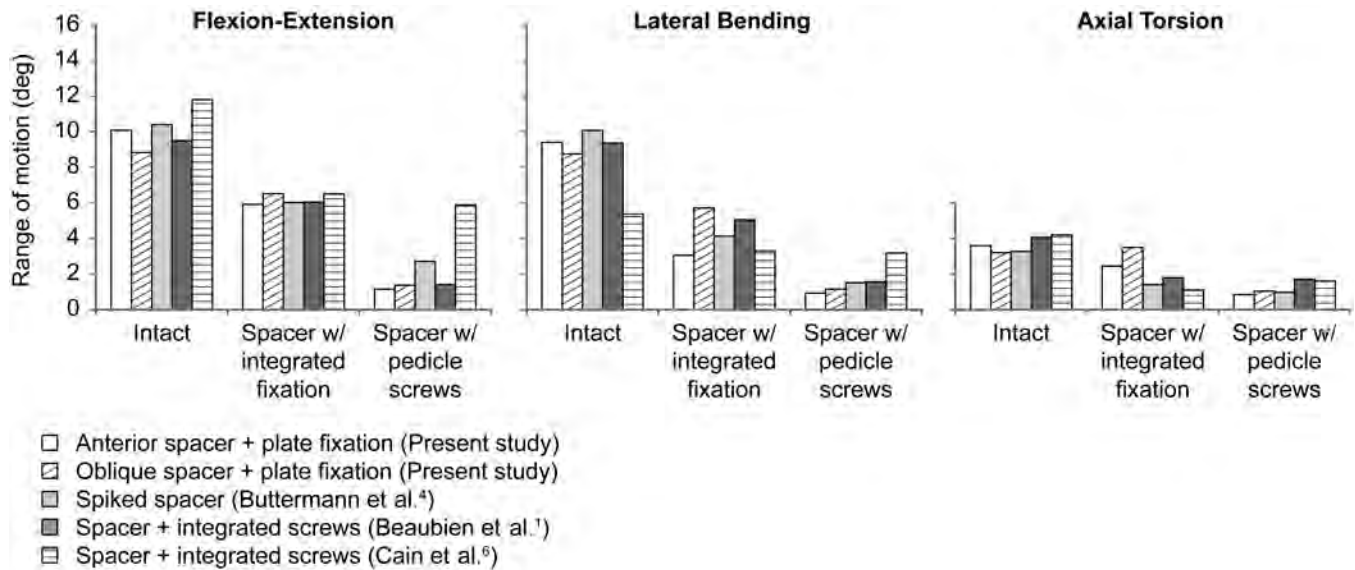


FIG. 5. Range of motion data for the anterior and oblique interbody cages with integrated fixation plates in comparison with similar anterior lumbar interbody fusion cages with integrated fixation.

included in the present study, which found subsidence to occur typically within the first 2500 cycles. We expected, but were unable to find, a relationship between subsidence and DEXA score, probably due to the small number of specimens used in this study. Although not statistically significant, subsidence was greater in the cases in which the oblique spacer was used relative to the anterior device. The testing protocol for this study required that the annulotomy window for implantation of the oblique spacer not pass the midsagittal plane. Because of this smaller annular window, typically smaller interbody spacers were used. This meant that spacers had a smaller “footprint” for the oblique case, and often these interbody devices were placed more centrally rather than having peripheral endplate support, which is related to endplate fracture and subsidence.^{16,18}

Although this study exhibited a number of strengths—including the use of a well-standardized flexibility test protocol that allowed direct comparison with prior studies, and unique fatigue loading to simulate early in vivo performance—the study also demonstrated some weaknesses. Limitations included the inherent variability found in cadaveric specimens, among which are variation in size, bone quality, and endplate thickness and strength, which could affect subsidence and fixation of the integrated plates. Microfracture, which was not apparent during the implantation, was found to occur in 2 oblique specimens, which skewed the results for the oblique case. Although the overall sample size was large (26 motion segments), a post hoc power analysis indicated that the sample size would need to be more than doubled (60 motion segments) to provide adequate statistical power. Due to both testing time and funding constraints a larger sample size could not be used. Another limitation is that selected implant size was left to surgeon preference at the time of implantation, rather than being based on a strict criterion whereby a specific cage required a predetermined area of coverage

for a given endplate size; this variable may have affected stability. Despite cyclic testing, it remains possible that, clinically, patients may have greater subsidence than we found in the present study for the standalone condition. On the other hand, fatigue loading was not performed with supplemental pedicle screw fixation, as may be used clinically, and so the subsidence found in this study may also be considered a worst case.

Clinically, the current study suggests that the interbody cage tested, with its integrated fixation plates, gives the surgeon the option of implanting such a device through a more limited exposure while retaining the same ability as other devices to enhance rigidity required for fusion and avoid cage migration or displacement. Particularly at L4–5, where exposure may be difficult, the oblique spacer may have a clinical advantage yet perform similarly to its anterior counterpart and other devices currently available for this type of procedure. A lumbar interbody device that requires less exposure offers the secondary benefit of minimizing scar tissue at adjacent levels, which is relevant should the adjacent levels ever require future treatment.

Conclusions

Lumbar interbody cages with integrated fixation to the vertebral endplates reliably enhance motion segment rigidity, and oblique interbody devices are as effective as anteriorly placed devices. Rigidity was greatest with the use of supplemental posterior fixation. Pullout testing required greater than 600 N and required vertebral body fracture for failure; therefore, anterior displacement of these types of devices is an unlikely mode of clinical failure. Subsidence of 1–3 mm with 30,000-cycle compressive and bending fatigue loading was insignificantly greater for the oblique spacer, which had a smaller footprint. The correlation between subsidence, implant stability, fusion rate, and clinical outcomes requires further study.

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Disclosure

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Author Contributions

Conception and design: Freeman, Camisa, Buttermann. Acquisition of data: Freeman, Camisa. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Freeman, Buttermann. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Freeman. Statistical analysis: Buttermann. Study supervision: Freeman, Camisa.

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ROI-C® Cervical Cage with VerteBRIDGE® Plating: Comparable Fusion with Lower Rates of Dysphagia & Secondary Surgery

Introduction

Anterior cervical discectomy and fusion (ACDF) and cervical disc arthroplasty (CDA) are two effective surgical procedures for the treatment of radiculopathy and myelopathy stemming from cervical degenerative disc disease (DDD). For patients who do not meet the inclusion criteria for CDA, ACDF is still considered the gold-standard surgical option. ACDF treats the potentially debilitating effects of DDD by providing long-term stabilization and decompressing the neural elements. The use of anterior plating is the traditional practice in ACDF to stabilize the segment, improve outcomes, and avoid pseudoarthrosis. However, the use of anterior plating with its inherent prominence can cause complications such as dysphagia, which may be due to compression and irritation of the surrounding soft tissues.

The development of the ROI-C cervical cage with VerteBRIDGE Plating Technology has resulted in a stand-alone fusion device with efficient fixation fully contained within the intervertebral space. ROI-C with VerteBRIDGE was designed to provide all the benefits of traditional ACDF, without the drawbacks of plating or posterior instrumentation when used in accordance with FDA-approved indications*. Here, we evaluate the use of an ROI-C cervical cage with VerteBRIDGE for single-level ACDF in patients with symptomatic DDD.



The ROI-C Cervical Cage in the stand-alone configuration



12-month post-operative ROI-C radiograph

Patient Sample / Study Design

Surgical data and patient demographic information were collected from 109 retrospectively identified patients at 7 study centers. Inclusion criteria included a diagnosis of DDD at one level between C2 and T1 with radiculopathy and/or myelopathy confirmed by radiographic imaging and corresponding pain and/or neurologic deficit. All subjects were treated with the stand-alone configuration of the ROI-C device with VerteBRIDGE and autograft bone. Time points were pre-op, operative, and where available, at 2 and 6 months. The final visit was prospectively planned and conducted, at least 12 months postoperatively. Fusion status was determined using A/P, lateral, and flexion/extension radiographs at each time point, and was defined by the presence of bridging bone with less than 2° segmental motion in flexion/extension and less than 3 mm of A/P translation. Device integrity was assessed radiographically for subsidence, pseudoarthrosis and device-related complications. Neck disability index (NDI) and visual analog scale (VAS) neck and arm pain scores were recorded at the final follow-up visit. Patient-reported adverse events and dysphagia were also collected. Outcomes of this study were compared to the outcomes of the control ACDF treatment group in published, peer-reviewed studies.

Results

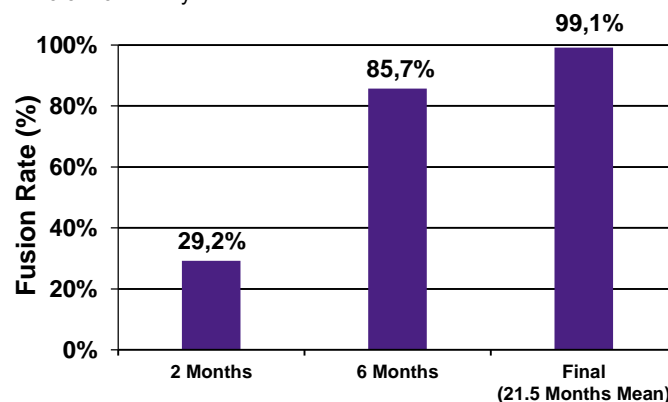
The study population included 63 females and 46 males. The mean age was 52.0 ± 10.2 years. The mean follow-up time was 21.5 ± 8.8 months. The mean operation time was 1.13 hours. Operated levels included C3-C4 (13), C4-C5 (16), C5-C6 (40), C6-C7 (38), and C7-T1 (3). The criteria for fusion were met for 29.2% of patients at 2 months, 85.7% at 6 months, and 99.1% of patients at the final follow-up visit. Comparatively, FDA IDE clinical trials involving patients treated with ACDF with anterior plating and

allograft bone had average operation times of 1.1 to 1.65 hours and fusion rates of 82% to 98.1% at 24 months^{1-3,5,11,15}.

Outcome	ROI-C with VerteBRIDGE® (Ave 21.5 mos)	ACDF ^{1-3,5,11,13,16} (12-24 mos)
NDI	17.9	11.8-23.1
VAS Neck	23.8	19.4-35.6
VAS Arm	11.1 (Right); 13.6 (Left)	1.2-26.9
Fusion	99.1%	82-98.1%
2° Surgery	0.91%	1.4-7.9%

Dysphagia	ROI-C with VerteBRIDGE®	ACDF ^{1-3,5,11,13,16}
2 Months	4.7%	2.5-32.2%
6 Months	8.2%	1.2-17.8%
12 Months	2.3%	3.7-12.5%

The mean NDI, VAS neck pain, VAS right arm pain, and VAS left arm pain scores at the final follow-up visit were 17.9, 23.8, 11.1, and 13.6, respectively. Treatment with ACDF with anterior plating and allograft bone by 12-24 months has shown comparable results^{1-3,5,11,13,16}. Rates of dysphagia were 4.7%, 8.2%, and 2.3% at 2 months, 6 months, and 12 months respectively, and were comparable or lower than the results of ACDF (2 Months: 2.5-32.2%; 6 Months: 1.2-17.8%; 12 Months: 3.7-12.5%)^{1,4}. Secondary surgeries in the ACDF literature report a rate of 1.4-4.7% at 1 year and 3.5-7.9% at 2 years⁵⁻¹⁶.



There was one instance of pseudoarthrosis (0.91%) and one instance of secondary surgery (0.91%). The first patient at 12 month follow-up had radiographically confirmed pseudoarthrosis resulting in device failure. This patient reported an overall NDI score of 4% and VAS neck and arm scores of 0 and did not undergo surgical treatment for the asymptomatic non-union. The second patient, with a diagnosis of cervical stenosis with myelopathy at multiple levels, had subsequent surgery after 8 months that included the level of the index surgery. The device was in place and fusion had occurred; the surgeon documented this reoperation as unrelated to the device.

Conclusion

Analysis of this retrospective study shows that the ROI-C Cervical Cage with VerteBRIDGE Plating Technology in a stand-alone construct is as effective as ACDF with anterior plating in patients with cervical DDD with shorter operative times, less dysphagia and fewer secondary surgeries. By the final time point, 99.1% of all ROI-C patients met the criteria for radiographic fusion. NDI and VAS pain scores were low and comparative with the traditional ACDF treatment with anterior plate.



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* The ROI-C Implant System is indicated for use in skeletally mature patients with degenerative disc disease (DDD) of the cervical spine with accompanying radicular symptoms at one disc level from C2-T1. DDD is defined as discogenic pain with degeneration of the disc confirmed by history and radiographic studies. These patients should have had 6 weeks of nonoperative treatment. The ROI-C Implant System is intended to be used with autogenous bone graft and implanted via an open, anterior approach. Supplemental internal fixation is required to properly utilize this system.

Document intended for the exclusive use of healthcare professionals. ROI-C®-Sterile anterior cervical cage- is a class IIb CE marked medical device made by the LDR Medical S.A.S. Company and for which the conformity assessment was carried out by the notified body G-Med N°0459. ROI-C® is intended for fixation of the cervical vertebrae by anterior approach. Before any surgical procedure, read carefully the instructions and the surgical technique.

Stand-alone ALIF with integrated intracorporeal anchoring plates in the treatment of degenerative lumbar disc disease: a prospective study on 65 cases

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Abstract

Purpose ALIF with cages is expected to restore disc height and stabilize the spine promoting fusion, while avoiding damage attributed to rod-pedicle screw fixation. However, it may be related to an increased risk of fusion failure and subsidence. A prospective study was conducted by five investigators across three centers to confirm performance of a PEEK cage for stand-alone ALIF in the treatment of lumbar degenerative disc disease (DDD).

Methods Sixty-five patients, with back \pm leg pain, requiring surgery for DDD, were included. Efficacy and safety were evaluated at 6 weeks, 3, 6, and 12 months post-operatively. Fusion and subsidence were assessed through CT-images at 12-month follow-up. Disc height was measured. Clinical outcomes included back and leg pain (VAS), disability (Oswestry Disability Index), Quality of Life (Short-Form 36), and adverse events.

Results The fusion and the subsidence rates were 96.3 and 2.0 %, respectively. ALIF surgery restored anterior and posterior disc height compared to baseline. There were

no device-related serious adverse events, and no revision surgeries. Clinical outcomes improved significantly through 12-month follow-up.

Conclusion Safety and efficacy of this stand-alone cage with integrated intracorporeal plates was confirmed through 12 months for treatment of degenerative conditions. The design of the cage and plates may contribute to the decreased subsidence rate observed.

Keywords ALIF · PEEK Cage · Stand-alone · Lumbar degenerative disc disease · Clinical study

Introduction

Among the various fusion techniques dedicated to surgically treat lumbar Degenerative Disc Disease (DDD), Anterior Lumbar Interbody Fusion (ALIF) with cage has been extensively used since introduced by Bagby in 1988 [1]. Reinforcement and stabilization of the anterior column of the spine, after disc removal, restores the disc height and the segmental lordosis and can have many mechanical advantages [2, 3]. Also, the anterior approach avoids posterior muscular damage [4] and neurological injuries [5]. Despite positive results [6], the stability of stand-alone cages has been questioned during the low muscular pre-loading phases when the cage has been suspected to be less stable [7]. The instability during the bone healing process is hypothesized to be one of the main reasons for pseudarthrosis [8–10] and subsidence [3]. Compared with stand-alone cage, supplementary fixation increases the stiffness and stability [3] and significantly improves the fusion rate [11]. The addition of rod-pedicle screw fixation increases the risk of compromising neurological and muscular elements and produces worse clinical outcomes when

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compared to stand-alone procedure [12] while also increasing the occurrence of adjacent disc degeneration [13]. Anterior plating has been proposed but increases blood loss and length of procedure. Furthermore, anatomical configuration in L4-L5 and L5-S1 can make it either difficult or impossible, so lower profile cages integrating anterior fixation screws were designed to facilitate these cases [10, 12, 14].

A new concept of lumbar cage integrating a zero-profile plating system has been designed and the purpose of this study was to evaluate the safety and efficacy of this system.

Population and methods

Study design

A prospective, non-interventional study has been conducted in France to evaluate the clinical efficacy and the stability of the device used for one-level ALIF procedures in the surgical treatment of DDD of the lumbar spine.

Participants

Inclusion criteria were

- adult patient, (≥ 18 years of age)
- with back \pm leg pain unresponsive to appropriate conservative treatment,
- requiring 1-level surgery for DDD with or without degenerative spondylolisthesis.

Exclusion criteria were

- contraindication to anterior approach of the lumbar spine,
- excluded disc herniation,
- narrow canal requiring a posterior decompression,
- presence of a prior posterior device at the level to be treated.

Patient enrollment began with the first implantation in September, 2007. Training cases have been included in the total 65-patient cohort. Patients were included regardless of smoking status, previous surgical history (with exception of exclusion criteria above), and work-related injuries. Five investigators from three centers were responsible for surgical procedures and patient follow-up.

According to French regulation, each patient was appropriately informed of his/her freedom to decline or agree to participate in the study and of his rights regarding medical data collection.

Surgical technique

ROI-A[®] (LDR Médical, Troyes, France) is an intersomatic Polyetheretherketone (PEEK) cage for ALIF, which includes an integrated supplemental fixation system—the intracorporeal locking system (VerteBRIDGE[®]) eliminates the need for additional fixation, such as anterior plate or pedicular screws (Fig. 1), in appropriate patients.

The anterior approach was either midline or anterolateral retroperitoneal according to the operated level. After the discectomy, endplate cartilage was removed with usual precautions and proper implant size was determined using the trial implants under fluoroscopy. In case of narrow disc space, the distraction was performed using a parallel distractor. Particular attention was placed to endplate preparation, which was achieved using a straight curette, as shavers were prohibited. An adjacent healthy disc was examined to obtain sagittal balance, and heights (anterior and posterior) to ensure optimal cage contact with both vertebral endplates. Once the proper cage was selected, filled with the bone grafting material (at the surgeon's discretion), it was inserted into the intervertebral space using fluoroscopy. Once the position of the cage was optimal, the anchoring plate (composed of two self-guided half-anchoring plates) was impacted. The half-anchoring plates were inserted one-by-one under fluoroscopy. Post-operative care was at the discretion of the surgeon.

Outcomes

Each patient was followed-up prospectively with pre-operative and post-operative evaluations (6 weeks, 3, 6, 12 months). The study is ongoing, and follow-up is planned for up to 10 years.

Primary clinical outcomes

The primary outcome was fusion rate, evaluated at the best from Computed Tomography (CT) images at 12-month follow-up using sagittal and coronary plane reconstructions [15]. The CT-reconstructions were evaluated by the principal investigator and an orthopedic senior spine surgeon, independent of the investigator's group and unaware of the clinical results. In case of disagreement, both readers reconsidered the images to obtain a final statement. Fusion rate was evaluated as follows:

- acquired fusion: trabecular bone continuity between the two vertebrae within and/or out of the cage on at least one image in the sagittal and/or coronary plane.
- Fusion failure: no trabecular bone continuity between the two vertebrae within and/or out of the cage in both planes of the CT.
- Doubtful fusion

Fig. 1 The ROI-A[®] cage with its intracorporeal self-locking system (VerteBRIDGE[®])



Secondary clinical outcomes

Usual demographics and peri-operative data were collected. Analgesic use (class and frequency) was documented pre-operatively and at each post-operative visit. Early or late complications and re-operations were monitored up to the final follow-up. Each adverse event was graded as serious (leading to death, life-threatening condition, requiring hospitalization or lengthening of hospital stay, leading to permanent or significant disability) and not serious.

At each visit, patients filled an auto-questionnaire, including Visual Analog Scale (VAS) for lumbar and leg pain (0–10 cm), the Oswestry Disability Index (ODI 0–100 %), and the Short-Form 36 (SF-36) quality of life scale.

In a self-satisfaction index, patients were asked to rate their satisfaction (Very satisfied/satisfied/not satisfied/dissatisfied) of overall result of the surgery, back and leg pain. Their willingness to undergo the operation again under the same conditions was recorded.

Secondary radiographic outcomes

The index disc height was measured anteriorly and posteriorly. Post-operative X-ray calibration/sizing was performed using the known length of each implanted plate. These index measurements were performed pre-operatively, before discharge, and at final follow-up by a single reader using the OsiriX software.

The radiographic behavior of the cage was assessed by the two readers mentioned above. The following events were systematically monitored:

- Subsidence of the cage was defined as any violation of vertebral endplate integrity which could be visible on CT-images in sagittal and/or coronal plane, as

recommended by Lee et al. [16], and assessed by comparing images on the CT-scan completed before discharge and at final follow-up.

- Cage displacement out of the disc space was assessed by comparing cage positioning before discharge and at final follow-up from standing neutral lateral X-rays.
- Plate mobilization, plate fracture and bony fracture were assessed by comparing standing neutral lateral X-rays before discharge and at late follow-up.

Statistical analysis

The data were analyzed using Prism 5.03 software. Comparisons between pre-op and post-op continuous variables were performed using 2-sided *t* tests or Wilcoxon matched-pairs signed rank tests, depending on normal distribution of the data. The MacNemar's test was used for comparison of categorical data. The significance level was $p < 0.05$. All available data have been taken into account.

Results

Sixty-five patients were included and operated on between September, 2007 and November, 2010.

Baseline data

On average, the population (16 Men, 49 Women) was 57.1 ± 11.1 years old (range 35–82). 20 patients (30.8 %) were smokers, and 6 (9.2 %) had work-related injury.

Baseline data and clinical characteristics are summarized in Table 1, and intra-operative data in Table 2.

All procedures were performed with the PEEK cage and VerteBRIDGE[®] plates without any additional anterior or posterior fixation (stand-alone configuration).

Table 1 Baseline data and clinical characteristics of the patient population

Previous surgery	None: 40/65 (61.5 %) At least 1 surgical event: 25/65 (38.5 %) Previous surgery on the index level Discectomy/nucleolysis: 16 patients Fusion (with pseudarthrosis): 1 patient (no posterior device at the time of the ALIF surgery) Laminectomy: 3 patients
Indication for ALIF surgery	DDD without spondylolisthesis: 28/65 patients (43.1 %) DDD with degenerative spondylolisthesis: 37/65 patients (56.9 %)
Index level	L2–L3: 4/65 patients (6.2 %) L3–L4: 10/65 patients (15.4 %) L4–L5: 37/65 patients (56.9 %) L5–S1: 14/65 patients (21.5 %)

Table 2 Intra-operative data in the patients' population

Cage type	Midline: 17/65 patients (26.2 %) Antero-Lateral: 48/65 patients (73.8 %)
Cage size	Cage 27 × 30: 31/65 patients (47.7 %) Cage 30 × 33: 32/65 patients (49.2 %) Cage 33 × 36: 2/65 patients (3.1 %)
Graft	Autologous bone and BMP: 59/65 patients (90.8 %) Autologous bone: 4/65 patients (6.2 %) Other: 2/65 patients (3.0 %)
Blood loss	Mean 205.8 ± 161.7 ml (range 0–800 ml)
Surgery duration	Mean 133.0 ± 30.7 min (range 75–200 min)

Twelve-month follow-up was achieved by 64/65 patients (98.9 %). At the time of database lock, no deaths and no premature study endings were reported.

Fusion rate

At 12 months, 54/65 CT's were available for fusion assessment (11 CT's were incomplete: not performed, or with missing views).

Results indicate 52/54 levels were fused; 2/54 levels were doubtful. One was a 73-year-old male smoker with a BMI of 31.8 with autologous bone graft used. The other was a 50-year-old non-smoking male, with autologous bone and bone morphogenetic protein used. There were no fusion failures.

The fusion rate was 96.3 % (52/54 at 12-month follow-up (95 % confidence interval ranging from 86.74 to 99.70 %); Fig. 2.

Secondary outcomes

Clinical and radiographic adverse events

Two serious adverse events were reported: one superior level reoperation by posterior approach for another lumbar spine disease and one persistent L5 paresia.

All the other adverse events were graded as “not serious”: 13 surgery-related: 12 resolved without sequelae (1 phlebitis, 2 peritoneal tears, 3 motor complications, 3 sympathetic complications, 2 sexual complications, 1 urinary complication.) and 1 sensitive complication was persistent at 12 months.

No infections, eventrations, dural tears or vascular tears were reported.

Two device-related events were reported from the radiological evaluation: one migration of superior plate, remaining stable through time; one cage subsidence occurred within 12-month follow-up in a 76-year-old female; however, interbody fusion was attained. Neither event had clinical consequence.

Subsidence rate was 2.0 % at 12-month follow-up (1 subsidence/51 CT analyzed; 3 cases not analyzed because the CT before discharge was not performed).

The radiological analysis reported neither cage migration nor plate or bony fracture (60 complete radiographic files were available for analysis at 12-month follow-up).

There were no revision surgeries at the index level in this population.

Pain and disability

Both back and leg pain decreased immediately after surgery. The difference from baseline was statistically significant from 6 weeks and through the follow-up period (Fig. 3).

Functional outcomes also showed improvement: mean ODI decreased significantly compared to baseline, from early post-op and up to 12-month follow-up (Fig. 4). The change in ODI score at 12-month follow-up compared to baseline averaged 26.6 points (range −30 to 60 %). Within the ODI questionnaire, walking, ranging from 0 to 5, also decreased significantly from baseline to 12 months (1.94 and 0.64 respectively, $p < 0.0001$).

Quality of life

Outcomes for quality of life also show improvement (Fig. 5): SF-36 increased significantly compared to baseline for both physical and mental scales.

Figure 6 shows the use of any class of analgesic, opioids or non-steroidal anti-inflammatory drugs over time:



Fig. 2 Patient 1–13, anterolateral L4–L5 ROI-A[®]. Pre-operative neutral lateral X-ray (a) and Computed Tomography-reconstruction (b); neutral lateral X-ray (c) and Computed Tomography-

reconstruction (d) performed 7 days following surgery; Computed Tomography-reconstruction at 12 months of follow-up (e) with achieved fusion

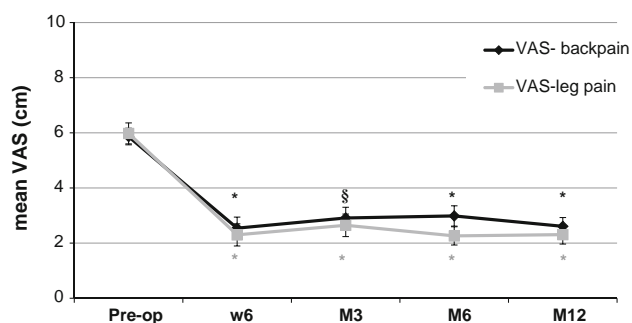


Fig. 3 Visual Analog Scale (VAS 0–10 cm) results for back pain (black line) and for leg pain (gray line) over time-course of the follow-up (pre-op; and 6 weeks, 3, 6, and 12 months after ALIF procedures). Results are expressed as mean \pm SEM. * $p \leq 0.0001$ compared to pre-op baseline; § $p = 0.0003$ compared to pre-op baseline

medication use decreased following the ALIF procedures. The rate of patients using analgesics was significantly lower at 12 months compared to baseline ($p < 0.0001$).

Satisfaction

Patient satisfaction is shown in Table 3. At 12-month follow-up, 88.7 % of patients were very satisfied or satisfied with overall surgery results, 81.1 % with results on back pain, and 78.9 % with results on leg pain.

Additionally, at 12-month follow-up, 80.4 % of the patients (41/51) reported their willingness to undergo the same surgery again.

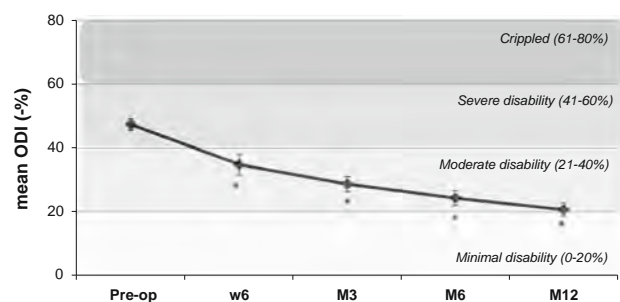


Fig. 4 Oswestry low back pain disability index (ODI 0–100 %). Evolution of the ODI score over time-course of the follow-up (pre-op; and 6 weeks, 3, 6, and 12 months after ALIF procedures). Results are expressed as mean \pm SEM. * $p \leq 0.0001$ compared to pre-op baseline

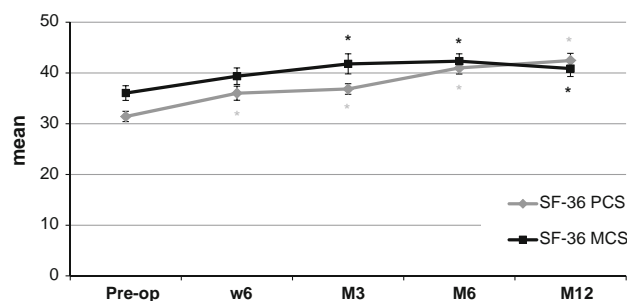


Fig. 5 SF-36 results over time-course of the follow-up (pre-op; and 6 weeks, 3, 6, and 12 months after ALIF procedures). PCS (gray line): Physical Component Scale; MCS (black line): Mental Component Scale. Results are expressed as mean \pm SEM. * $p < 0.05$ compared to pre-op baseline

Fig. 6 Analgesic use (any class) frequency over time-course of the follow-up (pre-op; and 6 weeks, 3, 6, and 12 months after ALIF procedures)

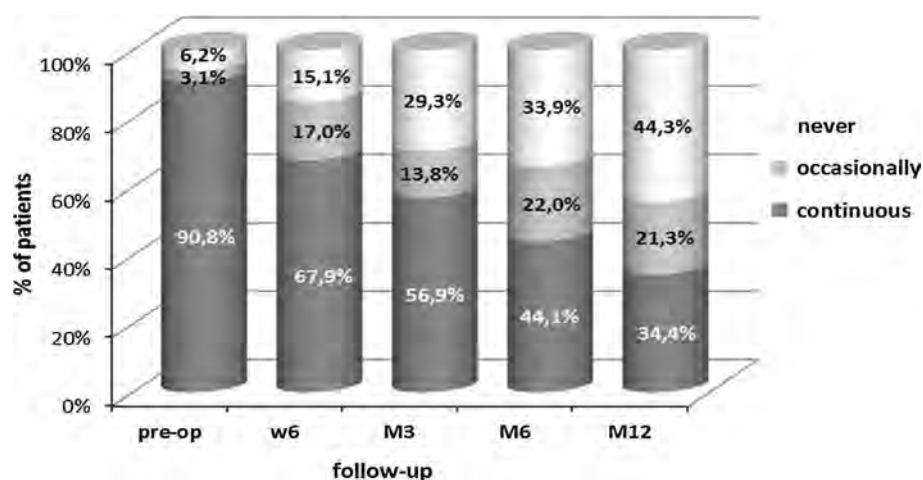


Table 3 Patient satisfaction reported 12 months following the ALIF procedures

	Very satisfied	Satisfied	Not satisfied	Dissatisfied
Overall result	24/53 (45.3 %)	23/53 (43.4 %)	6/53 (11.3 %)	0
Back pain result	13/53 (24.5 %)	30/53 (56.6 %)	10/53 (18.9 %)	0
Leg pain result	17/52 (32.7 %)	24/52 (46.2 %)	11/52 (21.2 %)	0

(): % associated with each response

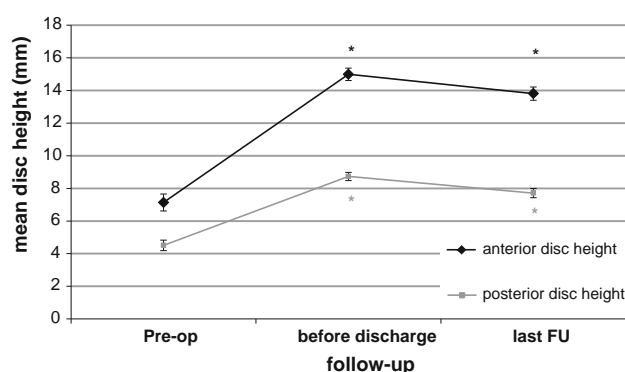


Fig. 7 Evolution of disc height at the treated level, measured anteriorly (black line) and posteriorly (gray line) over time-course of the follow-up (pre-op, before discharge and at the last visit after ALIF procedures). Results are expressed as mean \pm SEM. * $p < 0.0001$ compared to pre-op baseline

Radiographic performances

Anterior and posterior disc heights increased significantly after ALIF procedure (Fig. 7).

Discussion

Despite some positive results [17–19], stand-alone cages have not proven their full efficacy [9, 20]. Stand-alone ALIF with integrated screws have shown better clinical outcomes when compared to classical cages with posterior pedicle screws [12].

In our study, we observed similar improvements of clinical outcomes. Symptom relief was similar for back and radicular symptoms, suggesting that surgeries were effective in treating both. Furthermore, no revision surgeries were reported. Limitations of this study arise from the small size of the population and a selection bias due to the fact that 74.7 % of the inclusions were made by one highly experienced surgeon, which could have had an influence regarding the results transposability. However, smoking, work-related injury, previous lumbar surgeries, and training cases have been included.

The main goals of an ALIF are a solid fusion of the segment, and preservation or restoration of disc height and spinal alignment. Fusion rate data are very heterogeneous in the literature. Li et al. [9] reported a range between 51.9 and 88.9 % fusion in a literature review. Anjarwalla et al. [21] assessed the fusion rate of one stand-alone cage ALIF versus the same ALIF cage with different techniques of posterior supplemental fixation. The fusion rate for the stand-alone cage was 51 % versus 89 % and 88 % for the two groups supplemented with pedicle screws. The difference was significant. Strube et al. [12] using a cage with four integrated screws reported 91.2 %.

This heterogeneity is mainly related to the difficulty of assessing fusion via non invasive methods. Authors generally consider the radiographic assessment as reliable, but the threshold value of motion on dynamic X-rays varied from 1° for Brantigan to 5° for Kuslich [22]. In our study,

we chose CT assessment. As Santos [15] and Zebdlick [2] reported, CT is the best way to visualize the bone continuity, because technical measurements errors are unavoidable on standard X-rays and finally because we can avoid the disputed motion threshold. In our study we reported a fusion rate of 96.3 %. We assume that among other biomechanical reasons supporting this result, the wide grafting area provided by this implant (up to 388 mm²) is crucial and despite some heterogeneity in graft type (90.2 % of it was made of autologous bone + BMP), which could be regarded as a limitation of this study.

Subsidence is a common problem with cages and difficult to define. Le et al. [23] considers subsidence as “any compromise of either endplate” due to the cage. For Beutler et al. [24], subsidence is characterized by a decrease in the specific vertical height on lateral X-rays. Another difficulty faced is the way to measure subsidence and to determine a threshold. Le et al. [23] have used a viewing station with calibrated linear measurements. Beutler et al. [24] defined subsidence as a height loss of greater than 2 mm. Lee et al. [16] measured the “endplate destruction length” on CT in coronal and sagittal planes, which is definitely the most accurate measurement technique published to date.

Choi et al. [25] reported 76.7 % subsidence with a carbon cage. Weiner et al. [26] in their Brantigan ALIF cage series reported 50 %, while Butler [24] reported 10 % in ALIF with a pair of threaded cages, and Lee et al. [16], in a study on 54 patients with supplemented posterior lumbar interbody fusion, reported 22 and 28 % subsidence rates in sagittal and coronal planes, respectively.

We have reported 1 subsidence (out of 51 analyzed cases) from CT examination. Several reasons are possible: the preparations of the endplates was meticulous, without drilling or shaving; the design of the integrated self-guided titanium plating and the size of contact surface of the PEEK cages (up to 835 mm²) theoretically provide immediate stability in a safe way and share the loading [22] (the typical surface of vertebral endplates is 1,259 mm²).

Conclusion

Safety and efficacy of this new concept of supplemented stand-alone cage was confirmed at these 12 months for treatment of degenerative conditions with significant improvement in both pain and function, a low subsidence rate, no device-related serious adverse events, and no revision surgeries at the index level. We intend to proceed further in this study (up to 10 years) to confirm these results and to analyze the rate of adjacent level disease.

Conflict of interest J. A is currently receiving royalties for the development of the considered product. T. V. has currently or previously financial activity for the work under consideration.

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Clinical Study

Applying the Mini-Open Anterolateral Lumbar Interbody Fusion with Self-Anchored Stand-Alone Polyetheretherketone Cage in Lumbar Revision Surgery

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The author retrospectively studied twenty-two patients who underwent revision lumbar surgeries using ALLIF with a self-anchored stand-alone polyetheretherketone (PEEK) cage. The operation time, blood loss, and perioperative complications were evaluated. Oswestry disability index (ODI) scores and visual analog scale (VAS) scores of leg and back pain were analyzed preoperatively and at each time point of postoperative follow-up. Radiological evaluation including fusion, disc height, foraminal height, and subsidence was assessed. The results showed that the ALLIF with a self-anchored stand-alone PEEK cage is safe and effective in revision lumbar surgery with minor surgical trauma, low access-related complication rates, and satisfactory clinical and radiological results.

1. Introduction

Posterior approaches, such as posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF), are commonly used in revision lumbar surgery partially because of their advantage of directly removing problematic implants and fractured screws and rods [1, 2]. Solid lumbar fusion requires internal fixation to help achieve immobilization. However, these approaches also increase the risk of damaging the posterior muscular elements, leading to long-term back pain [1]. In addition, extensive adjacent-level facet joint violations have been reported with posterior revision surgery, which theoretically leads to instability of the upper adjacent level and may accelerate adjacent segment degeneration (ASD) [3, 4]. Significantly higher incidental durotomy rates have been found in posterior revision surgery than in primary surgery due to scar tissue adhesion [5]. Anterior lumbar interbody fusion (ALIF) is an alternative approach when dealing with ASD, recurrent disc herniation, cage migration, and pseudarthrosis. It provides direct access to the vertebral column and allows more extensive decompression of the disc space and better end plate preparation for arthrodesis, while simultaneously restoring disc height and correct lumbar kyphosis [6]. Moreover, ALIF avoids posterior

muscle trauma, adjacent-level facet joint violation, and acceleration of ASD [6, 7]. Nevertheless, access-related complications have been documented, such as urethral injury, bowel perforation, incisional hernia, neurological injury, ileus, and retrograde ejaculation in men, with vascular injury being the most disastrous [2, 7–11]. The transposas exposure of extreme lateral interbody fusion (XLIF) reduces manipulation of the aorta and vena cava; hence, the incidence of vascular injury is lower [12–15]. However, this approach is associated with access-related thigh symptoms, such as numbness, pain, and weakness, resulting from injury of the lumbar plexus or motor nerves, especially when the L4/5 level is involved [16].

Minimally invasive lumbar surgery techniques were first described by Mayer in 1997, which were advocated as an alternative to anterior or posterior approaches for lumbar fusion with less surgical trauma and quicker recovery [17]. This approach used a psoas-preserving access to the lumbar spine via the anterior oblique retroperitoneal approach, but with less invasion of the psoas muscle and lumbar plexus than XLIF. To distinguish this new technique from other minimally invasive ALIF, Silvestre et al. renamed it the oblique lumbar interbody fusion (OLIF) [13]. However, the L5/S1 level can only be achieved through transperitoneal approaches, which provides only indirect decompression. It is

still not possible to treat conditions such as recurrent lumbar disc herniation without subsequent posterior surgery, which inevitably increases the surgical trauma.

The recently developed mini-open OLIF allows psoas-preserving access to the lumbar spine via the anterior oblique retroperitoneal approach with less invasion of the psoas muscle and a reduced incidence of lumbar plexus and motor nerve injury [18]. However, this approach allows only a limited operative field, and direct decompression is hard to achieve. Although it has been reported that spinal stenosis could be resolved successfully by indirect decompression, posterior fixation cannot be avoided [18]. In this study, for the first time, an ALLIF using a self-anchored stand-alone polyetheretherketone (PEEK) cage was used to increase the visual field and to facilitate direct decompression. The safety and efficacy of this procedure were also evaluated to investigate whether it could serve as a new alternative to anterior revision surgery after posterior lumbar surgery.

2. Materials and Methods

2.1. Study Population. Between April 2012 and April 2014, a total of 22 patients who underwent the ALLIF revision surgery and met the following criteria were recruited: (1) initial posterior surgery for lumbar degenerative disc disease or lumbar spondylolisthesis, (2) age between 18 and 65 years, (3) patients with back and/or leg pain after initial surgery who were unresponsive to appropriate conservative treatment, (4) having conditions such as recurrent disc herniation, pseudarthrosis, adjacent segment degeneration, or cage migration confirmed by computed tomography (CT) or magnetic resonance imaging (MRI), and (5) having 24 months or more of follow-up data. Patients with the following criteria were excluded: (1) previous abdominal or anterior lumbar surgery history, (2) posterior scarred adhesion compressing the nerve structure confirmed by medical history or physical or radiological examination, (3) abdominal aortic aneurysm or severe peripheral vascular disease, (4) obesity with BMI $\geq 28 \text{ kg}\cdot\text{m}^{-2}$, and (5) severe osteoporosis. The characteristics of these included patients were listed in Table 1. The mean follow-up time was 24.6 ± 6.7 months. All procedures were performed by the same surgeon (Lü), who has rich experience with anterior lumbar surgery and laparoscopic lumbar surgery for lumbar degenerative disease, deformity, tumor, and infection.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in this study.

2.2. Surgical Procedure. Patients were placed in the supine position. A transverse skin incision of 4 to 6 cm was made on the lateral wall of abdomen, parallel to the projection of the affected disc level (Figure 1). The external oblique, internal oblique, and transverse abdominal muscles were

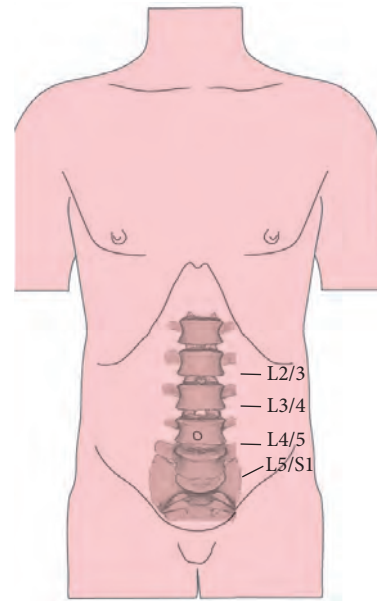


FIGURE 1: A transverse or oblique 4 to 6 cm skin incision was made on the lateral wall of the abdomen, parallel to the projection of the affected disc level.

then bluntly dissected. The peritoneal content was mobilized inwardly. Headlights were used to illuminate the operation field. The lateral edges of the iliac artery and the iliac vein were bluntly separated from the spine using gentle, peanut sponge, and fingertip dissection. A hand-held abdominal retractor was placed on the anterolateral part of the spine with vessels and the peritoneal contents retracted medially. For operations at and above L4/L5, the psoas muscle and lumbar plexus were identified and mobilized. Another hand-held abdominal retractor was placed on the lateral side of the spine gently retracting the psoas muscle and sympathetic nerves posteriorly. The intervertebral disc was exposed between the psoas muscle and aorta. For operations at L5/S1, exposure was carried out below the aortic bifurcation or over the shoulder of the aortic bifurcation (between the psoas muscle and left iliac artery) according to the relationship of aorta and the L5/S1 disc, assessed by CTA or MR preoperatively (Figure 2). The operation levels were identified fluoroscopically. After discectomy, a nerve hook was used to explore the lateral recess and posterior edge of the vertebra to confirm complete decompression. Endplate preparation was performed using curettes. The disc space was distracted using a parallel distractor. A proper-sized self-anchored PEEK cage (ROI-A® Oblique, LDR Médical, Troyes, France) (Figure 2(c)) was determined by trials under fluoroscopy. Cages were inserted obliquely into intervertebral space using fluoroscopy after filling with porous bioceramic artificial bone (Dragonbio®, Hubei, China). Once the position of the cage was optimal, two self-guided anchoring plates were inserted into the adjacent vertebrae under fluoroscopy.

2.3. Clinical Outcome Measurements. Operative time, blood loss, and intra- and postoperative complications were noted.

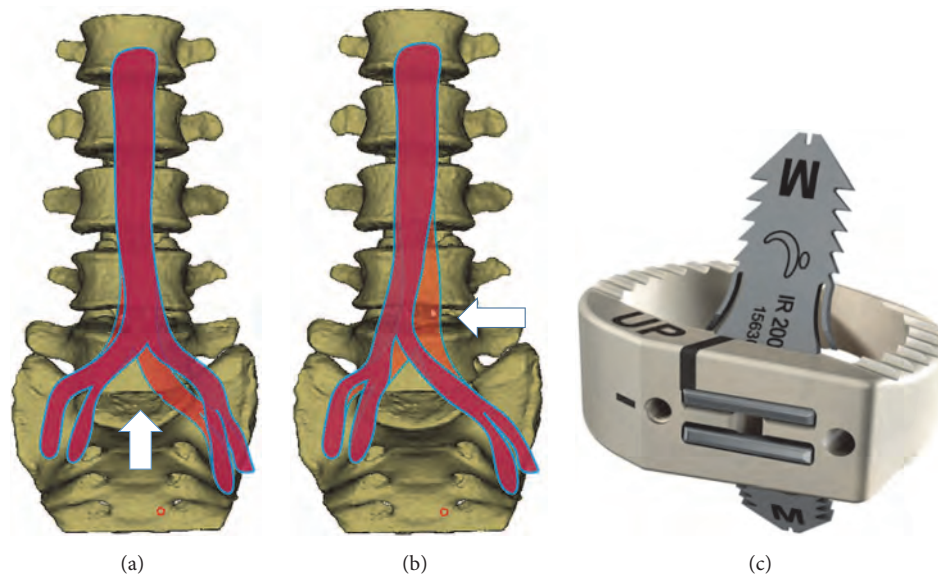


FIGURE 2: (a) The access to L5/S1 when the aortic bifurcation is high. (b) The access to L5/S1 when the aortic bifurcation is low. (c) The self-anchored PEEK cage we used in the study (ROI-A Oblique, LDR Médical, Troyes, France).

Clinical outcomes including the Oswestry low back pain disability index (ODI) and visual analog scale (VAS) for back pain and leg pain were measured preoperatively and postoperatively at 3, 6, 12, and 24 months.

2.4. Radiological Outcome Measurements. Fusion was identified by the presence of continuous bridging trabeculae at the graft and end plate junction on radiographs or CT scans [19]. Pseudarthrosis was defined when assessment failed to meet the fusion criteria at the last follow-up. Other radiological outcomes (foraminal height, disc height, and subsidence) were measured preoperatively and at 2 days and 3, 6, 12, and 24 months postoperatively. Disc height was defined as the mean value of the anterior disc height and posterior disc height. The foraminal height was determined as the longest distances between the craniocaudal dimensions of the foramen [20]. Subsidence was defined as any compromise of either vertebral endplate visible on CT scan or X-ray [21].

2.5. Statistical Analysis. All statistical analyses were conducted using SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA). Comparisons between the preoperative and postoperative parameters within the groups were performed using a paired *t*-test. A *p* value < 0.05 was considered statistically significant.

3. Results

Patient characteristics including age, gender, primary surgery, primary operation levels, reasons for revision surgery, and revision levels are summarized in Table 1. There were 13 females and 9 males aged between 48 and 63 years with a total of 27 segments enrolled in this study. There were 7 patients excluded for meeting the exclusion criteria. The

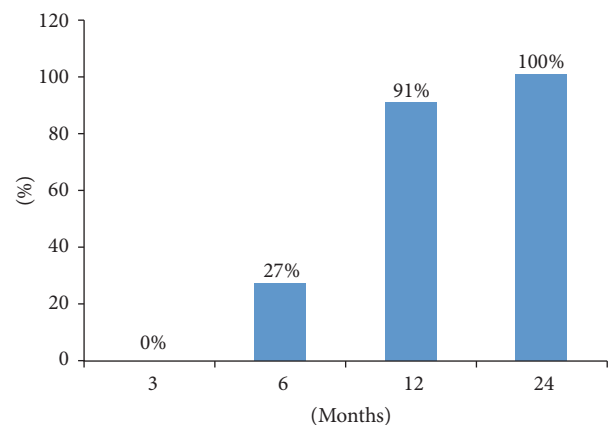


FIGURE 3: A column diagram demonstrating the fusion rate of the patients at each time point.

average age was 55.4 ± 5.5 years. Of all these 22 patients, 19 had posterior instrumentation in their previous surgery. And 7 of them experienced the failure of the posterior instrumentation before the revision surgery. The single-level cases included 9 cases at L4/5, 2 cases at L3/4, and 6 cases at L5/S1; 5 cases were with two levels. Only one patient suffered from peritoneal rupture during the exposure. No other perioperative complications were found. Four patients with 4 operated levels suffered cage subsidence without clinical symptoms (Table 1). Fusion was achieved in all patients (Figure 3).

The average operating time was 68.6 ± 22.9 minutes, and the average estimated blood loss was 85.4 ± 34.7 mL. As shown in Table 2, the VAS back pain score decreased from 5.8 ± 1.5 preoperatively to 2.2 ± 0.9 , 2.4 ± 1.0 , 2.4 ± 0.8 , and 2.3 ± 0.9 postoperatively at 2 weeks and 3, 6, 12, and 24 months, respectively (*p* < 0.05). The average VAS leg pain score also

TABLE 1: Characteristics of 22 patients who underwent revision lumbar surgery using ALLIF with self-anchored stand-alone PEEK cage.

Patient number	Gender	Age	Primary surgery	Reasons for revision surgery	Operation levels	Posterior fixation	Cage subsidence
1	Female	56	TLIF for L4/5 LDH	Implant migration	L4/5	Intact	No
2	Male	61	TLIF for L3/L4, L4/5 LDH	Implant migration	L3/4, L4/5	Intact	No
3	Female	61	TLIF for L4/5, L5/S1 LDH	Pseudarthrosis	L4/5, L5/S1	Breakage of the screw	L4/5
4	Female	49	PLIF for L4/5 LDH	ASD	L5/S1	Intact	No
5	Female	57	TLIF for L5/S1 LDH	ASD	L4/5	Intact	No
6	Female	50	PLIF for L5/S1 LDH	ASD	L4/5	Intact	No
7	Male	52	TLIF for L5/S1 LDH	ASD	L4/5	Intact	No
8	Female	63	TLIF for L4/5 LDH	ASD	L5/S1	Intact	No
9	Male	53	TLIF for L3/L4, L4/5 LDH	Pseudarthrosis	L3/4, L4/5	Breakage of the rod	L4/5
10	Male	48	L5/S1 discectomy	Recurrent disc herniation	L5/S1	None	No
11	Female	42	L4/5 discectomy	Recurrent disc herniation	L4/5	None	No
12	Male	62	L4/5 discectomy	Recurrent disc herniation	L4/5	None	No
13	Female	55	TLIF for L5 spondylolisthesis	ASD	L4/5	Intact	No
14	Female	58	Decompression and PLF for L5/S1 LDH	Recurrent disc herniation	L5/S1	Intact	No
15	Male	56	TLIF for L4/5 LDH	Pseudarthrosis	L4/5	Breakage of the rod	No
16	Male	60	Decompression and PLF for L4/5 LDH	Recurrent disc herniation	L4/5	Intact	No
17	Female	59	TLIF for L5 spondylolisthesis	Pseudarthrosis at L5/S1 and ASD at L4/5	L4/5, L5/S1	Breakage of the rod	L4/5
18	Female	63	TLIF for L4 spondylolisthesis	ASD	L5/S1	Intact	No
19	Male	52	TLIF for L5 spondylolisthesis	Pseudarthrosis	L5/S1	Screw loosening	L5/S1
20	Female	57	PLIF for L3/4, L4/5 LDH	Pseudarthrosis	L3/4	Intact	No
21	Female	50	TLIF for L3/4, L4/5 LDH	Pseudarthrosis at L4/5 and ASD at L5/S1	L4/5, L5/S1	Intact	No
22	Male	54	PLIF for L3/4, L4/5, L5/S1 LDH	Pseudarthrosis at L4/5	L4/5	Breakage of the rod	No

PLIF: posterior lumbar interbody fusion, TLIF: posterolateral lumbar fusion, TLIF: transforaminal lumbar interbody fusion, LDH: lumbar disc herniation, and ASD: adjacent segment degeneration.

TABLE 2: Clinical outcomes measured by VAS and ODI scores.

	Preop	3 months	6 months	12 months	24 months
VAS back pain	5.8 ± 1.5	2.2 ± 0.9*	2.4 ± 1.0*	2.4 ± 0.8*	2.3 ± 0.9*
VAS leg pain	5.3 ± 1.6	2.0 ± 1.3*	2.2 ± 1.3*	2.3 ± 1.0*	2.1 ± 1.1*
ODI	42.7 ± 12.6%	25.5 ± 8.5%*	23.8 ± 6.8*	23.4 ± 6.1%*	24.0 ± 6.5%

*Statistically significant compared with preoperation ($p < 0.05$).

Preop: preoperatively, 3 months: 3 months postoperatively, 6 months: 6 months postoperatively, and 12 months: 12 months postoperatively.

TABLE 3: Radiological outcome measured by disc height and foraminal height (mm).

	Preop	Postop	3 months	6 months	12 months	24 months
Disc height	8.6 ± 2.5	12.3 ± 1.5*	11.8 ± 2.2*	11.6 ± 2.3*	11.3 ± 2.3*	11.0 ± 2.0*
Foraminal height	15.8 ± 3.4	19.4 ± 2.8*	19.0 ± 3.1*	18.7 ± 2.7*	18.5 ± 2.5*	18.2 ± 2.7*

*Statistically significant compared with preoperation ($p < 0.05$).

Preop: preoperatively, postop: postoperatively, 3 months: 3 months postoperatively, 6 months: 6 months postoperatively, and 12 months: 12 months postoperatively.

decreased from 5.3 ± 1.6 preoperatively to 2.0 ± 1.3 , 2.2 ± 1.3 , 2.3 ± 1.0 , and 2.1 ± 1.1 at 3, 6, 12, and 24 months, respectively ($p < 0.05$). The average preoperative ODI score was $42.7 \pm 12.6\%$. Similarly, at 3, 6, 12, and 24 months after surgery, the postoperative ODI scores were significantly decreased to $27.5 \pm 8.2\%$, $25.5 \pm 8.5\%$, $23.8 \pm 6.8\%$, and $23.4 \pm 6.1\%$, respectively ($p < 0.05$).

The average foraminal height was 15.8 ± 3.4 mm before surgery and increased postoperatively to 19.4 ± 2.8 mm at 2 days, 19.0 ± 3.1 mm at 3 months, 18.7 ± 2.7 mm at 6 months, 18.5 ± 2.5 at 12 months, and 18.2 ± 2.7 mm at 24 months ($p < 0.05$). The average disc height also increased from 8.6 ± 2.5 mm preoperatively to 12.3 ± 1.5 mm, 11.8 ± 2.2 mm, 11.6 ± 2.3 mm, 11.3 ± 2.3 mm, and 11.0 ± 2.0 at 2 days and 3, 6, 12, and 24 months after surgery, respectively ($p < 0.05$). The results are summarized in Table 3.

4. Discussion

Anterior lumbar spinal surgery has been commonly used in conditions that include disc degeneration, trauma, infection, deformity, and tumor with approaches such as ALIF, XLIF, and OLIF [7]. Recently, these anterior approaches were adopted in lumbar revision surgery [5, 22]. Mamuti et al. retrospectively reviewed 35 patients who underwent mini-open retroperitoneal anterior lumbar interbody fusion using self-anchored cage device for the treatment of recurrent lumbar disc herniation following primary posterior instrumentation [23]. Their result showed good clinical and radiological outcomes without complications related to surgical technique and cage device. Furthermore, Mobbs et al. recommended that anterior lumbar interbody fusion could be a salvage technique for pseudarthrosis following posterior lumbar fusion surgery when the chronic low back pain raised by pseudarthrosis was nonresponsive to conservative management [24]. Anterior lumbar interbody fusion could provide a wider implant bed and more meticulous preparations of endplates for arthrodesis, which lead to the high fusion rate theoretically.

The approach-related complications concern most researchers. Bateman et al. performed a systematic review

to identify the types and incidence rates of complications associated with various approaches to anterior lumbar spine surgery. The results showed that the overall complication rate was 14.1% with intraoperative and postoperative complication rates of 9.1% and 5.2%, respectively. The most common complications reported were venous injury (3.2%), retrograde ejaculation (2.7%), neurologic injury (2%), prosthesis-related (2%), postoperative ileus (1.4%), superficial infection (1%), and complications classified as "others" (1.3%). Laparoscopic and transperitoneal procedures were associated with higher complication rates, whereas lower complication rates were observed in patients receiving mini-open techniques. A study by Fujibayashi et al. evaluated twenty-eight patients who underwent OLIF for lumbar degeneration disease [18]. Two cases of hip flexor weakness and 6 cases of thigh pain/numbness that resolved spontaneously within 3 months after operation were observed. In our study, no major approach-related complications, such as vascular injuries, ureteral injuries, visceral complication (bowel perforation), ileus, incisional hernia, or retrograde ejaculation, were observed. This suggested that the ALLIF technique is a relatively safe procedure. Other factors attributing to a low complication rate should also be considered. All procedures were performed by skilled surgeons with extensive anterior spinal surgery experience. Preoperative CT angiography was taken to evaluate difficulties in the exposure because vascular injuries were prone to occur in presence of anatomical variation, or with surrounding scar tissue [25]. Because micro-motion in the bone-graft interface is believed to be one of the main reasons for pseudarthrosis and cage subsidence [1, 26], additional pedicle screws have been used to provide sufficient primary stability after mini-open OLIF [18]. However, the self-anchored PEEK cage we used (ROI-A Oblique, LDR Médical, Troyes, France) has two integrated self-locking clips bridging the index levels which was designed to provide stronger lumbar stability, avoid the motions between the adjacent vertebral bodies, and promote solid fusion. A biomechanical test revealed that the self-locking stand-alone cage could provide immediate stability that was equivalent to that with anterior plate or posterior pedicle screw fixation [27]. Clinical studies have also demonstrated that a high

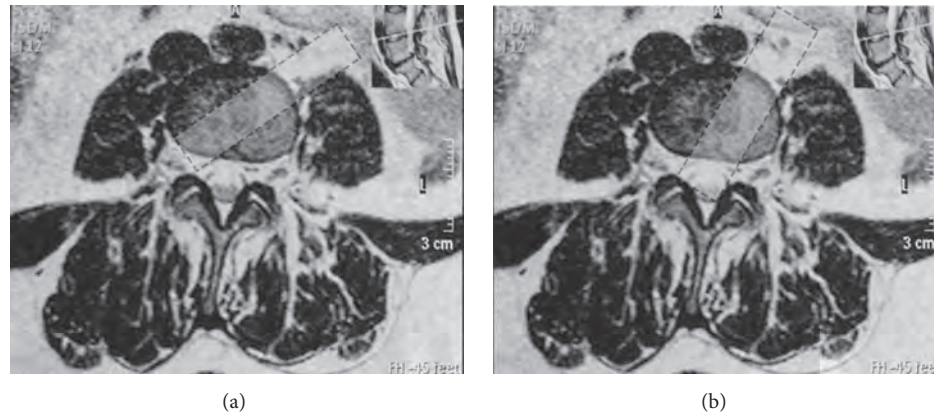


FIGURE 4: (a) Only indirect decompression can be achieved in OLIF because of the limited operation angle and field. (b) A wider operation angle and space can be provided for direct decompression in ALLIF with the skin incision placed closer to the middle line of the abdomen.

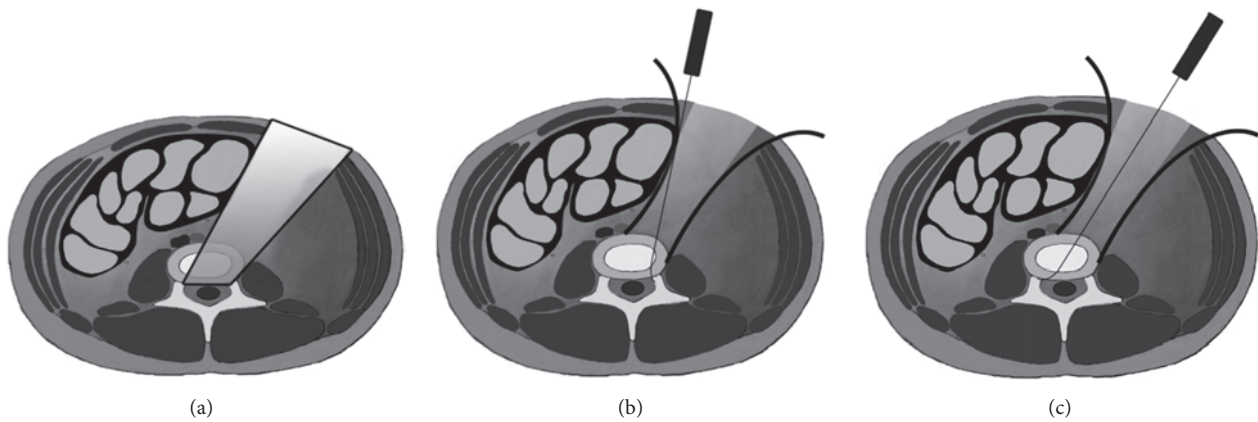


FIGURE 5: (a) The ideal operation field for direct decompression. ((b) and (c)) The operation field of the ALLIF.

fusion rate (90.6% to 97.3%) with good clinical results could be achieved using these self-anchored designed stand-alone cages [3, 25, 28]. In our study all patients achieved solid fusion at the last follow-up which supported the hypothesis that these self-anchored stand-alone cages could provide immediate stability after surgery and reach high fusion rate.

In our ALLIF, a transverse skin incision placed closer to the middle line of the abdomen was made on the lateral wall at the outer rim of abdominal rectus muscle, compared with the typical incision for OLIF. This slight adjustment provides a wider visual and operative field (Figure 4). All discectomy procedures could be performed under direct visualization, which made it possible to decompress the neurological structure bilaterally without damaging the nerve element or dural sac, thus avoiding posterior decompression surgery. A nerve hook could be used to explore the lateral recess and posterior edge of the vertebra to confirm complete and thorough decompression, which could not be achieved in the OLIF because of the operation angle (Figure 5). The indirect decompression in OLIF is achieved by disc distraction and not by the removal of the compressing element. The better operation angle in ALLIF also makes it possible to access

every L5/S1 level, even in patients with a high-riding pelvis, which may not be possible in OLIF. Moreover, the cage was easily inserted obliquely along this access angle, which largely reduced the manipulation of the aorta and vena cava, decreasing the risk of vascular injury compared with ALIF. Retraction of vascular structures throughout an entire procedure was blamed for the increase in vessel injuries and thrombotic events in OLIF [7, 29]. Therefore, we used hand-held abdominal retractors instead of self-retaining retractors to expose the discs, for they could be released intermittently to minimize the risk of vascular thrombosis. Besides, in the traditional OLIF, the access to disc of L5/S1 was below the aortic bifurcation. In our ALLIF, the access to L5/S1 disc could be below the aortic bifurcation or over the shoulder of the aortic bifurcation (between the psoas muscle and left iliac artery) according to the vascular windows at L5/S1 disc assessed by CTA or MR preoperatively. In an anatomy study by Molinares et al., 31% of MR images of patients (31/100) showed no anterior access to L5/S1 disc. However, in 4 (12.9%) of these 31 MR images, an oblique access to L5/S1 disc was found between the psoas muscle and iliac artery. We also adopted the muscle-splitting approach in our study as the

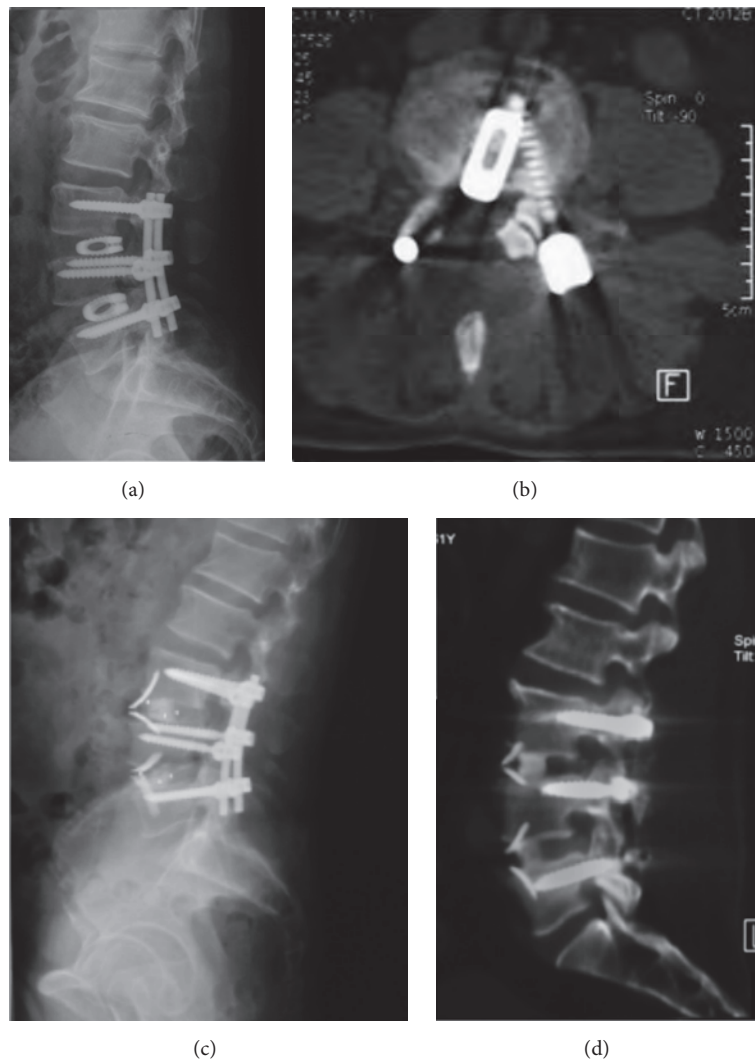


FIGURE 6: Case presentation. A 61-year-old male patient with previous PLIF surgery at L3-L5 10 months ago was admitted because of the recurrence of back and leg pain. Cage migration was confirmed by both radiograph and CT scan ((a) and (b)). ALLIF revision surgery using a self-anchored cage was performed. Good position of cage levels and satisfactory alignment of the lumbar spine were achieved (c). Fusion was achieved at 12-month follow-up (d).

so-called “sliding window” technique described by Mayer [17]. Thus, we could easily expose two discs with a slight increase in skin incision length.

The patients in our study showed significant improvement in disc height and foraminal height compared with the preoperation status at each time point (Figure 6). In addition, the VAS and ODI scores decreased significantly after surgery compared to baseline. Studies by Siepe et al. [3] and Allain et al. [28] have shown similar results with significant improvement in disc height and foraminal height and decrease in VAS and ODI scores at each time point of follow-up after surgery. Subsidence of the implant into the vertebral endplate may lead to progressive lumbar deformity and recurrence of foraminal stenosis and neurological symptoms, which have been of concern to researchers. The subsidence rate has varied in different studies using a self-anchor stand-alone cage without posterior fixation. In the

study by Allain et al., 1 out of 51 analyzed cases experienced subsidence at a 12-month follow-up using cages similar to those we used [28]. Behrbalk et al. reported that 16% (5/32) of cases of subsidence were observed with ALIF using another kind of self-anchor stand-alone cage (SynFix-LR) without posterior instrumentation [30, 31]. A decreased bone mineral density, an increased number of fused segments, damage of the endplate, overdistraction of the surgical segment, and use of oversized cages are thought to contribute to subsidence [32–34]. Beutler and Peppelman Jr. found that most of the subsidence cases happen in the first 3 months postoperatively [32]. Besides, they demonstrated that the cage subsidence is usually accompanied by the appearance of the pseudarthrosis. The long-term micromotion at the nonfused segment damaged the endplate and absorbed the cancellous bone underneath. In the present study, 18.2% (4/22) of patients suffered subsidence and all cases of subsidence were observed

before the first 6-month follow-up. Nevertheless, all cases of subsidence reached solid fusion at the last follow-up. Study showed that although the subsidence was not uncommon, the rate of symptomatic subsidence is relatively low. In the study of Le et al., radiographical subsidence occurred in 14.3% (20/140) and the symptomatic subsidence was noted only in 2.1% (3/140) of all patients [33]. In our series, all patients with cage subsidence had no clinical symptoms. Researches demonstrated that the caudal endplate is weaker than the cranial one [33, 34]. Thus the caudal endplate is at higher risk of injury with the stronger cranial endplate usually remaining intact. Similarly, in our series, the damage of caudal endplate was found in all cases with only one case of cranial endplate damage.

This study has several potential limitations. It was a non-controlled study with a relatively small number of patients, and the inclusion criteria were restrictive. Patients with osteoporosis or with risk factors of access-related complication were excluded, which may have led to an underestimation of the rates of nonunion, subsidence, and access-related complications.

5. Conclusion

The ALLIF using a self-anchored stand-alone PEEK cage is a relatively new surgical technique for lumbar revision that provides a wide visual field for operations such as direct decompression. This technique is a safe and effective method in revision lumbar surgery with only limited surgical trauma, low access-related complication rates, and satisfactory clinical and radiological results. The decreased incidence in nonunion and cage subsidence observed may be attributed to the delicate design of this self-anchored PEEK cage.

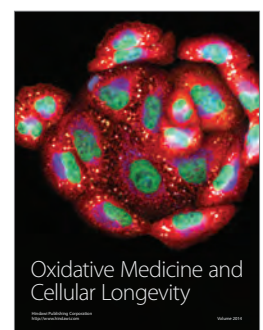
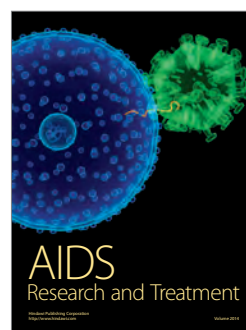
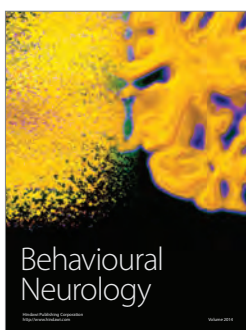
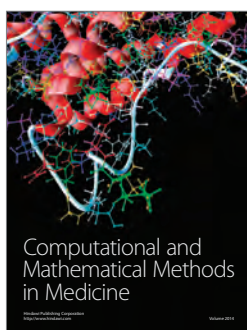
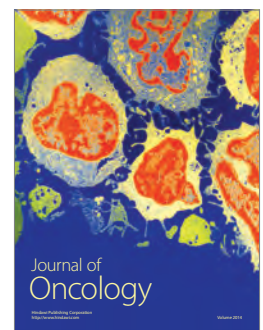
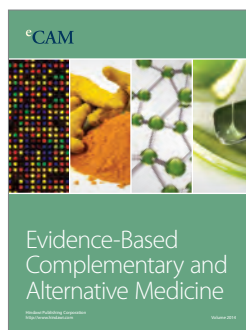
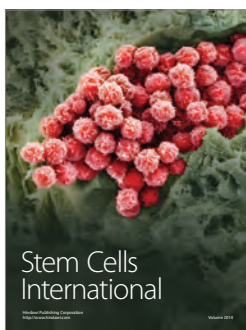
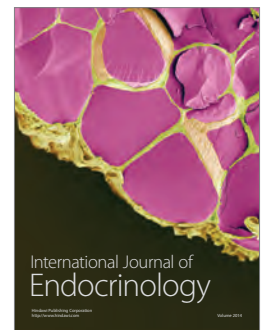
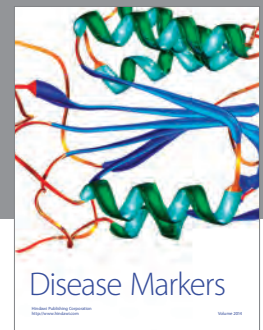
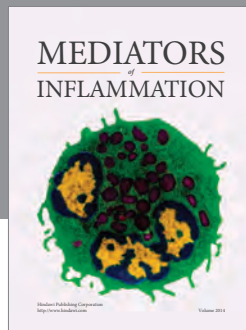
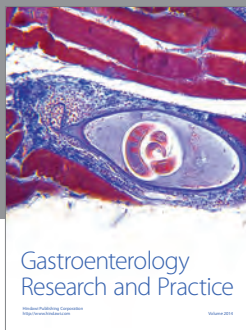
Competing Interests

The authors declare that they have no conflict of interests. None of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

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Long-term Evaluation of Cervical Disc Arthroplasty with the Mobi-C® Cervical Disc: A Randomized, Prospective, Multicenter Clinical Trial with Seven-Year Follow-up

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Abstract

Background

Cervical total disc replacement (TDR) is an increasingly accepted procedure for the treatment of symptomatic cervical degenerative disc disease. Multiple Level I evidence clinical trials have established cervical TDR to be a safe and effective procedure in the short-term. The objective of this study is to provide a long-term assessment of TDR versus anterior discectomy and fusion for the treatment of one- and two-level disc disease.

Methods

This study was a continuation of a prospective, multicenter, randomized, US FDA IDE clinical trial comparing cervical TDR with the Mobi-C® Cervical Disc versus ACDF through 7 years follow-up. Inclusion criteria included a diagnosis of symptomatic cervical degenerative disc disease at one or two cervical levels. TDR patients were treated using a Mobi-C® artificial disc (Zimmer Biomet, Austin TX, USA). ACDF with allograft and anterior plate was used as a control treatment. Outcome measures were collected preoperatively and postoperatively at 6 weeks, at 3, 6, 12, 18 months, annually through 60 months, and at 84 months. Measured outcomes included Overall success, Neck Disability Index (NDI), VAS neck and arm pain, segmental range of motion (ROM), patient satisfaction, SF-12 MCS/PCS, major complications, and subsequent surgery rate. The primary endpoint was an FDA composite definition of success comprising clinical improvement and an absence of major complications and secondary surgery events.

Results

A total of 599 patients were enrolled and treated, with 164 treated with one-level TDR, 225 treated with two-level TDR, 81 treated with one-level ACDF, and 105 treated with two-level ACDF. At seven years, follow-up rates ranged from 73.5% to 84.4% (overall 80.2%).

The overall success rates of two level TDR and ACDF patients were 60.8% and 34.2%, respectively ($p < 0.0001$). The overall success rates of one level TDR and ACDF patients were 55.2% and 50%, respectively ($p > 0.05$). Both the single and two level TDR and ACDF groups showed significant improvement from baseline NDI scores, VAS neck and arm pain scores, and SF-12 MCS/PCS scores ($p < 0.0001$). In the single level cohort, there was an increased percentage of TDR patients who reported themselves as “very satisfied” (TDR 90.9% vs ACDF 77.8%; $p = 0.028$). There was a lower rate of adjacent level secondary surgery in the single level TDR patients (3.7%) versus the ACDF patients (13.6%; $p = 0.007$).

In the two level TDR group, the NDI success rate was significantly greater in the TDR group (TDR: 79.0% vs. ACDF: 58.0%; $p = 0.001$). There was significantly more improvement in NDI change score at 7 years in the TDR patients versus ACDF. The TDR group had a significantly higher rate of patients who were “very satisfied” with their treatment compared to the ACDF group (TDR: 85.9% vs. ACDF: 73.9%). The rate of subsequent surgery at the index level was significantly lower in the TDR group compared to the ACDF group (TDR: 4.4% vs. ACDF:

16.2%; $p=0.001$). The rate of adjacent level secondary surgery was significantly lower in the two level TDR (4.4%) patients compared to the ACDF (11.3%; $p=0.03$) patients. In both single and two level cohorts, the percentage of patients with worse NDI (2.5%-3.8% of two level surgeries and 1.2%-2.5% of single level surgeries) or worse neck pain (5%-6.8% of the two level surgeries and 1.3% - 3.8% of the single level surgeries) was strikingly low in both groups but trended lower in the TDR patients.

Conclusions

At seven years, the composite success analysis demonstrated clinical superiority of two level TDR over ACDF and non-inferiority of single level TDR versus ACDF. There were lower rates of secondary surgery and higher adjacent level disc survivorship in both groups. Both surgeries were remarkably effective in alleviating pain relative to baseline and the rate of patients with worse disability or neck pain was surprisingly low. Overall, greater than 95% of patients (from both groups) who underwent TDR and 88% of patients who underwent ACDF were “very satisfied” at seven years. The differences in clinical effectiveness of TDR versus ACDF becomes more apparent as treatment increases from one to two levels, indicating a significant benefit for TDR over ACDF for two-level procedures.

Ethical Standards

The Mobi-C Clinical Trial (ClinicalTrials.gov registration number: NCT00389597) was conducted at 24 sites in the US and was approved by the Institutional Review Board, Research Ethics Committee, or local equivalent of each participating site.

Level of Evidence

1.

TDR

KEYWORDS: CERVICAL TOTAL DISC REPLACEMENT, ACDF, DEGENERATIVE DISC DISEASE, MOBI-C

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Introduction

Neck and arm pain have shown to negatively impact multiple facets of patient health¹ and neck pain alone remains one of the largest contributors to the overall global health burden.² Since the mid-20th Century, the standard surgical procedure for treating symptomatic cervical spondylosis has been anterior discectomy and fusion (ACDF). While ACDF is a highly effective procedure, there are two major, procedure-specific complications: pseudoarthrosis and adjacent segment degeneration (ASD).³

The causative relationship between ACDF and ASD most likely lies in the kinematics and functionality of the partially fused spine. As motion in treated segments is eliminated through fusion, adjacent segments become hypermobile and adjacent discs experience increased loads and stresses.⁴⁻⁷ In turn, these kinematic changes have the potential to initiate or accelerate pathologies in intact segments. Unfortunately, the immobility of treated segments is the very nature of the fusion procedure, required for stabilization

after discectomy. As such, it seems only natural to seek an alternative surgical technique in which natural, healthy motion is preserved or restored.

Cervical total disc replacement (TDR) was developed in an effort to preserve natural spinal kinematics while providing mechanical stabilization after neural decompression and discectomy. Several Level I evidence randomized clinical trials have confirmed both the safety and efficacy of TDR in both the short- and long-term.⁸⁻¹⁴ TDR has shown to have many possible advantages over ACDF including lower rates of subsequent surgical intervention,^{15,16} lower rates of adjacent segment degeneration,^{13,17,18} and an advantage in cost-effectiveness.^{19,20} Furthermore, kinematic analyses have shown TDR to maintain functional biomechanics at the level treated while mitigating excess motion at adjacent segments.²¹

The purpose of this study is to expand on results from the Mobi-C® Cervical Disc FDA IDE clinical trial with 7-year data. Previously reported 2-^{13,22}, 4-^{14,23}, and 5-year^{24,25} follow-up results from this ran-

domized clinical trial have shown equivalent or better performance of TDR compared to ACDF at both one and two levels of treatment. Here, we present 7-year results from the one and two level arms for a comprehensive, long-term evaluation of TDR with Mobi-C®.

Methods

Study Design and Patient Population

The study was a prospective, randomized multicenter clinical trial conducted at 24 sites in the US. The study was divided into two separate arms of one-level and two-level treatment, conducted in tandem. Enrollment criteria included a diagnosis of degenerative disc disease with radiculopathy or myeloradiculopathy at either one or two contiguous levels from C3 to C7. General inclusion and exclusion criteria are listed in Table 1.

Patients were randomized in a 2:1 ratio (investigational: control) and received surgery between April 2006 and March 2008. The investigational group was treated with TDR using the Mobi-C® Cervical Disc (Mobi-C, Zimmer Biomet, Austin, TX, USA) (Figure 1). The control group received ACDF with allograft and anterior plate. A total of 164 patients were treated with one-level TDR, 81 with one-level ACDF, 225 with two-level TDR, and 105 with two-level ACDF. Surgeons were blinded up to the time of the procedure and patients were blinded until after surgery. Blinding afterwards was not possible due to differences in postoperative recovery protocols and the ability for patients to view their own radiographs.

Postoperative recovery schemes were left to the discretion of the treating surgeons. All patients were instructed to refrain from taking non-steroidal anti-inflammatory drugs (NSAIDs) a week before surgery until 3 months post-surgery. Patients were followed at 6 weeks, 3 months, 6 months, annually to 5 years, and then again at 7 years. A detailed description of the study design, including surgical technique, has been previously published by Davis et al (2013).¹³ A CONSORT diagram is included in the Appendix.

Outcome Measures

Patient reported clinical outcomes included the neck

disability index (NDI), the visual analog scale (VAS) for neck and arm pain, the short-form 12-item questionnaire (SF-12) for physical health (PCS) and mental health (MCS), and a patient satisfaction survey. For VAS arm pain, the mean improvement from baseline is reported for the most symptomatic arm at preoperative. In the event that a patient had equal preoperative VAS arm pains scores, the improvement in both arms was taken as the average improvement of both arms. To account for differences at presentation between patients and facilitate explanation

Table 1. Study Inclusion and Exclusion Criteria.

Inclusion Criteria
<ul style="list-style-type: none"> • Age 18-69 years; • Symptomatic cervical degenerative disc disease in one or two levels between C3-C7 with: <ul style="list-style-type: none"> ◦ Myelopathy or myeloradiculopathy and/or ◦ Decreased muscle strength and/or ◦ Abnormal sensation and/or abnormal reflexes; • Deficit confirmed by CT, MRI, or X-ray; • NDI Score of $\geq 30/100$; • Unresponsive to non-operative treatment for at least 6 weeks or presence of progressive symptoms or signs of nerve root/spinal cord compression despite continued non-operative treatment; • No prior surgical procedures at the operative level and no prior fusions at any cervical level; • Physically and mentally able and willing to comply with the protocol; • Signed informed consent; • Willingness to discontinue all use of non-steroidal anti-inflammatory drugs (NSAIDs) from one week before surgery until 3 months after surgery;
Exclusion Criteria
<ul style="list-style-type: none"> • More than two vertebral levels requiring treatment; • Immobile levels between C1 and C7 from any cause; • Any prior surgery at the operative level or any prior fusion at any cervical level; • Disc height less than 3 mm; • T-score less than -1.5 (osteoporosis evaluation); • Paget's disease, osteomalacia, or any other metabolic bone disease other than osteoporosis; • Active infection of surgical site or history of or anticipated treatment for systemic infection including HIV and/or Hepatitis C; • Active malignancy: a history of any invasive malignancy (except non-melanoma skin cancer), unless treated with curative intent with no clinical signs or symptoms of malignancy in the past 5 years; • Marked instability of the cervical spine on resting lateral or flexion-extension radiographs; • Known allergy to device materials including cobalt, chromium, molybdenum, or polyethylene; • Segmental kyphosis of greater than 11° at treatment or adjacent levels; • Rheumatoid arthritis, lupus, or other autoimmune disease; • Any diseases or conditions that would preclude accurate clinical evaluation; • Daily, high-dose oral and/or inhaled steroids or a history of chronic use of high dose steroids; • Morbid obesity (BMI > 40); • Use of any other investigational drug or medical device within 30 days prior to surgery; • Pending litigation relating to spinal injury (worker's compensation not included); • Smoking more than one pack of cigarettes per day; • Reported to have a mental illness or belonging to a vulnerable population.

of the data to non-spine providers, recovery ratios (RR) were calculated as the percentage difference between pre- and post-operative scores using the method of Hirabayashi:²⁶

$$RR = ([\text{Follow-up score}] - [\text{Baseline score}]) / ([\text{Optimum score}] - [\text{Baseline score}])$$

where optimum score is the best possible score for that outcome measure (e.g. 0 for VAS, 100 for SF-12). The recovery ratio represents the improvement in outcome normalized to the patient's baseline outcome score relative to the possible improvement in outcome.

Patients were asked two questions related to satisfaction. For patient satisfaction, patients were surveyed if they were "very satisfied," "somewhat satisfied," "somewhat dissatisfied," or "very dissatisfied" with their treatment. Patients were also asked how likely they were to recommend their respective surgery to a friend with possible responses of "definitely," "probably," "probably not," and "definitely not." For the purposes of this investigation, high likelihood to recommend was calculated as the proportion of patients who answered "definitely yes" or "probably yes" for the questionnaire.

Radiographic outcomes included measurements of flexion-extension and lateral bending range of motion (ROM), functional spinal unit height, heterotopic ossification, and adjacent segment degeneration. Heterotopic ossification was assessed using the grading system adapted from McAfee and Mehren.^{27,28} Adjacent

segment degeneration was assessed using the grading system adapted from Kellgren and Lawrence.²⁹ A team of independent radiologists (Medical Metrics, Inc., Houston, TX) made all radiographic determinations.

Primary Success Endpoint

The primary endpoint for the study was a composite definition of patient success. In order to be considered a success, a patient had to meet each of the following criteria:

- An improvement in NDI score of at least 30 points for a patient with a preoperative NDI score of 60 or greater; or an improvement of at least 50% of preoperative NDI score for patients with a preoperative score of less than 60;
- No subsequent surgical intervention at the index level(s);
- No adverse events (AEs) classified as major complications by a clinical events committee (CEC);
- Maintenance or improvement in neurologic function;
- Radiographic success.

All subsequent surgeries were collected and documented in detail consistent with previous descriptions.^{13,15,24,25} The study protocol did not specify the indications for reoperation in either treatment group. The decision for subsequent surgical intervention was determined solely by the treating surgeon and the patient's personal decision to proceed. Consistent with other analyses,^{9,11,15,18} index-level secondary surgeries were categorized when possible as a revision, removal, reoperation or supplemental fixation. Essentially, any surgery that touched the index level was considered as an index-level reoperation, even if the primary goal of surgery was to correct an adjacent level problem. Secondary operations at adjacent levels were documented as well. Thus, operations at adjacent levels only were not considered in the primary success-or-failure study endpoint. However, operations that involved both index and adjacent levels were considered in the primary success or failure study endpoint. For plate removals, if the plate was removed from the index level to extend the fusion to an adjacent level, this event was considered a removal per the study protocol and considered a failure

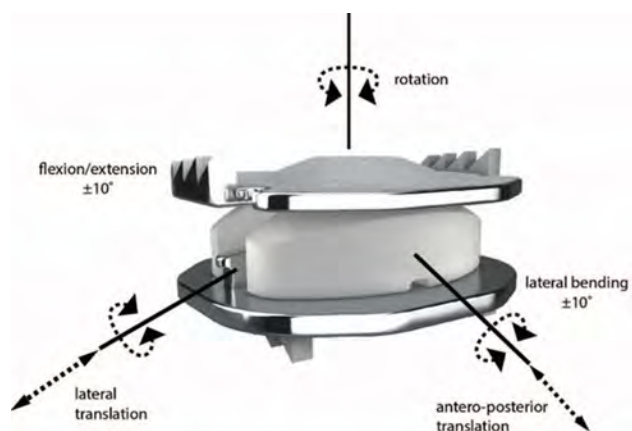


Fig. 1. The Mobi-C® Cervical Disc.

for the primary endpoint.

Adverse events (AEs) were defined as any clinically adverse sign, symptom, syndrome, or illness that occurred or worsened during the operative and post-operative period. AEs were assessed by a Clinical Events Committee (CEC) composed of two orthopedic surgeons and one neurosurgeon. The members of the CEC were not investigators on the study and were blinded to treatment whenever possible. Any patient with an AE that was determined by the CEC to be a major complication of the treatment was considered a study failure.

Neurological assessments were performed by the investigator using tests of sensory, reflex, and motor function. Any patient with a decrease in sensory, reflex, or motor function from preoperative status was considered a failure.

For the TDR group, radiographic success was defined as at least 2° of segmental motion in flexion-extension or no evidence of bridging bone across the disc space. Grade IV heterotopic ossification was an indication of bridging bone. For the ACDF group, radiographic success was defined as fusion of the treated level(s), less than 2° of segmental motion in flexion-extension, and evidence of bridging bone across the disc space with radiolucent lines at no more than 50% of the graft vertebral interfaces.

Statistical Methods

The primary endpoint was assessed with the hypothesis of non-inferiority of TDR versus ACDF with a 10% non-inferiority margin. Non-inferiority was tested using a 95% one-sided lower confidence bound of the difference between the investigation and the control group. A closed testing procedure was prespecified for superiority, to be tested in the event that non-inferiority was confirmed. If non-inferiority was confirmed, superiority was tested using a 95% lower confidence bound.

There were two distinct methods of outcome assessment. To evaluate the change in outcomes specifically at seven years, p-values for differences in improvement from baseline in NDI, VAS, and SF-12 scores at 84 months were calculated using repeated measures,

mixed effects ANOVA adjusted for multiplicity.

A global outcome assessment was also performed to evaluate the aggregate change in outcome over the entire seven year study period (inclusive of all of the previous time points including two year, five year, and seven year time points). Global p-values for differences in absolute NDI, VAS, and SF-12 scores between TDR and ACDF were calculated using repeated measures, mixed effects ANOVA across all post-operative time points.

Secondary surgery survival function estimates were generated using the Kaplan-Meier method, with the log-rank test to compare survival functions. Patients undergoing a removal, revision, or supplemental fixation procedure were censored at all time points after the surgery for secondary outcomes (e.g. NDI, VAS). P-values for categorical endpoints were calculated using a two-sided Fisher's exact test. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All patients that were discontinued (e.g. withdrawn, lost-to-follow-up, device removal) were censored at their last follow-up prior to study withdrawal. A scenario analysis was performed to determine the potential influence of discontinued patients, including last observation carried forward (best-case scenario), and all discontinued patients counted as failures (worst-case scenario analysis). Under each scenario analysis, TDR remained either superior or non-inferior to ACDF.

Results

Preoperative patient characteristics and clinical outcomes were similar between treatment groups within treatment arms (Table 2). The inclusion criteria required that patients smoke less than one pack per day, but the preoperative smoking status of each patient was not collected as part of the study protocol. However, a post-hoc survey conducted by the investigators estimated the proportion of smokers in the study to be 15.1% for ACDF patients and 18.7% for TDR patients.³⁰ At 7 years, the follow-up rate was 84.4% for the two-level TDR group, and 75.0% for the two-level ACDF group, and 80.1% for the one-level TDR group and 74.3% for the one-level ACDF group. The follow-up rates were calculated using the FDA

guidelines for orthopedic device clinical trials.³¹

Two-Level Treatment Arm

Primary Success Analysis – Two level

At 7 years, two-level TDR demonstrated superiority compared to two-level ACDF (Figure 2). The rate of success was 60.8% (104/171) in the TDR group and 34.6% (27/78) in the ACDF group with a difference of 26.2% and lower 95% confidence bound of 15.4%. Analyzing the individual components of success illustrates that the primary driver of 2-level TDR superiority was due to a significant difference in percentage of successful NDI scores (TDR 79% vs ACDF 58%), lower incidence of subsequent surgery (4.4% vs 16.2%), and lower incidence of neurological failure (6.4% vs 17.1%; Table 3). The differential success of TDR was not attributable to differences in the rate of adverse events or radiological deterioration between groups.

Patient Reported Outcomes - Two level

Two-level TDR and ACDF patients had similar pre-operative NDI scores, and NDI at all follow-ups was significantly improved from baseline for both treat-

ments though seven years. Globally, TDR patients had significantly lower NDI scores than ACDF patients ($p < 0.0001$; Figure 3) averaged across all follow-up periods. Specifically at the seven year follow-up endpoint, the TDR group also had greater improvement in NDI scores (35.6 ± 20) than the ACDF group (28.2 ± 21.7 ; $p = 0.04$) at 7 years (Table 4). Considering the recovery ratios, NDI scores improved 67% over baseline in the TDR group and 53% in the ACDF patients. For two-level patients, the most improved NDI item was Pain Intensity for ACDF (2.0 points) and Recreation for TDR (2.4 points). For

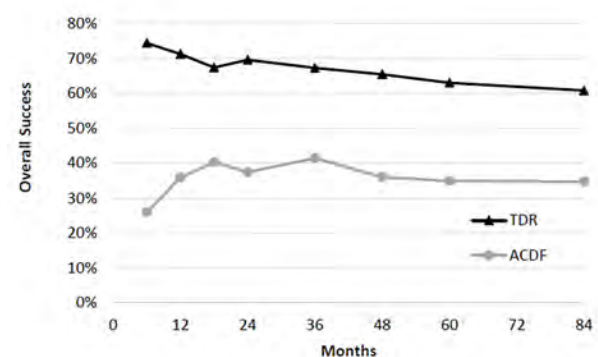


Fig. 2. Overall treatment success of two-level TDR and ACDF.

Table 2. Preoperative Patient Characteristics for TDR and ACDF.

Characteristic	2-Level		1-Level	
	TDR	ACDF	TDR	ACDF
N	225	105	164	81
Age (years) (range)	45.3 ± 8.1 (21-67)	46.2 ± 8.0 (27-65)	43.3 ± 9.2 (23-67)	44.0 ± 8.2 (27-66)
Gender n (%)				
Male	113 (50.2%)	45 (42.9%)	78 (47.6%)	36 (44.4%)
Female	112 (49.8%)	60 (57.1%)	86 (52.4%)	45 (55.6%)
BMI (SD)	27.6 (4.5)	28.1 (4.2)	27.3 (4.4)	27.4 (4.2)
Work Status n (%)				
Able to work	141 (62.7%)	64 (61.0%)	108 (65.9%)	46 (56.8%)
Not able to work	50 (22.2%)	22 (21.0%)	37 (22.6%)	22 (27.2%)
Does not work	34 (15.1%)	19 (18.1%)	19 (11.6%)	13 (16.0%)
Worker's Compensation n (%)				
Receiving	11 (4.9%)	7 (6.7%)	6 (3.7%)	5 (6.2%)
Not Receiving	214 (95.1%)	98 (93.3%)	158 (96.3%)	76 (93.8%)
Treated Segment(s)				
C3-C5	1 (0.4%)	2 (1.9%)		
C4-C6	60 (26.7%)	23 (21.9%)		
C5-C7	164 (72.9%)	80 (76.2%)		
C3-C4			1 (0.6%)	4 (4.9%)
C4-C5			11 (6.7%)	2 (2.5%)
C5-C6			92 (56.1%)	46 (56.8%)
C6-C7			60 (36.6%)	29 (35.8%)

Values given are mean ± SD unless otherwise indicated.

Table 5. NDI and pain status (% of patients) at last follow-up in 2-level TDR and ACDF.

Status*	NDI			VAS Neck Pain		
	TDR	ACDF	P value†	TDR	ACDF	P value†
Improved	80.8%	70.2%	0.10	86.0%	77.7%	0.15
Not improved	16.5%	25.9%		9.0%	15.5%	
Worse	2.7%	3.8%		5.0%	6.8%	

* NDI: Improved: $\geq 15/100$ point increase from baseline. Not improved: < 15 point change (\pm) from baseline. Worse: $\leq -15/100$ point decrease from baseline.

Neck pain: Improved: $\geq 10/100$ point increase from baseline. Not improved: < 10 point change (\pm) from baseline. Worse: $\leq -10/100$ point decrease from baseline.

† Fisher's exact test.

VAS neck pain and arm pain scores, both groups improved significantly compared to baseline by six weeks and maintained the improvement averaged across all followup periods (Figure 3). TDR patients had significantly lower VAS neck pain scores than ACDF patients averaged across all followup periods ($p=0.0002$; Figure 3). At the specific 7 year followup time-point, the TDR group showed a nonsignificant trend toward more improvement in VAS neck scores (50.9 ± 30.6) than the ACDF group (44.1 ± 39 ; $p=0.21$; Table 4). At the 7 year followup endpoint, VAS neck pain improved 72% over baseline in the TDR group and 57% over baseline in the ACDF group. There was no apparent difference between TDR and ACDF with respect to VAS arm pain at the 7-year follow-up endpoint (Table 4).

The vast majority of patients demonstrated improvement in NDI in the two level cohort (80% TDR and 70.2% ACDF; Table 5) and there was a strikingly low percentage of patients who had worse NDI scores (2.7% TDR and 3.8% ACDF; $p=0.10$). Overall, the vast majority of patients demonstrated improvement in VAS neck pain in both the two level cohort (86%

TDR and 77.7% ACDF; $p=0.15$) and the single level cohort (87.5% TDR and 83.8% ACDF; $p=0.21$). Similarly, there was a strikingly low percentage of patients who had worse NDI scores in both the two level cohort (5% TDR and 6.8% ACDF) and the single level cohort (3.8% TDR and 1.3% ACDF; Table 5).

Both patient groups saw a significant improvement in SF-12 PCS/MCS scores from baseline. TDR had significantly higher postoperative SF-12 PCS scores averaged across all time points ($p=0.0003$), but SF-12 MCS scores were similar in both treatment groups (Figure 3). At the specific seven year time point, there were no statistically significant differences in SF12 PCS or MCS scores.

Table 3. Overall success and components of success for 2-level TDR and ACDF.

	TDR	ACDF	Difference
Composite success	60.8%	34.6%	26.2%*
NDI success	79.0%	58.0%	21.0%†
Subsequent Surgery	4.4%	16.2%	11.8%†
Neurologic failure	6.4%	17.1%	10.7%†
Adverse events	5.3%	8.6%	3.3%
Radiographic failure	10.1%	9.1%	1.0%

* Superiority of TDR vs. ACDF established with 95% lower confidence bound of difference $> 0\%$. † $p < 0.05$; Fisher's exact test.

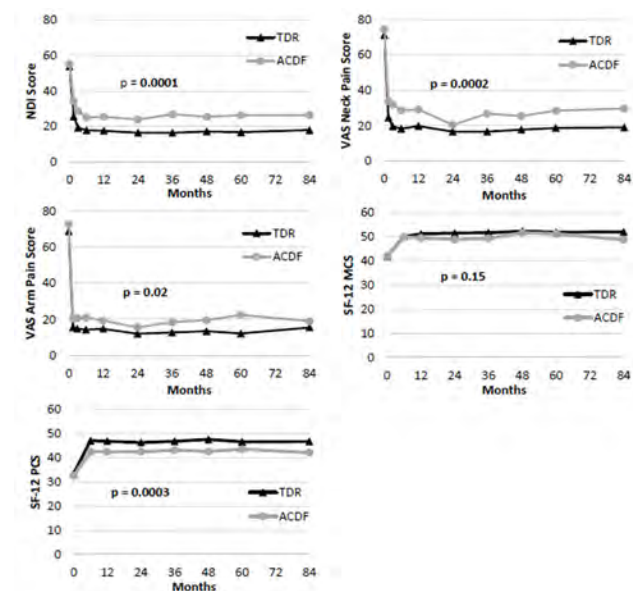


Fig. 3. Patient-reported outcomes for two-level TDR and ACDF Patients from preoperative to 7 years follow-up. P-values are from global test of the difference between TDR and ACDF patient scores, generalized across all time points. Top Left: Mean NDI scores. Top Right: Mean VAS Neck Pain scores. Middle Left: Mean VAS arm pain scores. Middle Right: Mean SF-12 MCS. Bottom Left: Mean SF-12 PCS.

Overall patient satisfaction was high in both groups with high proportions of patients in both groups describing themselves as “very satisfied” [TDR: 86.0% (160/186) vs. ACDF: 73.9% (51/69); $p = 0.039$]. However, a higher proportion TDR patients answered they would “definitely” or “probably” recommend their treatment to a friend, when compared to the ACDF group [TDR: 96.8% (179/185) vs. ACDF: 88.4% (61/69); $p = 0.025$].

Radiographic Outcomes - Two level

The TDR grouped maintained range of motion in flexion/extension and lateral bending at both treated levels (Figure 4). Both groups experienced a marginal decrease in functional spinal unit height relative to postoperative measurements at both the superior and inferior treated levels (Table 6). For 2-level TDR patients, bridging bone at either level was present in 11.1% of patients (6.5% superior level/4.7% inferior level). At 7 years, 90.9% of ACDF patients met the criteria for radiographic fusion. Both groups experienced adjacent segment degeneration. However, the ACDF group presented with double the prevalence of radiographic degeneration compared to the TDR group at both the inferior (TDR 30.3% vs ACDF 66.7%) and superior (TDR 37.5% vs ACDF 80.8%) adjacent levels, respectively (Table 6).

Safety Outcomes - Two level

CEC classified adverse events rates were also similar between groups (TDR: 5.3% (12/225), ACDF: 8.6% (9/105)). TDR patients had significantly fewer subsequent surgical interventions than ACDF patients

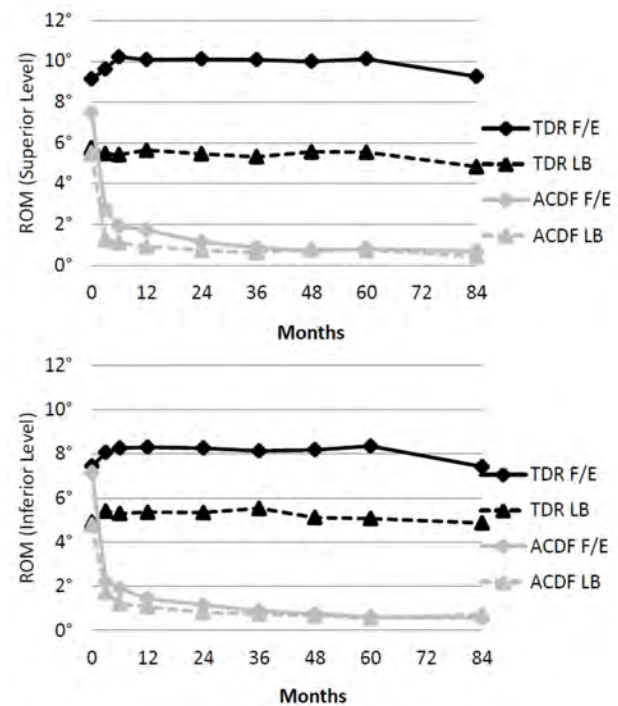


Fig. 4. Range of motion in flexion/extension (F/E) and lateral bending (LB) for two level patients. Top: Range of motion at the superior level. Bottom: Range of motion at the inferior level.

Table 4. Outcomes for 2-Level TDR and ACDF.

Study	Outcome	Treatment arm	Baseline	7 Years	Mean Δ at 7 years*	P value†	Recovery Ratio
2-Level	NDI	TDR	53.8 \pm 15.4	18.0 \pm 19.1	35.6 \pm 20.3	0.04	67%
		ACDF	55.7 \pm 15.2	26.2 \pm 22.4	28.2 \pm 21.7		53%
	VAS neck pain	TDR	71.2 \pm 20.5	19.0 \pm 27.1	50.9 \pm 30.6	0.21	72%
		ACDF	75.1 \pm 18.9	28.7 \pm 30.4	44.1 \pm 33.9		57%
	VAS arm pain	TDR	68.8 \pm 25.0	15.9 \pm 25.7	54.1 \pm 32.8	0.99	74%
		ACDF	73.1 \pm 21.9	18.4 \pm 27.0	55.1 \pm 32.0		76%
	SF-12 PCS	TDR	33.4 \pm 6.7	46.3 \pm 11.1	12.7 \pm 10.9	0.55	19%
		ACDF	32.5 \pm 7.7	43.7 \pm 11.9	10.3 \pm 11.4		15%
	SF-12 MCS	TDR	41.9 \pm 11.3	52.0 \pm 10.1	10.5 \pm 12.7	0.30	16%
		ACDF	42.0 \pm 12.0	49.1 \pm 12.7	7.2 \pm 14.3		10%

*Mean of differences in outcomes between 7 years and preoperative follow-up. † Adjusted p-value for difference in change from baseline between TDR and ACDF at 7-year follow-up. Values given are mean \pm SD unless otherwise indicated. NDI, neck disability index; VAS, visual analog scale; SF-12, Short Form 12-item Health Survey; MCS, Mental Composite Score; PCS, Physical Composite Score.

did at both the treated and adjacent levels. By 7 years, subsequent surgeries at the treated level, defined as any reoperation, revision, removal, or supplemental fixation, occurred in 4.4% (10/225) of TDR patients and 16.2% (17/105) of ACDF patients ($p = 0.0008$). The TDR secondary surgeries were Removal (5), Reoperation (2), Revision (2) and Supplemental Fixation (1). Among ACDF patients, the secondary surgeries were Removal (8), Revision (4), Supplemental Fixation (3) and Reoperation (2). Discounting the plate removals at the index level (presumably to be able to access adjacent level pathology), the adjusted index level secondary surgery rate for ACDF was 10.5% for two-level. The most common reason for additional surgical intervention at the index level(s) was persistent radiculopathy and/or neck pain ($n = 7$) and pseudoarthrosis ($n = 9$), for the TDR and ACDF group, respectively. In the TDR group, there was one case of device migration that was asymptomatic, and one case of instability of the TDR due to over-preparation of the vertebral endplate that required surgical intervention. Subsequent surgeries that involved at least one adjacent level occurred in 4.4% (10/225) of TDR patients and 11.4% (12/105) of ACDF patients ($p = 0.03$). The most common reason for additional surgical intervention at an adjacent level was adjacent level disease or herniation for both the TDR ($n = 10$) and ACDF ($n = 8$) group. Kaplan-Meier survival function estimates demonstrated that TDR patients were less likely to

have subsequent surgery due to either index or adjacent level indications (Figure 5).

One-Level Treatment Arm

Primary Success Analysis - Single level

Based on the FDA required measure of composite success, there was no significant difference in overall success between TDR and ACDF in the single level cohort patients. Therefore, one-level TDR demonstrated non-inferiority compared to one-level ACDF at 7 years (Table 7; Figure 6). The rate of success was 55.2% (64/116) in the TDR group and 50.0% (25/50) in the ACDF group with a difference of 5.2% and lower 95% confidence bound of the difference of -8.7%. The main driver of the (nonsignificant) difference in success rates was a significantly lower incidence of subsequent surgery at the index level in TDR patients (TDR 3.0% vs ACDF 12.3%; Table 7).

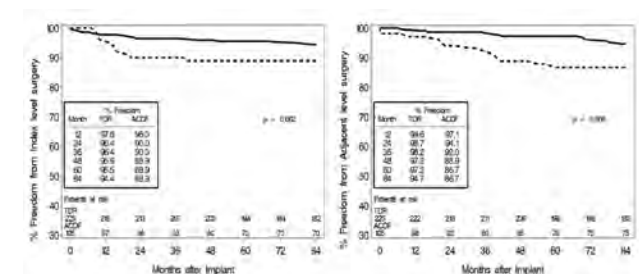


Fig. 5. Kaplan-Meier survival function estimates for subsequent surgery in two-level patients. P-value based on log-rank test. Left: Subsequent surgery for index level indications. Right: Subsequent surgery at the adjacent level.

Table 6. Radiographic Outcomes for 2-Level TDR and ACDF at 7 years.

Outcome	Treatment	Superior Level	Inferior Level
ROM in Flexion/Extension	TDR	9.3 ± 5.8°	7.4 ± 5.2°
	ACDF	0.2 ± 0.2°	0.6 ± 0.8°
ROM in Lateral Bending	TDR	4.8 ± 3.4°	4.9 ± 3.4°
	ACDF	0.4 ± 0.4°	0.7 ± 0.9°
FSU Height Change from PreOp	TDR	0.8 ± 1.2 mm	0.2 ± 1.1 mm
	ACDF	1.5 ± 0.8 mm	1.6 ± 0.9 mm
FSU Height Change from PostOp*	TDR	-0.5 ± 0.4 mm	-0.4 ± 0.4 mm
	ACDF	-0.7 ± 0.7 mm	-0.9 ± 0.9 mm
Adjacent Segment Degeneration	TDR	37.5% (57/152)	30.3% (33/109)
	ACDF	80.8% (42/52)	66.7% (28/42)

Values given are mean ± SD unless otherwise indicated. * Prior to discharge from hospital.

Patient Reported Outcomes - Single level

Mean NDI scores improved significantly for both groups by six weeks, and improvement was maintained through seven years in both groups compared to baseline (Figure 7). There was no statistically significant difference between groups in global NDI in the single level cohort averaged across all time points ($p=0.11$). While the TDR group showed greater improvement at early time points, both groups demonstrated comparable mean NDI scores and mean NDI improvement from baseline (TDR 35.4 ± 20.6 vs ACDF 33.8 ± 20.2 ; $p=0.99$) at the specific seven year endpoint (Table 8). On average, NDI recovery ratios improved 67% over baseline in the TDR patients and 64% over baseline in the ACDF patients. For one-level patients, the most improved NDI item was Recreation for both ACDF (2.4 points) and TDR (2.4 points). Both the mean improvement (35 points) and the recovery ratio (67%) are strikingly similar in the one- and two-level TDR cohorts. Similarly, for VAS neck pain and arm pain scores, both groups saw a significant improvement from baseline by six weeks, which was maintained through seven years (Table 8). There was no statistically significant difference in global VAS neck pain in the single level cohort averaged across all time points. The TDR group

showed a greater level of VAS Neck Pain improvement at early time points, but this difference attenuated at the seven year endpoint, where both groups showed a similar level of pain score improvement (TDR 51.1 ± 33 vs ACDF 48.2 ± 30 ; Table 8). Overall, both groups of patients had similar VAS neck pain recovery ratios (71% TDR vs 67% ACDF). Again, the single level TDR VAS neck pain improvement (51 ± 33) and recovery ratio (71%) was strikingly similar to the two-level cohort (Table 8). There was a significantly lower global VAS arm pain in the TDR cohort averaged across all time points ($p=0.03$). However, at the specific 7 year endpoint, there was no significant difference in VAS arm pain between groups ($p=0.35$, Table 8).

In the single level cohort, the vast majority of patients demonstrated improvement in NDI (84.6% TDR and 84.8% ACDF). Similarly, there was a strikingly low percentage of patients who had worse NDI scores in the single level cohort (1.2% TDR and 2.5% ACDF; Table 9). Overall, the vast majority of patients demonstrated improvement in VAS neck pain in the single level cohort (87.5% TDR and 83.8% ACDF; $p=0.21$). Similarly, there was a strikingly low percentage of patients who had worse NDI scores in the single level cohort (3.8% TDR and 1.3% ACDF;

Table 7. Overall success and components of success for 1-level TDR and ACDF.

	TDR	ACDF	Difference
Composite success	55.2%	50.0%	5.2%*
Subsequent Surgery	3.0%	12.3%	9.3%†
Radiographic failure	9.3%	4.5%	4.8%
Adverse events	6.1%	3.7%	2.4%
NDI success	76.5%	77.8%	1.3%
Neurologic failure	11.4%	11.5%	0.1%

* Non-inferiority of TDR vs. ACDF established with 95% lower confidence bound of difference $> -10\%$. † $p < 0.05$; Fisher's exact test.

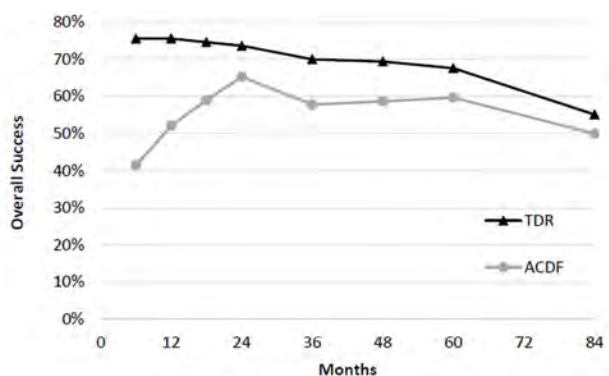


Fig. 6. Overall treatment success of one-level TDR and ACDF.

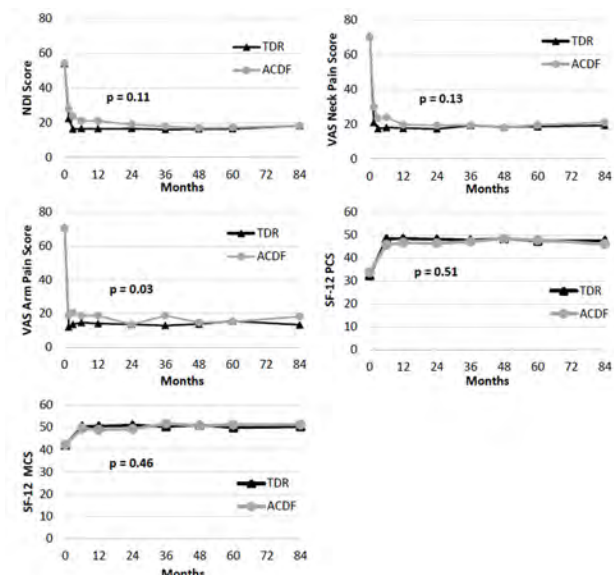


Fig. 7. Patient reported outcomes for one-level TDR and ACDF Patients from preoperative to 7 years follow-up. P-values are from a global test of the difference between TDR and ACDF patient scores, generalized across all time points. Top Left: Mean NDI scores. Top Right: Mean VAS Neck Pain Scores. Middle Left: Mean VAS Arm Pain Scores. Middle Right: Mean SF-12 PCS. Bottom Left: Mean SF-12 MCS.

Table 9).

Overall, patients saw a significant improvement in SF-12 PCS/MCS scores, and both treatment groups had similar SF-12 scores through seven years (Figure 7; Table 8).

Both groups maintained a high level of patient satisfaction, calculated as the proportion of patients who answered “very satisfied” for the satisfaction questionnaire [TDR: 90.9% (120/132) vs. ACDF: 77.8% (42/54); $p = 0.028$]. A high proportion of patients from both groups answered that they would “definitely” or “probably” recommend their treatment to a friend [TDR: 96.2% (127/132) vs. ACDF: 88.9% (48/54); $p = 0.08$].

Radiographic Outcomes - Single level

Range of motion at the level treated was maintained in the TDR group with an average range of motion of $10.2 \pm 6.3^\circ$ in flexion/extension and $5.1 \pm 3.5^\circ$ in lateral bending (Figure 8). As expected, the average range of motion for the ACDF group was 1° or less in both flexion/extension and lateral bending at the level treated (Table 10). Both groups experienced a marginal decrease in functional spinal unit height relative to baseline postoperative measurements (Table 10). Bridging bone was present in 11.1% (12/108) of TDR patients. By 7 years, 95.5% of ACDF patients had achieved radiographic fusion. Both groups experienced adjacent segment degeneration, defined as at least one increase in Kellgren-Lawrence grade from baseline. However, the ACDF group demonstrated a noticeably greater prevalence of adjacent segment

Table 8. Outcomes for 1-Level TDR and ACDF.

Study	Outcome	Treatment arm	Baseline	7 Years	Mean Δ at 7 years*	P-value†	Recovery Ratio
1-Level	NDI	TDR	54.0 ± 14.0	17.9 ± 19.7	35.4 ± 20.6	0.99	67%
		ACDF	54.1 ± 14.6	18.2 ± 17.6	33.8 ± 20.2		64%
	VAS neck pain	TDR	70.8 ± 22.4	19.0 ± 26.9	51.1 ± 33.3	0.89	71%
		ACDF	70.1 ± 21.5	21.1 ± 24.4	48.2 ± 30.1		67%
	VAS arm pain	TDR	71.0 ± 23.8	12.8 ± 23.3	57.5 ± 33.7	0.35	73%
		ACDF	70.7 ± 26.8	20.9 ± 27.1	53.2 ± 36.2		63%
	SF-12 PCS	TDR	32.5 ± 5.9	47.8 ± 11.2	15.2 ± 11.5	0.11	22%
		ACDF	33.8 ± 6.4	46.1 ± 10.1	11.6 ± 10.7		17%
	SF-12 MCS	TDR	42.1 ± 13.1	50.4 ± 10.6	8.0 ± 13.7	0.99	11%
		ACDF	42.2 ± 10.4	51.3 ± 10.6	8.3 ± 11.7		13%

* Mean of differences in outcomes between 7 years and preoperative follow-up. † Adjusted p-value for difference in change from baseline between TDR and ACDF at 7-year follow-up. Values given are mean \pm SD unless otherwise indicated. NDI, neck disability index; VAS, visual analog scale; SF-12, Short Form 12-item Health Survey; MCS, Mental Composite Score; PCS, Physical Composite Score.

Table 9. NDI and pain status (% of patients) at last follow-up in 1-level TDR and ACDF.

Status*	NDI			VAS Neck Pain		
	TDR	ACDF	P value†	TDR	ACDF	P value†
Improved	84.6%	84.8%	0.72	87.5%	83.3%	0.21
Not improved	14.2%	12.7%		8.8%	15.4%	
Worse	1.2%	2.5%		3.8%	1.3%	

* NDI: Improved: $\geq 15/100$ point increase from baseline. Not improved: < 15 point change (\pm) from baseline. Worse: $\leq -15/100$ point decrease from baseline. Neck pain: Improved: $\geq 10/100$ point increase from baseline. Not improved: < 10 point change (\pm) from baseline. Worse: $\leq -10/100$ point decrease from baseline. † Fisher's exact test.

degeneration (65.1%/63.0%) than the TDR group (40.4%/43.8%) at both the superior and inferior adjacent levels, respectively (Table 10).

Safety Outcomes - Single level

CEC classified adverse events rates were similar between treatment groups as well [TDR: 6.1% (10/164), ACDF: 3.7% (3/81)]. TDR patients had significantly fewer subsequent surgical interventions than ACDF patients did at both the treated and adjacent levels. By 7 years, subsequent surgeries (including all secondary surgeries such as index level instrumentation removals to access adjacent level pathology) at the

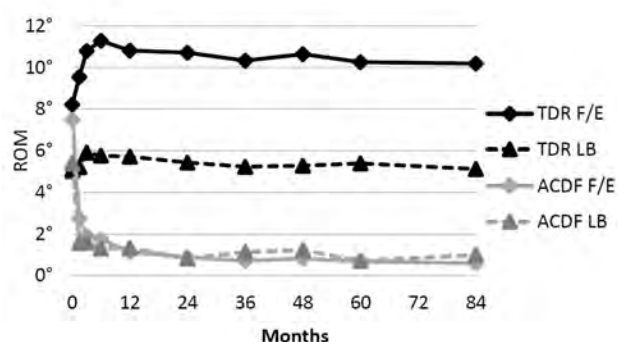


Fig. 8. Range of motion in flexion/extension (F/E) and lateral bending (LB) for one level patients.

Table 10. Radiographic outcomes for 1-Level TDR and ACDF at 7 years.

Outcome	Treatment	7 Years
ROM in Flexion/Extension	TDR	10.2 ± 6.3°
	ACDF	0.2 ± 0.2°
ROM in Lateral Bending	TDR	5.1 ± 3.5°
	ACDF	0.4 ± 0.4°
FSU Height Change from PreOp	TDR	1.5 ± 0.8 mm
	ACDF	0.2 ± 1.3 mm
FSU Height Change from PostOp*	TDR	-0.5 ± 0.5 mm
	ACDF	-0.7 ± 0.7 mm
Adjacent Segment Degeneration		
Superior Level	TDR	40.4% (42/104)
	ACDF	65.1% (28/43)
Inferior Level	TDR	43.8% (38/89)
	ACDF	63.0% (17/27)

Values given are mean ± SD unless otherwise indicated. * Prior to discharge from hospital.

treated level occurred in 3.0% (5/164) of TDR patients and 12.3% (10/81) of ACDF patients ($p = 0.008$). The TDR secondary surgeries were Removal (4) and Reoperation (1). The ACDF secondary surgeries were for Removal (7) or Supplemental Fixation (3). Discounting the plate removals at the index level (presumably to access adjacent level pathology), the adjusted index level secondary surgery rate for ACDF was 6.2% for one-level. The most common reason for additional surgical intervention at the index level was persistent radiculopathy and/or neck pain ($n = 3$) and pseudoarthrosis ($n = 5$), for the TDR and ACDF group, respectively. There were no cases of device malfunction, though there was one instance where the TDR device was malpositioned and required additional surgical intervention. Additionally, there was one case in which gross motion of the caudal endplate of the TDR device was noted between flexion and extension radiographs at 3 months. It was concluded that the TDR device loosened from the vertebral endplate. Thus due to over distraction of the spinal segment, possibly caused by an oversized implant; the patient had the device removed and replaced with fusion. The surgeon-investigator opined that the loosening might have occurred due to oversizing and/or over distraction of the implant. Subsequent surgeries that involved at least one adjacent level occurred in 3.7% (6/164) of TDR patients and 13.6% (11/81) of ACDF patients ($p = 0.007$). The most common reason for additional surgical intervention at an adjacent level was adjacent level disease or herniation for both the TDR ($n = 4$) and ACDF ($n = 8$) group. Kaplan-Meier survival function estimates demonstrated that TDR patients were less likely to have subsequent surgery across time (Figure 9).

Discussion

These results indicate that cervical spine surgery for properly selected patients with myelopathy or radiculopathy is tremendously effective at improving patient pain and quality of life. Overall, greater than 95% of patients (from both groups) who underwent TDR and 88% of patients who underwent ACDF were “very satisfied” at seven years. When comparing TDR to ACDF, these results add to the growing body of literature supporting the long-term outcome and decreased secondary surgery rate of TDR com-

pared to ACDF.

Although the change in disease specific outcome measures and statistical testing is of value to the scientific community, patients may struggle to understand the specific implications of this data. As one recent study reported, “interpretation of the data is very difficult or even impossible for most patients due to lack of adequate knowledge.” “From a patients perspective a total NDI score or a difference in NDI score, that is however important for scientific evaluation, is meaningless. It will not help him/her in decision-making about any treatment for neck-related problems.”³² Therefore, in this study, we have attempted to transform the outcome scores into expressions that can easily be understood by patients to help them in making a decision about their eventual treatment. Here we report that the vast majority of patients in both single and two level cohorts improved in neck disability after surgery (70.2%-80.8% of two-level surgeries and 84.6%-84.8% of single level surgeries) and neck pain (83.3%-87.5% of single level surgeries and 77.7%-86.0% of two-level surgeries).

In contrast to the conventional wisdom of “50 percent improved and 50 percent worse” outcome distribution, the percentage of patients with worse neck disability (2.5%-3.8% of two-level surgeries and 1.2%-2.5% of single level surgeries) and worse VAS neck pain (5%-6.8% of two-level and 1.3% - 3.8% of single level) was strikingly low. To further facilitate patient education and individualized treatment ap-

proaches, the data in this study are also reported in terms of recovery ratios. A higher recovery ratio implies more improvement in outcome normalized to maximal possible improvement. For instance, a patient with a preoperative NDI of 80 and a postoperative NDI of 20 would have a 75% recovery ratio. In this study, patients who underwent two-level total disc replacement experienced a mean 72% reduction in neck pain, 74% improvement in arm pain, and 67% improvement in disability relative to an idealized improvement. Similarly, patients in this study who underwent a single-level total disc replacement experienced a mean 71% reduction in neck pain, 73% improvement in arm pain, and 67% improvement in disability relative to maximal possible improvement. We believe that it is imperative that our clinical trial results be translated into lay language to aid patients, non-spine providers such as insurance medical directors, and policy makers in their decision-making.

There was a clear reduction in secondary surgery rates following TDR at long-term follow-up in both the single and two level cohorts. Index level secondary surgery rates were significantly lower in the TDR population at seven years in the single level (3.0% TDR vs 12.3% ACDF) and two level (4.4% TDR vs 16.2% ACDF) when all index level procedures (including plate removal) were included. Radiographic pseudoarthrosis was present in 9.1% of the 2-level ACDF patients and 4.5% of the single level ACDF patients who did not undergo secondary surgery by seven years. The rate of secondary surg-

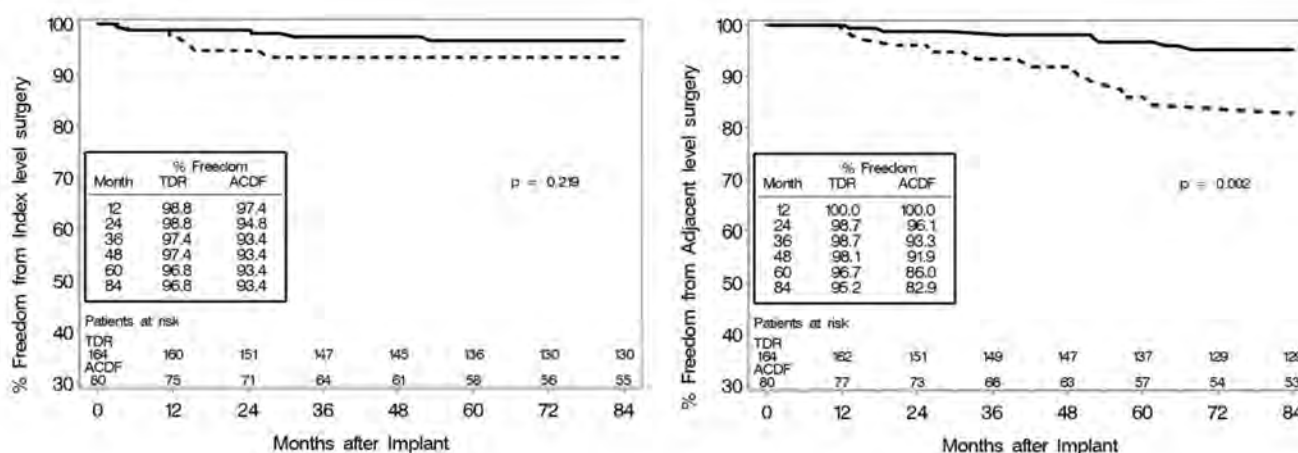


Fig. 9. Kaplan-Meier survival function estimates for subsequent surgery in one-level patients. P-value based on log-rank test. Left: Subsequent surgery for index level indications. Right: Subsequent surgery at the adjacent level.

eries due to pseudoarthrosis was 8.6% for 2-level and 6.2% for one-level. Adjacent segment secondary surgery rates were also significantly lower in the TDR patients in the single level (3.7% TDR vs 13.6% ACDF) and two level (4.4% TDR vs 11.4% ACDF) patients. The difference in adjacent level secondary surgery rates is consistent with the observed increase in radiographic adjacent segment disease rates in the ACDF patients.

Our data are consistent with other Level I evidence clinical trials that have reported on the safety and efficacy of TDR with follow-up periods up to 7 years.³³ Overall, the results have been favorable for TDR, with results comparable to or better than ACDF control groups. In a 7-year study on the ProDisc-C device, Janssen et al. reported comparable results of one-level TDR compared to ACDF with respect to disease specific outcomes.⁹ Additionally, investigators observed a lower rate of subsequent surgical procedures at both the treated level and adjacent levels.⁹ Burkus et al. published similar 7-year findings on the Prestige device with comparable or better outcomes for the TDR group with almost three times fewer index and adjacent level surgeries in the disc group.¹⁸ In a 5-year study on the PCM device, Phillips et al. reported better outcomes for neck pain, similar AE rates, and lower rates of subsequent surgery and radiographic degeneration for their one-level disc group compared to ACDF controls.¹¹ Although some early studies of other discs did not report a statistically significant difference in secondary surgery rates at early time points, long-term follow-up has demonstrated that motion preservation reduces secondary surgery rates.

While several high-quality studies have validated the long-term safety and efficacy of one-level TDR, to the authors' knowledge, this study is one of two high-quality, randomized clinical trial to evaluate the long-term performance of two-level TDR. The results of other, short-term studies, while limited in quantity, are in accordance with these results presented here. In a prospective, randomized, 65-patient study of two-level TDR versus ACDF, Chen et al. demonstrated favorable outcomes for two-level TDR (Bryan), with significantly more improvement in NDI and neck pains scores over an ACDF compari-

son group at two years.³⁴

The dramatic difference seen between TDR and fusion when moving from one-level to two-levels of treatment is also noteworthy.³⁵ As discussed in the results, the outcome of TDR is remarkably similar at one and two levels. Although there previously was a statistically significant difference between single level TDR and ACDF, at long term follow-up the differences in success rate, NDI score, VAS score, and other clinical outcome measures are no longer statistically significant. While one-level treatment with TDR offered similar results in patient reported outcomes versus ACDF in the long-term, a sizeable difference in treatment effectiveness was observed between two-level TDR and ACDF. Treatment with ACDF appeared to experience diminishing returns as the number of treated levels increases, while TDR does not, or does to a much lesser extent.^{35,36} A likely explanation for this phenomenon lies in the apparent biomechanical differences between fusion and disc replacement.^{7,37,38} In accordance with this hypothesis of transfer of biomechanical stresses in multilevel disc replacement, there was a striking difference in the recovery ratios of VAS neck pain between groups. In the single level cohort, neck pain improved on average 67% relative to idealized improvement from baseline score. In the two level group, neck pain improved only 57%. Therefore, although the difference in mean VAS improvement is small (4 points on a 0-100 scale), there was a 10% difference in the recovery ratio. Additionally, there was an increase in the incidence of radiographic adjacent segment degeneration in the ACDF patients between cohorts (2-level 80.8% vs 65.1% 1-level). The observed increase in radiographic degeneration is also in accordance with the theory that there is increased mechanical stress following two level fusion.

There is no doubt that ACDF is still a highly useful and successful procedure, especially for treating symptomatic spondylosis accompanied by marked cervical instability, facet arthropathy, disc space collapse, or kyphosis. One limitation of this study was the specific inclusion and exclusion criteria for entry into the study. At the time of conception, the intention of the Mobi-C study was to enroll patients without significant conditions that could confound the

outcome of an artificial disc. Other studies have demonstrated that less than half of the patients who present to a spine surgeon's office with cervical spine complaints are candidates for a TDR based upon IDE study criteria.³⁹ Therefore, the generalizability of these results to patients outside of IDE study conditions may be limited. There may also be other variables that affect the outcome of TDR that were not captured in this report. As the understanding of TDR has improved since the conception and initiation of this study almost 10 years ago, several technical factors have been identified that may be potential confounders. For example, a retrospective analysis of the Discover disc revealed that a preoperative disk height of <3.5 mm or excessive intraoperative lordosis, (such as increasing the functional spinal unit angle by >3 degrees) was associated with a 3.5 times greater risk of not achieving the MCID in NDI ($p=0.016$).⁴⁰ Another recent study demonstrated that subtle micromotion between the implant and the vertebral endplates (less than the threshold for macro-motion and migration described as an adverse event above) might affect clinical outcome.⁴¹ Therefore, there may also be subtle surgical factors, such as height,⁴² alignment,^{43,44} or removal of the PLL,^{44,45} that may affect TDR kinematics and that limit the generalizability of the results.⁴⁴ Additionally, we acknowledge that the indications and rate of secondary surgery are somewhat subjective. One group of authors reported a higher rate of secondary surgery in ACDF patient within an IDE study than a concurrent group of ACDF patients outside of IDE study conditions.⁴⁶ The authors inferred that IDE study conditions might lead to a subtle bias towards increased rates of secondary surgery in ACDF patients who would otherwise be managed without surgery. Although we acknowledge possible bias in the subjective decision on the part of the surgeon and patient to consider a secondary surgery, we also report concordant clinical failure measured in objective parameters such as radiographic adjacent segment disease rates and clinical outcome measures. We believe it is entirely reasonable that, in a group of patients with an increased rate of radiographic degeneration and worse clinical outcomes, we would observe an increased rate of secondary surgery. Additionally, at least 47% of secondary surgeries were performed by non-investigator surgeons, which may also reduce

likelihood of investigator bias. The FDA composite success endpoint (that consists of clinical and radiographic measures) is an attempt to capture all treatment failures, including secondary surgeries or patients who have a poor outcome who choose not to undergo secondary surgery. All IDE clinical trials of TDR have used a composite success endpoint to test for non-inferiority against ACDF; however, the definition of overall success has varied among these studies.⁴⁷ The composite success endpoint used the Mobi-C trial was mandated by the FDA from the beginning of the IDE and has been reported in earlier studies.²³ At various times during this study, however, the FDA imposed alternative definitions of overall success.^{24,25} For the purposes of this study, we used the original FDA definition of success criteria. However, we acknowledge that, due to the small changes in FDA definitions of success, direct comparisons of overall success rates across studies may not be valid. Another limitation is that the study was funded by industry. Some authors perceive industry funding to induce a source of bias, although this is true for all medical device studies. Most spine device trials, particularly multicenter studies, are industry funded.⁴⁸ Additionally, authors have declared potential conflicts of interest. Another source of bias was affirmation bias or confirmation bias, although that is probably true for most medical device studies. Due to the differences in postoperative rehabilitation, it was not possible to blind patients to their treatment allocation. For treating symptomatic spondylosis in which the spine is generally stable, these data suggest that the stability provided by fusion is not worth the sacrifice in motion. With an apparent reduced risk for reoperation and adjacent segment pathologies, motion-preserving treatment with TDR seems to be an excellent alternative to ACDF, given the data presented here and in many other studies.

Conclusion

For the treatment of one- or two-level symptomatic cervical disc disease, TDR with the Mobi-C Cervical Disc is a safe procedure with excellent long-term effectiveness. Compared to an anterior fusion alternative, TDR provided a similar reduction in patient reported outcomes of pain and function while providing a lower risk for reoperation at both treated and

adjacent levels. The improvement in outcome between TDR and ACDF appears to be durable from the two-year to the seven-year follow up. The difference in clinical effectiveness of TDR versus ACDF becomes more apparent as treatment increases from one to two levels, indicating a significant benefit for TDR over ACDF for two-level procedures.

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The ROI-C zero-profile anchored spacer for anterior cervical discectomy and fusion: biomechanical profile and clinical outcomes

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Introduction: Anterior cervical discectomy and fusion (ACDF) has been the gold standard for treating cervical degenerative disc disease (cDDD). The use of anterior plates in ACDF poses an increased risk of complications such as screw or plate dislodgement, soft tissue injury, esophagus perforation, and dysphagia. The ROI-CTM implant system consists of a zero-profile interbody fusion cage with self-locking plates designed for stand-alone fusion without external plates or screws.

Objective: The purpose of this report is to describe the ROI-CTM implant system with VerteBRIDGETM anchor plates, including indications for use, surgical technique, preclinical testing, and clinical study results. The objectives of the clinical study were to assess fusion status, incidence of dysphagia and other device-related complications, and patient reported outcomes.

Methods: This was a retrospective, multicenter cohort study of 110 patients who underwent ACDF with ROI-C at seven study centers. Patient charts and radiographs were reviewed for any complications or device malfunction. The final follow-up was conducted prospectively and included collection of neck disability index, and visual analog scale (VAS) neck and arm pain scores.

Results: The mean operation time was 73 minutes, and mean blood loss was 25 mL (range 0–75 mL). Mean follow-up was 20.7 months (range 9.5–42.2). Dysphagia was reported in two patients (1.8%), and 99.1% of patients achieved fusion. One patient had radiographically confirmed pseudarthrosis at 12 months that was asymptomatic and did not require surgery. One patient had subsequent surgery owing to adjacent level degeneration. The mean neck disability index, VAS neck pain, and VAS right and left arm pain scores at final follow-up were 19, 26.5, 12.5, and 15.3, respectively.

Conclusion: The ROI-C interbody cage with VerteBRIDGE anchor plates achieved a high rate of fusion, with a low incidence of dysphagia. These patients had similar or better outcomes compared to ACDF with anterior plating reported in peer-reviewed literature.

Keywords: ROI-C, zero-profile spacer, ACDF, stand-alone cage, cervical disc degeneration

Introduction

Degenerative conditions of the cervical spine (eg, degenerative disc disease or cervical spondylotic myelopathy) are characterized by the degeneration of the intervertebral discs of the cervical spine. Cervical disc degeneration is a common cause of neck pain. A damaged vertebral disc due to degenerative disc disease can cause discogenic pain; however, not all degenerated discs cause pain. In addition to having the low-grade pain of a stiff or inflexible neck, many patients with cervical disc degeneration have numbness, tingling, or even weakness in the neck, arms, or shoulders as a result of nerves in the cervical area becoming irritated or pinched. Aging, genetics, metabolic

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disorders, and mechanical stress are known risk factors for cDDD.¹ The progression of cDDD can lead to the collapse of the intervertebral space, disc herniation, spinal stenosis, and radicular arm pain with or without neurologic deficit. If conservative therapy fails, patients frequently undergo anterior cervical discectomy and fusion (ACDF). Since the initial description of ACDF by Smith and Robinson as well as by Cloward,^{1,2} many technical modifications have been reported.

Currently, surgeons may use autologous bone graft, allograft, synthetic material, and/or interbody cages as interposition grafts. The use of anterior iliac bone graft for anterior interbody fusion has been the gold standard for decades. Although highly successful fusion is achieved by autologous iliac bone graft, the use of this graft has greatly diminished owing to donor-site morbidity.³⁻⁷

Interposition grafts are often combined with anterior locking plates to increase the immediate postoperative stability after bone grafting between vertebral bodies. Anterior plates enhance rigidity of fixation and decrease risk of nonunion, which may lead to kyphosis and pseudarthrosis, particularly in multilevel cases.⁸⁻¹² Moreover, anterior plating may also reduce the risk of graft extrusion.¹³ However, implantation of a plate in the anterior cervical spine poses an increased risk of hardware-related complications such as screw or plate dislodgement, soft tissue injury, esophagus perforation, nerve palsy, and dysphagia, and may contribute to adjacent level degeneration and osteophyte formation.¹⁴⁻¹⁹

To prevent these complications, cages have been studied and applied in humans as potential bone substitutes for autograft in interbody fusion. The ROI-C™ implant system (ROI-C, Zimmer Biomet, Austin, TX, USA) is composed of the ROI-C zero-profile interbody fusion cage with VerteBRIDGE™ self-locking plates designed for stand-alone fusion. First clinical use of the ROI-C occurred in 2008, and in February 2009, the US Food and Drug Administration approved the ROI-C system for single-level treatment of degenerative cervical spine conditions. The purpose of

the clinical study was to assess the occurrence of fusion, dysphagia, and other short-term complications, and the postoperative effectiveness in patients who underwent ACDF with the ROI-C system.

ROI-C™ with VerteBRIDGE™

The ROI-C implant system consists of “D”-shaped blocks in a variety of footprints and heights (Figure 1). The ROI-C implant system is comprised of a radiolucent Poly-etheretherketone (PEEK) Optima® LT1 cage with tantalum alloy radiologic position markers. PEEK is a nonabsorbable biopolymer that has been used in a variety of industries, including medical devices. The PEEK cages are biocompatible, radiolucent, and have modulus of elasticity similar to bone. The ROI-C titanium-coated implant offers a porous plasma titanium coating made of unalloyed nonferromagnetic titanium (Ti), sprayed onto the superior and inferior surfaces of the implant.

The curved shape of the ROI-C anatomic implants allows for optimum surface area contact with vertebrae that embody a curved surface morphology. Both the ROI-C and ROI-C titanium-coated implant systems include a lordotic shape as well, which allows for optimum surface area contact with vertebrae that embody a flat surface morphology. To promote faster rates of fusion, the ROI-C cage features an enclosed chamber that may be filled with autologous or allogenic bone graft. To prevent device migration and provide increased joint stability, both the superior and the inferior surfaces of the implants have a pattern of teeth.

The ROI-C implant system is intended for insertion using an anterior approach. In order to provide the stability needed for successful fusion, the cage is implanted with two VerteBRIDGE anchor plates. The VerteBRIDGE plates are manufactured from surgical titanium (Ti6Al4V), and are used to affix the ROI-C implant to the superior and inferior vertebral bones of the index level. The VerteBRIDGE anchor plate technology allows the ROI-C implant to be used as a

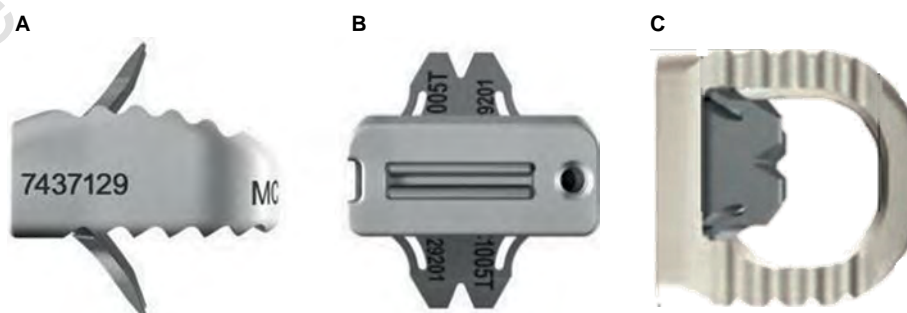


Figure 1 The ROI-C cervical cage with VerteBRIDGE plating technology.
Notes: (A) Lateral view; (B) Anterior view; (C) Superior view.

stand-alone construct, although supplemental fixation may be used as patient needs dictate.

Indications for use

The ROI-C implant system is indicated for use in skeletally mature patients with cervical degenerative disc disease (cDDD) with accompanying radiculopathy and/or myelopathy at a single disc level from C2 to T1. These patients should have 6 weeks of nonoperative treatment unless they have severe or progressive neurologic dysfunction. The ROI-C implants are intended for use with autogenous or allogenic bone graft composed of cancellous and/or corticocancellous bone graft.

The ROI-C implant system is implanted via an open, anterior approach. Supplemental internal fixation with two VerteBRIDGE anchor plates is required to use this system properly. The ROI-C implant system has been designed to be compatible with optional supplemental fixation specifically for the system using the VerteBRIDGE anchor plates to affix the ROI-C cage to the underlying vertebral bone, and to specifically allow for the option of a stand-alone construct. Additional or other supplemental fixation may be used, as patient needs dictate.

Surgical technique

The ROI-C is designed for implant as an intervertebral spacer via the anterior approach. The patient is positioned supine, and radiographic imaging is obtained in the anterior-posterior (AP) and lateral planes to identify the level of diseased disc(s), sizing and placement of the implant, and plate insertion. After successful general anesthesia, the basic techniques for exposure, discectomy, and decompression are performed using a standard right- or left-sided approach. When indicated, the posterior longitudinal ligament is resected to allow for excision of extruded disc material and/or to determine the appropriate intervertebral disc height. The endplates are abraded before fusion by removing the cartilaginous tissue from the endplates using surgeon preferred tools such as rongeurs, curettes, or shaving spatulas. Only the cartilaginous portion of the vertebral endplate is removed, and the bony endplate is preserved as much as possible to prevent cage subsidence.

After the midline is determined, the cage trial is used. The ROI-C trials have the same dimensions as the implants and provide optimal endplate coverage, height restoration, and stability. The trial is placed in front of the space to visually determine width, and the selected trial is inserted into the space. Under lateral radiographic imaging the following are confirmed:

- Implant depth and height
- Endplate coverage (AP)
- Conformity with the superior dome for the anatomic design
- Restoration of the lordotic curve for the lordotic design.

The distraction is released in order to assess the height that will best restore the anatomic shape of the operated space, as well as the best stability to the implant. The trial should not protrude past the edge of the vertebrae.

The trial is then removed, and the appropriate-sized final cage endplates are inserted to an adequate depth under lateral fluoroscopic guidance. The central space of the ROI-C may be filled with autologous bone to facilitate bony integration. The cage is then inserted into the disc space using an impactor. The implant is inserted by gently tapping the end of the implant holder as necessary. If the implant position is too anterior, the AP positioning can be adjusted by dialing the adjustable stop from 0 to 5 mm. For each millimeter the depth stop advances, the implant moves 1 mm posterior.

Under radiographic imaging, insertion of the implant is completed, and a final assessment of implant depth and endplate coverage is performed. A tantalum marker is located 1 mm from the posterior implant edge for positioning reference. The surgeon should verify that the marker is at least 1 or 2 mm anterior to the canal to avoid compression of the dura mater. Following this, AP and lateral fluoroscopy is performed to confirm the appropriate positioning and size of the device.

After implantation of the cage, the two cervical anchoring clips are placed into the lower and upper vertebra through the anterior part of the cage to ensure primary stabilization by the self-locking function of the anchoring clips. The VerteBRIDGE plates are inserted one after the other, as the plate paths cross in the plate housing portion of the implant holder (ie, the plate inserted into the cranial slot will be anchored into the caudal vertebral body, and the plate inserted into the caudal slot will be anchored in the cranial vertebral body). The second plate can be inserted only after the first plate is locked. Upon radiographic confirmation of plate location, the implant holder is removed, and the surgical incision is irrigated and closed in the standard manner.

Standard surgeon practice should be followed for postoperative care after implantation, including normal precautions for cervical fusion. As many of these procedures are done in an outpatient setting, most patients are ambulatory on the day of surgery.

Preclinical evidence

Biomechanical evaluation of the ROI-C

The ROI-C system was subjected to preclinical biomechanical testing to assess stability and pullout force. The aim of this study was to biomechanically evaluate the ROI-C construct compared to conventional bone grafts with anterior plating and to stand-alone PEEK cages with integrated screws.

Cadaveric motion segments from two cervical spines (C2–C3, C4–C5, and C6–C7) were mounted in epoxy and tested using a hydraulically actuated spinal loading system (MTS 810, MTS Systems, Eden Prairie, MN, USA). The flexibility protocol using application of pure moments was chosen to provide a direct comparison to the intact specimens, as well as to published data. Pure moments of 2.5 Nm in flexion-extension, bilateral lateral bending, and axial torsion were applied with a 20 N machine-applied axial preload to maintain compression of the segment. Pullout testing was used to compare resistance to expulsion. Force was applied at 10 mm/min under a 50 N axial preload to measure peak extraction loads. The vertebrae were allowed to rotate during pullout testing.

The intact construct averaged $12.9 \pm 3.6^\circ$ in flexion-extension, $9.7 \pm 2.6^\circ$ in lateral bending, and $10.3 \pm 1.3^\circ$ in axial torsion. Range of motion (ROM) of the ROI-C with VerteBRIDGE plates was 39%–53% relative to the intact construct, with mean flexion-extension of $6.6 \pm 3.3^\circ$, lateral bending of $3.8 \pm 2.4^\circ$, and axial torsion of $5.5 \pm 2.5^\circ$. In each test direction, the range of motion of ROI-C was significantly reduced ($p \leq 0.01$) compared to the intact specimen. ROI-C also had less range of motion (% of Intact ROM) in all directions compared to a stand-alone PEEK cage with two screws, as well as to a traditional PEEK cage with cervical plate construct (Figure 2). Average pullout loads for ROI-C were greater than reported pullout loads for a conventional cervical plate (232.7 N vs 202 N, respectively), which are well above the expected physiologic loads.²⁰ Pullout failure of the ROI-C only occurred due to plowing of the device through the bone and opening (lordosing) of the segment.

In flexion-extension, lateral bending, and axial torsion, the ROI-C with VerteBRIDGE anchoring plates showed lower ROM than published data²¹ of a similar stand-alone PEEK

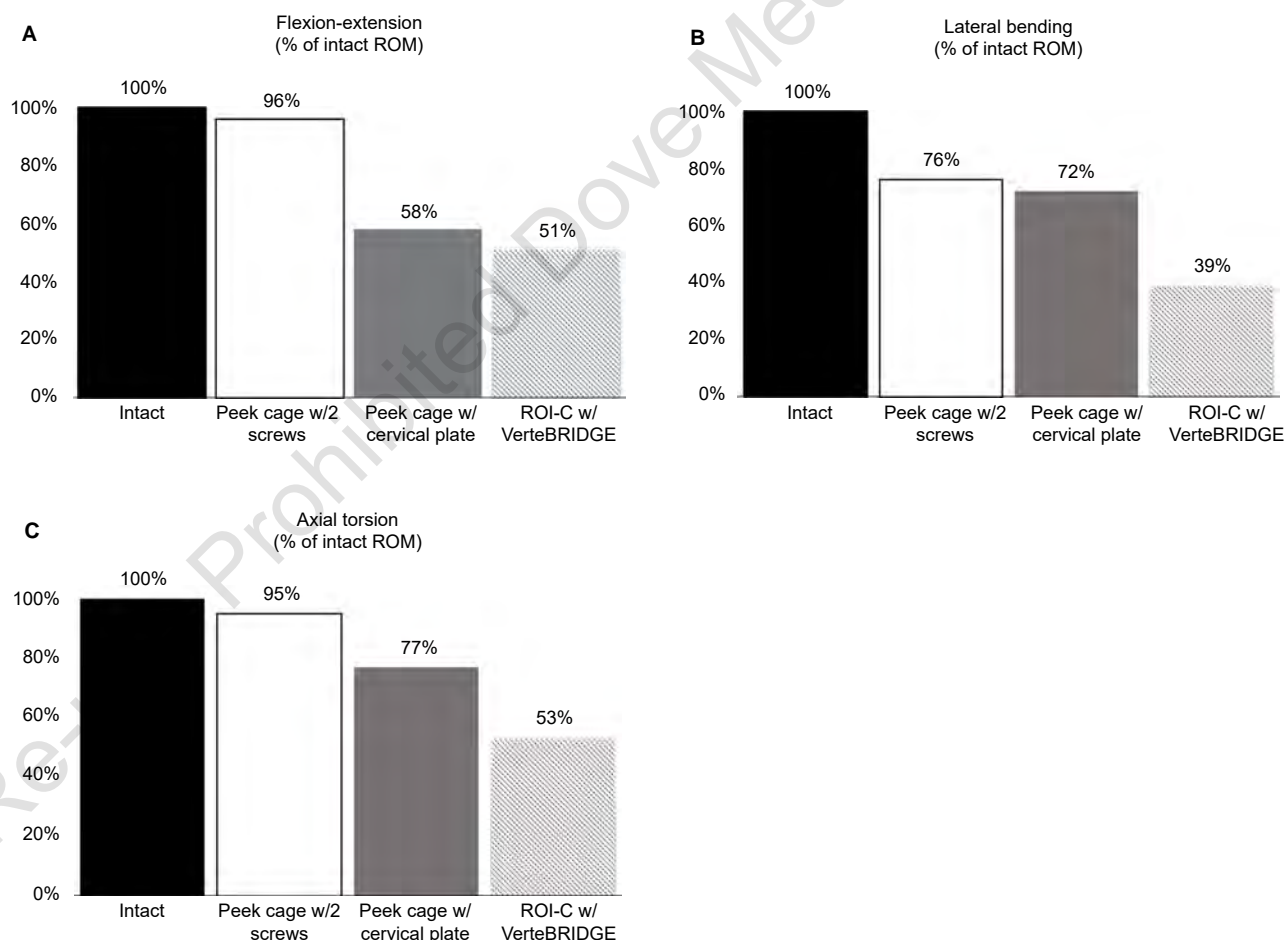


Figure 2 Range of motion of ROI-C with VerteBRIDGE anchor plates, Polyetheretherketone (PEEK) cage with anterior plating, and PEEK cage with screws.

Notes: Range of motion is expressed as a percentage of the Intact specimen ROM. Data for PEEK Cage obtained from Freeman et al.²¹

Abbreviations: ROM, range of motion; w/, with; w/2, with 2

cage with two integrated screws and a conventional construct comprised of a PEEK cage and metal cervical plate. The pullout resistance of the ROI-C with VerteBRIDGE plating is comparable to published data²² of a bone graft with cervical plate and screws. When additional resistance to expulsion vs a cage alone is desired, the ROI-C with VerteBRIDGE plating was shown to be a viable option.

Clinical evidence

ROI-C retrospective study

Methods

This was a retrospective, multicenter study of patients who underwent single-level ACDF with the stand-alone configuration of the ROI-C cage with VerteBRIDGE anchor plates and autograft bone (Figure 3). Surgical data and patient demographic information were collected from 110 patients at seven study centers in the US (Registration number NCT02104167; ClinicalTrials.gov). All patients signed a written informed consent to take part in the study. The Western Institutional Review Board (IRB) approved the study protocol for five centers, and approval was granted at two centers by local hospital IRBs (Baystate Medical Center, Springfield, MA, USA; St. Joseph Medical Center, Tacoma, WA, USA). Inclusion criteria included a diagnosis of DDD at one level between C2 and T1 with radiculopathy and/or myelopathy confirmed by radiographic imaging and corresponding pain and/or neurologic deficit. Implants occurred between January 2011 and November 2013. All patients were consented prior to data collection. Data were collected retrospectively from the pre-operative and operative periods, and at 2 and 6 months. The final follow-up visit was conducted prospectively between December 2013 and January 2015. Fusion status was determined using AP, lateral, and flexion/extension radiographs at each time point, and was defined by the presence of bridging bone with less than 2° segmental motion in flexion/extension

and less than 3 mm of AP translation. Device integrity was assessed radiographically for subsidence, pseudarthrosis, and device-related complications. Clinical examination at the final follow-up included measurement of neck disability index (NDI), and measurement of neck and radicular arm pain using a visual analog scale (VAS) of 0–100, with 0 representing no pain and 100 representing severe pain. Adverse events and dysphagia were also collected. Study outcomes were compared to results from recent publications of ACDF. Literature controls were obtained from peer-reviewed publications of US Food and Drug Administration randomized studies reporting the 2-year outcomes of single-level ACDF with plate and screws.

Results

The study cohort included 64 females and 46 males. The mean age was 51.9±10.2 years (Table 1). Twenty-eight patients (25.5%) had undergone previous cervical spine surgery. All patients presented with radiculopathy and/or myelopathy with pain and paresthesia. All procedures were single-level ACDF with the ROI-C. Operated levels included C3–C4 through C7–T1. Autograft was added to the cage in each case, and no supplemental fixation was used. The mean

Table 1 Preoperative and operative details

Preoperative characteristics	
Patients, n	110
Age, mean ± standard deviation (range)	51.9±10.2 (24–75)
Gender, n (%)	
Female	64 (58.2%)
Male	46 (41.8%)
BMI (kg/m ²), mean ± standard deviation	29.8±5.7
Obese (BMI ≥30 kg/m ²), n (%)	52 (47.3%)
Previous cervical spine surgery, n (%)	28 (25.5%)
Smoking, n (%)	16 (14.5%)
Diagnosis, n (%)	
Radiculopathy	57 (52.3%)
Myelopathy	14 (12.8%)
Radiculopathy + Myelopathy	38 (34.9%)
Not reported	1
Operative characteristics	
Operated Levels, n (%)	
C3–C4	13 (11.8%)
C4–C5	16 (14.5%)
C5–C6	40 (36.4%)
C6–C7	38 (34.5%)
C7–T1	3 (2.7%)
Operative time (minutes), mean ± standard deviation (range)	73±22 (30–161)
Blood loss (mL), mean (range)	25 (0–75)
Hospital stay (days), mean ± standard deviation (range)	0.7±0.5 (0–2)
Follow-up time (months), mean (range)	20.7 (9.5–42.2)

Abbreviation: BMI, body mass index.

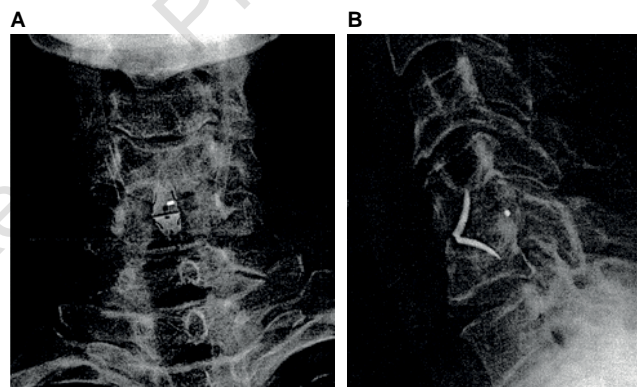


Figure 3 Postoperative radiographs of the ROI-C with VerteBRIDGE anchor plates at the C4–C5 level.

Notes: (A) anterior–posterior view; (B) lateral view.

Table 2 Outcomes at final follow-up in the ROI-C study

Outcome	ROI-C with VerteBRIDGE (mean 20.8 months)	ACDF w/plating (12–24 months)
NDI	19.0	10–40.1 ^{34–38,49–51}
VAS neck	26.5	16–31 ^{34–38,49–51}
VAS arm		8–28 ^{34–38,49–51}
Left arm	15.3	
Right arm	12.5	
Secondary surgery	0.9%	2.9%–9.8% ^{34–38,49–52}

Abbreviations: ACDF, anterior cervical discectomy and fusion; NDI, neck disability index; VAS, visual analog scale.

operation time was 73 minutes. Mean estimated blood loss was 25 mL (range 0–75 mL). Patients left the hospital after an average stay of 0.7 days (range 0–2 days).

The mean follow-up time was 20.7±8.8 months. The mean NDI, VAS neck pain, VAS right arm pain, and VAS left arm pain scores at the final follow-up visit were 19, 26.5, 12.5, and 15.3, respectively (Table 2). Rates of dysphagia were 8.2%, 2.3%, and 1.8% at 2 months, 6 months, and 12 months, respectively (Table 3). Fusion was achieved in 29.2% of patients at 2 months, 85.7% at 6 months, and 99.1% of patients at the final follow-up visit.

There was one instance of pseudarthrosis (0.9%) and one secondary surgery (0.9%). One patient had radiographically confirmed pseudarthrosis at 12 months. This patient was asymptomatic (NDI score =4; neck and arm pain scores =0) and did not undergo surgical treatment. The second patient, who initially underwent a C3–C4 procedure with ROI-C, presented with a diagnosis of cervical stenosis with myelopathy at multiple adjacent levels (C4–C6). Although the ROI-C had successfully fused, the patient had subsequent C3–C6 fusion 8 months after the initial procedure.

Discussion

In the current study, we demonstrate that the zero-profile ROI-C cage allows for similar or better clinical and radiographic outcomes compared with ACDF with anterior plating. During the postoperative follow-up period, no internal fixation loosening, detachment, fractures, instability, or subsidence occurred in our study. Subsidence of an interbody

cage can lead to a variety of complications, including loss of foraminal and disc height, segmental spinal instability, and loss of lordosis.²³ Preserving the cortical endplates is a critical factor in preventing interbody cage subsidence, and it has been proven that endplate preparation decreases the strength and stiffness of the vertebral bodies.^{24,25} The surgical technique of the ROI-C implant system requires minimal preparation of the endplates, and the clinical evidence suggests that ROI-C and other interbody fusion cages should have low subsidence rates because of this.²⁴

Compared to ACDF with plate and screws, implant of the ROI-C leaves less hardware in the patient. Moreover, while use of the ROI-C cage does not always mean a smaller skin incision compared to ACDF using a plate; it does involve less dissection and a smaller exposure in the prevertebral space. The associated benefit is less trauma to the surrounding soft tissues. It also holds distinct advantages when doing a C7–T1 fusion, where one would not need to expose further caudally than the disc space itself. Implant of the ROI-C is particularly valuable in cases where there is an existing plate at an adjacent level. Such cases would require a much bigger exposure extending to the other end of the plate to remove it, in order to place a new plate across the new target level. With the ROI-C, there is no need to remove an existing adjacent plate, in fact no need to expose it at all, as it can just be left alone. In the occasional situation where the anchor encounters an existing screw in the shared vertebral body, the screw can just be removed and not the entire plate, which requires minimal extension of exposure.

Because nonunion has been linked to poor outcomes,¹⁰ the primary goal of ACDF is to achieve solid bony fusion, which prevents delayed kyphotic deformity with concomitant foraminal stenosis that may cause root compression and neck pain.^{26,27} We found that the ROI-C was associated with a high rate of bony fusion (99.1%). Grasso et al²⁸ and Wang et al²⁹ reported 100% fusion in ROI-C patients followed for 2 years, and Hoffstetter et al³⁰ reported similar fusion rates for ROI-C (95.2%) vs ACDF (96%) after a mean follow-up of 13.9 months. Increased rates of fusion have been reported in ACDF with anterior plating compared with ACDF without

Table 3 Rates of dysphagia and fusion for ROI-C compared to literature

Outcome	ROI-C with VerteBRIDGE			ACDF w/plating (12–24 months)
	2 months	6 months	Final follow-up ^a	
Dysphagia	8.2%	2.3%	1.8%	0.7%–17.1% ^{35,37,40,49–51,53}
Fusion	29.2%	85.7%	99.1%	89%–100% ^{34–38}

Notes: ^aMean follow-up of 20.8 months.

Abbreviations: ACDF, anterior cervical discectomy and fusion.

plate.^{13,31–33} Fusion rates of ACDF with cervical plating have been estimated to be 97.1% for single-level procedures.³³ Comparatively, randomized control clinical trials involving patients treated with ACDF with anterior plating and allograft bone had fusion rates of 89% to 96.6% at 24 months.^{34–38}

The zero-profile ROI-C anchored cage combines interbody support and supplemental fixation into a single device. An integral part of the ROI-C system is the two VerteBRIDGE anchoring plates, which eliminate the basic disadvantage of stand-alone cages. These unique structures offer a fixation mechanism that is similar to the function of a plate and screws. We believe that the self-locking VerteBRIDGE plates ensure excellent primary stability of the implant and promote early fusion. Furthermore, the elastic modulus of the anchored cage is similar to that of bone, which theoretically helps to decrease stress shielding and increase bony fusion. The anatomical shape of the anchored cage (with its upper convex part in the frontal and sagittal planes) allows a wide grafting space and close contact between the endplate bone and the implant.

In our study, the ROI-C implant system with VerteBRIDGE anchoring plates demonstrated low rates of dysphagia at 6 (2.3%) and 12 months (1.8%), respectively. Other studies of ROI-C have reported similarly low rates of dysphagia (0%–3.1%).^{28–30} In contrast, dysphagia rates as high as 35.1% have been reported after ACDF with anterior plating.³⁹ Several studies suggest that the use of anterior locking plates is associated with a higher rate of postoperative dysphagia.^{13,40,41} Bazaz et al⁴⁰ observed a lower rate of dysphagia (14.1%) in patients without anterior plating compared with the case in patients (21.1%) who received a construct including an anterior locking plate. Mobbs et al¹³ observed a similar trend, with a significantly higher rate of dysphagia in patients who received an anterior locking plate (4.5%) compared with constructs without anterior plating (0.8%).

Although the causes of dysphagia after ACDF procedures are not well understood, several physiologic mechanisms have been proposed. The occurrence of dysphagia and dysphonia has been linked to causes such as damage or compression of the soft tissues of the trachea or esophagus from the anterior plate^{41,42} or scar tissue from the incision.⁴³ Irritation or impingement can occur because the anterior cervical locking plate is placed directly posterior to the esophagus.^{13,40,41,44} The design and thickness of anterior locking plates also correlate with postoperative dysphagia.⁴¹ Another possible mechanism for postoperative dysphagia after ACDF with anterior plating may be additional traction required to place an anterior locking plate. Increased pressure on the esophagus during implantation

of an anterior plate has been suggested to contribute to dysphagia in patients who undergo ACDF with anterior plating.⁴⁵ In contrast, the ROI-C implant system stabilizes the joint without the need for anterior plating. This zero-profile design decreases the likelihood for dysphagia and dysphonia by avoiding compression of the soft tissues, and the use of the curved anchor plates instead of screws allows for a smaller surgical incision that does not extend beyond the size of the cage.

There is a growing consensus that ACDF alters the natural history of cervical spondylosis and hastens the development of degenerative changes at levels immediately above and below fused regions. In this retrospective study, one patient (0.9%) had adjacent segment degeneration that required a subsequent fixation at an adjacent level. Hofstetter et al³⁰ reported that two ROI-C patients (5.7%) required repeat surgery for adjacent level disease. Schwab et al⁴⁶ found that cervical fusion reduced the number of vertebrae with active function and caused biomechanical changes. To maintain the function of the entire cervical spine, the body increases the activity of the adjacent fused vertebral segments to compensate, causing adjacent segment degeneration. The presence of a plate and screws is also likely to accelerate degenerative changes in adjacent segments,⁴⁷ and anterior interbody fusion can also contribute to adjacent segment degeneration,⁴⁸ but the exact pathophysiologic mechanism of adjacent segment degeneration remains unknown.

Conclusion

The design of the ROI-C implant system utilizes the core principles of previous interbody cages to take advantage of the safety and successful clinical history of anterior interbody fusion devices, while addressing some of the drawbacks of previous interbody implants. The clinical results of the ROI-C implant system have demonstrated positive clinical outcomes with high fusion rates and low rates of subsidence, dysphagia, reoperation, and adjacent segment degeneration. The elegant design and ease of use of the ROI-C with VerteBRIDGE locking plates represent an improved surgical option for a stable anterior interbody fusion without the need for anterior plating or posterior fixation. Possible advantages of the ROI-C for spinal fusion surgery include a short operative time, less dissection and smaller exposure of the prevertebral space, and less implanted hardware, with the associated benefit of less trauma to the surrounding soft tissues.

Acknowledgments

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preparation of the draft manuscript, tables, and figures were performed by W B Dolman (Zimmer Biomet).

Disclosure

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Clinical study

Multilevel cervical fusion without plates, screws or autogenous iliac crest bone graft

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Abstract

Objective: This prospective study was performed to evaluate the safety and efficacy of polyetheretherketone (PEEK) cages packed with demineralized bone matrix (DBM) mixed with autologous blood and curettage microchip material for treatment of multilevel cervical disc disease and spondylosis without the use of plates, screws or autogenous iliac crest bone graft.

Material and methods: Sixteen patients underwent multilevel anterior cervical discectomy and fusion (ACDF) for a total of 42 levels. Minimum follow-up was 18 months. Neurological outcomes were evaluated using the Japanese Orthopaedic Association (JOA) scoring system; cervical lordosis and cervical fusion status was assessed on X-ray. Statistical analysis was performed to compare preoperative and postoperative scores using a dependent *t*-test ($P < 0.05$).

Results: Eight patients underwent two-level, six underwent three-level and two underwent four-level operations. The fusion rate was 90.5% and non-fusion rate was 9.5%, but reoperation was not required for these patients in the follow-up period. Cervical lordosis was preserved and neurological status was improved. No cage migration or cage failure occurred.

Conclusion: ACDF using PEEK cages packed with DBM is a safe and efficient method for treatment of multilevel cervical disc disease and spondylosis. It preserves cervical lordosis and obviates the complications related to iliac crest graft harvest and screw-plate fixation. © 2006 Elsevier Ltd. All rights reserved.

Keywords: Cervical degenerative disc disease; Multilevel fusion; PEEK cage; Demineralized bone matrix

1. Introduction

Since the initial description by Robinson and Smith in 1955,¹ the technique of anterior cervical arthrodesis has been refined. Although anterior cervical discectomy and interbody fusion (ACDF) for treatment of degenerative cervical disease is a highly successful procedure,^{2–6} the success rates decline in multilevel discectomies as the number of levels increase.^{7,8} Graft collapse with the use of autogenous bone has been reported in 20–30% of multilevel fusion

patients.^{10–12} Moreover, even with solid fusion, kyphosis often develops in multilevel discectomies with autogenous iliac crest graft fusion.^{10,13} Additionally, morbidity due to bone graft harvest remains high and can compromise the satisfactory clinical result of cervical nerve root and spinal cord decompression.^{14–16}

Multilevel cervical discectomy is often combined with plate and screw fixation to maintain the spinal curvature, and increasing the graft fusion rate. However, plates and screws may cause complications, such as screw breakage, screw pull out, esophagus perforation and spinal cord or nerve injury.^{17–21}

The deficiencies mentioned above have favoured ongoing development of cage technology.^{14,15,22} There has been a rapid increase in the use of cervical spine interbody fusion cages in view of their theoretical ability to prevent graft

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collapse, with the potential advantage of indirect foraminal decompression by restoration and preservation of intervertebral height and lordosis. However, in most studies, cages filled with autologous cancellous bone were used. Although this is likely to reduce graft harvesting complications, donor site pain still remains a common problem.^{23–25}

The purposes of this study were to evaluate the safety and efficacy of polyetheretherketone (PEEK) cages and to determine if it is possible to eliminate donor site and plate complications and to achieve good outcomes for multilevel discectomy and fusion if the cage packed with demineralized bone matrix (DBM) is used without plates. To the authors' knowledge, a similar prospective study has not been reported in the literature.

2. Materials and methods

In our department, between February 2000 and September 2002, 16 patients (11 women and 5 men) with a mean age of 56 years (range, 40–63) underwent multilevel ACDF using PEEK cages (Spine Next, Bordeaux-France and Eurospine, L'Hay-Les-Roses, France) packed with DBM (Grafton, Osteotech, Eatontown, NJ, USA) mixed with autologous blood and curettage microchip material. Only patients operated for treatment of degenerative cervical disc disease and spondylosis were included in this study. Patients with trauma, infection and neoplasms were excluded. Conforming to international ethical standards, all patients were given detailed information on the operation, the follow-up protocol and radiological investigations, and their consent was obtained. Indication for operation was intractable radiculopathy, myelopathy, or a combination of both due to nerve root or spinal cord compression and compatible magnetic resonance imaging (MRI) findings.

The operative procedure was performed as described by Smith and Robinson.¹⁶ The disc, posterior longitudinal ligament, and osteophytes, including the posterior part of the uncinate process, were removed under the surgical microscope. Endplate cartilage was also removed with a high-speed drill and curette. Curettage microchip material was conserved. Cages were inserted into the disc space after packing with DBM mixed with autologous blood and curettage microchip material. During cage placement, cranial traction was applied. The wound was closed with reapproximation of two anatomic planes over a suction drainage system. All patients wore a Philadelphia collar for 6 weeks after surgery. Most patients received physiotherapy after removal of the collar.

Clinical and radiological follow-up was performed at the 3rd, 12th, and 18th months postoperatively. In addition to standard neurosurgical examination, outcomes were assessed with Japanese Orthopedic Association (JOA) scoring.²⁶ We evaluated spinal curves, mobility and fusion status with X-ray. Four planes of X-rays were used, including anterior-posterior, neutral and flexion and extension lateral views.

A radiologist and a spine surgeon independently assessed fusion status with no knowledge of the clinical outcome. The operative segment was deemed to be fused if there was no change in position of the fused levels on dynamic views (flexion and extension). Additionally, the radiological images were evaluated using the classification of anterior fusion proposed by Vavruch et al.²⁵ In this classification; Type 1A is defined as bridging bone anterior and through the disc space; 1B as bridging bone anterior but not through the disc space; 2A as bridging bone not anterior but through the disc space; and 2B as no bridging bone at all. The radiological outcomes were classified as 'non-fusion' if 2B healing was observed, and as 'fusion' if 1A, 1B or 2A healing was observed at the levels subjected to surgery.

Lateral X-rays were performed to evaluate the spinal curve pre- and postoperatively. The Ishihara Curvature Index (ICI) was used for this evaluation.²⁷ A straight line was drawn from the posterior border of the dens to the posterior border of C7. Another line was drawn from the posterior border of C4 perpendicular to the first line, in which the intersected length was measured in millimeters as the degree of spinal curvature. A positive intersected length indicates the degree of lordosis. If the intersected length is negative, it indicates kyphosis. When the intersected length is zero, the spinal curve is referred to as straight.

Statistical analysis was performed to compare preoperative and postoperative scores using dependent *t*-tests using SPSS V.12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

There were five men and 11 women between the ages of 40 and 63 years, with a mean age of 56.3. Patients' demographic data and number of levels treated are shown in Table 1. Eight patients underwent two-level discectomy, six patients underwent three-level discectomy and two patients underwent four-level discectomy. All patients were followed up for at least 18 months (range, 18–34 months).

After surgery, none of the patients suffered neurological deterioration. There were no complications during the immediate postoperative period, and X-rays confirmed appropriate positioning of the vertebral cages.

Mean JOA scores were 13.7 ± 1.34 and 16.4 ± 0.97 pre- and postoperatively. Patients were significantly better ($p = 0.004$) clinically.

Table 1
Patients' demographic data ($n = 16$)

Mean age (years)	56.3 \pm 6.69 (range, 40–63)
Women	11
Men	5
Two treated levels	8
Three treated levels	6
Four treated levels	2
Total treated levels	42

Preoperative mean ICI was 10.4 ± 3.72 and postoperative mean ICI was 10.1 ± 3.14 . The difference was insignificant ($p > 0.05$); therefore, preoperative lordosis was said to be preserved at the 18th month after surgery.

At the final follow-up, the fusion rate (Types 1A, 1B, and 2A) was 90.5% (38/42 levels). The rate of Type 1A fusion was 35.7% (15/42 levels) (Fig. 1), the rate of Type 1B fusion was 40.5% (17/42 levels) (Fig. 2), the rate of Type 2A fusion was 14.32% (6/42 levels) (Figs. 3a and b), and the rate of Type 2B non-fusion was 9.5% (4/42 levels).

There were three patients with non-fusion levels: two non-fusion levels in one patient with a four-level operation (C5-6 and C6-7 levels) (Fig. 3b); one non-fusion level in one patient with a four-level operation (C6-7 level); and one level in one patient with a three-level operation (C5-6 level). In long-term follow-up, imaging showed no cage failure or dislodgement. Reoperation for non-fusion was not necessary. In addition, no mobility was seen on dynamic X-ray films at any operated segments.



Fig. 1. X-ray of Type 1A fusion.



Fig. 2. X-ray of Type 1B fusion.

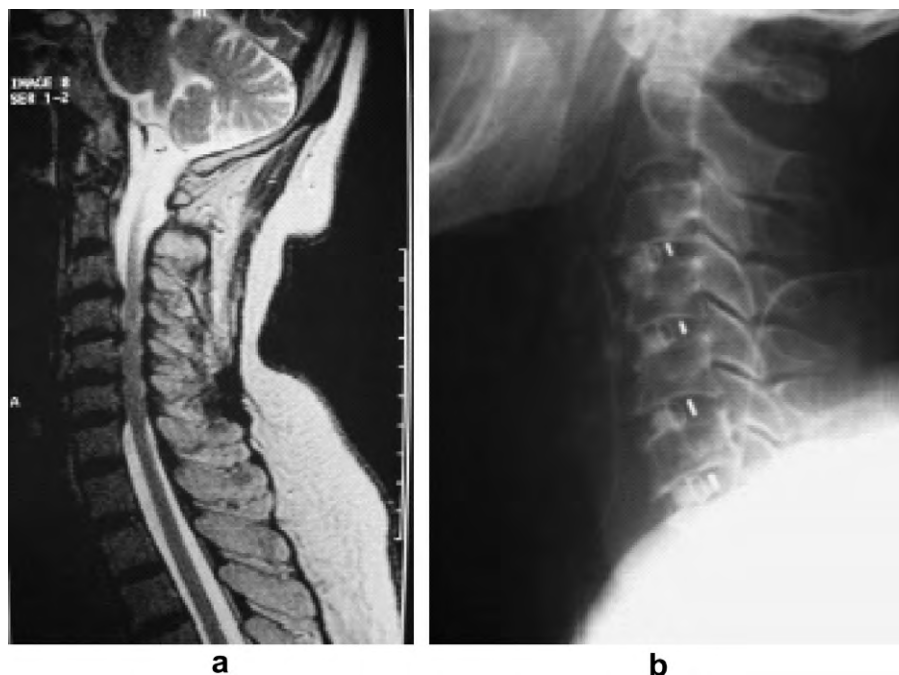


Fig. 3. Type 2A fusion. (a) preoperative MRI. (b) X-ray of non-fusion (Type 2B) at C5-6 and C6-7 levels and Type 2A fusion at C3-4 and C4-5 levels.

4. Discussion

Anterior cervical discectomy and interbody fusion is an efficacious procedure used to treat a variety of cervical spinal disorders, including spondylosis, myelopathy, herniated discs, trauma, and degenerative disc disease.

The success of this procedure relies on thorough decompression and development of a solid osseous fusion.^{2–6,25,28} Brown et al.²⁹ reviewed serial X-rays after anterior cervical fusion performed in a total of 139 levels in 98 patients and found arthrodesis in 97% of patients who underwent autograft procedures. In their series, Savolainen et al.³⁰ found a 98% fusion rate in patients who underwent procedures with autograft. According to the results obtained from other series, for single-level discectomy with autogenous bone fusion, ACDF can achieve a 92–100% fusion rate²⁰ and 70–90% neurologic and symptomatic improvement.^{5,6} Although, arthrodesis with autologous iliac crest graft is considered as the biological and biomechanical standard in anterior cervical reconstruction,^{9,31} the morbidity of the iliac bone harvest can often tarnish these results.^{4,15,23–25,28,30,32} Silber et al.¹⁵ observed that 26.1% of patients reported pain at the donor site. Summer et al. also reported chronic pain in the donor site in 25% of 290 patients.²⁴ According to Arrington et al., in addition to the minor complications of the donor site (superficial infections, hematoma, cosmetic problems, etc.) there were major complications in 5.8% of cases, requiring therapeutic modifications, surgical revision and prolongation of hospitalization.¹⁴ Castro et al.² reported a donor site complication rate of 22% in their series. In addition to the donor site problems, the graft complication rate in autogenous bone graft can be high.^{3,8,9,28,33,34} Matge reviewed patients who had undergone autogenous bone fusion procedures and found that there were many graft-related complications, including migration (2.1–4.6%), kyphosis (3–10%) and pseudoarthrosis (1–3%).³²

In the Cloward procedure, the best results have been reported for young male patients with soft disc disease, at the single level.^{35,36} Multilevel anterior cervical discectomy and fusion still remains a difficult problem. Autogenous bone does not maintain spinal instability in multilevel discectomy very well and the graft complication rate in autogenous bone graft in multilevel fusion is higher than at the single level.^{4,8,9,13} Graft collapse with autogenous bone is reported in 20–30% of multilevel fusions.^{10–12} Moreover, it has been reported that even with solid fusion, kyphosis often develops in multilevel discectomies with autogenous iliac crest graft fusion.^{10,17} The literature also reports a consistent rate of 10–12% non-fusion for single-level anterior discectomy and autogenous bone fusion, 20–27% for two-level, and approximately 30–56% for three-level fusions.^{7–9} It is clear that the success rates decline as the number of levels increase.

In the light of these reports, in multilevel ACDF procedures, augmentation with plate fixation, may seem to be preferable. Plate fixation may decrease the micromovement

of the cervical spine, enhance the fusion rate, and correct spinal curve to physiologic lordosis.^{6,15} In ACDF, additional plate fixation has been reported to result in a higher fusion rate, lower reoperation rate, and better pain relief.^{9,12,13,31} However, in their retrospective study, Das et al.¹³ studied 38 patients who had arthrodesis with cylindrical titanium cages filled with autologous bone graft harvested from the operative site and screw-plate fixation, and they reported the rate of pseudoarthrosis was 6–8% for one-level and 15–46% for treatment of several levels. Overall, in three- and four-level discectomies the successful fusion rate decreases 18–82%, even when a cervical spine locking plate is used.^{37–39} Moreover, plating has complications. Plate complication rate varies from 2.2–24.0%^{20,34} and includes screw pullout,^{21,40} screw breakage,²¹ injury of the laryngeal nerve,⁸ injury of oesophagus,¹⁹ injury of spinal cord or root, injury of vertebral artery, and wound infection.²¹ Additionally, the operative time is usually longer.

These complications of classical fusion procedures favoured ongoing development of cage technology. Because of the advantages of these devices, the use of cages in ACDF operations has been increasing in popularity. In parallel with this, there are several different types of interbody fusion cages commercially available.^{22–25,33} Cage-assisted ACDF has proven to be a safe and effective procedure for the treatment of degenerative disc disease. It has been reported that the cage achieves excellent fusion rates ranging from 93.1–100%.^{3,25,28,32,33,40,41} In our series, the fusion rate was 90.5%, comparable to the related literature. There were three patients with non-fusion. Although these non-fusions were seen in four-level operated patients no clinical signs or radiographic mobility of pseudoarthrosis were observed during the follow-up period.

With the use of a cage donor site morbidity was avoided.^{2,25,33} In our study, no cage failure or migration was encountered, even in patients who underwent fusion at more than two levels. The use of the cage was found to preserve the spinal lordosis and the height of the foramina.^{7,28,33,40,42} Bartels et al. reported that the cervical cage effectively increased foraminal height even after 1 year, which contributed to decompression of the nerve root.⁴² The wedge shape of the device may contribute to restoration of lordosis. In accordance with the current study, they showed that the PEEK cage resulted in preservation of the preoperative lordosis.

In our study, we preferred to use PEEK cages for multilevel fusion, because of the lower reported complication rates.²⁸ PEEK is a semicrystalline polyaromatic linear polymer that provides a combination of strength, stiffness, toughness, and environmental resistance.³³ In laboratory studies, this device demonstrated excellent resistance to compression.⁴³ It is also biocompatible.⁴⁴ The cage has been shown to have a stimulatory effect on the protein content of osteoblasts.⁴⁵ In one animal study, osteocalcin production, alkaline phosphatase activity, and the proliferation of fibroblasts were enhanced after the inser-

tion of a PEEK cage.⁴⁶ Furthermore, the cage structure (two titanium spikes on the upper and bottom frame, in addition to the retention teeth on the surface of the upper and bottom frame) offers a fixation mechanism which is similar to the functions of a plate and screws.^{28,33} Additionally, bone fusion can be evaluated easily by examining X-rays, because the PEEK cage is radiotransparent. It is also possible to evaluate postoperative MRI or CT scans, because artifacts are negligible.³³ Lastly, the PEEK cage is more elastic than the other cages which are made of metal, reducing the possibility of graft subsidence into the vertebral body.⁴⁷ Many of the complications associated with autologous tricortical iliac crest have been reduced significantly with the use of the cage. However, in most of these studies, cages packed with cancellous bone were used. To minimize the extent of surgery, and to avoid donor site complications, we filled the cage with DBM mixed with autologous blood and microchips of curettage material. To the authors' knowledge, clinical results after three- and four-level interbody cage and DBM-augmented ACDF have not been reported in the literature. However, our surgical results presented in this study are encouraging and provide an impetus to the use of interbody cage rather than a ventral cervical plate for structural support in the management of multilevel degenerative cervical disc disease.

5. Conclusion

Based on these findings, we conclude that interbody fusion with PEEK cages packed with DBM, autologous blood and microchips of curettage material is a safe and effective procedure and it may be an alternative to the posterior approach in the treatment of multilevel cervical disc disease. It preserves spinal lordosis, and obviates the complications related to graft harvest and screw-plate fixation.

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Two-level contiguous cervical disc disease treated with peek cages packed with demineralized bone matrix: results of 3-year follow-up

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Abstract Interbody cages are widely used instruments for cervical fusion operations. Long-term follow-up studies are needed to clarify if these devices are dependable. In this prospective study, 79 patients (42 women and 37 men) with a mean age of 51 years operated between January 2000 and December 2005 for treatment of degenerative cervical disc disease and spondylosis associated with radiculopathy or myelopathy were evaluated. Patients underwent two-level contiguous anterior cervical discectomy and fusion operations with standard anterior Smith–Robinson approach. To achieve fusion PEEK cages packed with demineralized bone matrix mixed with autologous blood were used. Clinical outcome was evaluated with Odom's criteria and results were evaluated as 'excellent', 'good', 'fair' and 'poor'. Spinal curves, mobility and fusion status were assessed with anterior–posterior and lateral (neutral, flexion and extension) radiographs obtained before surgery and at 3, 12, 24 and 36 months postoperatively. The Ishihara curvature index (ICI) was used for spinal curve evaluation. Lateral dynamic (flexion and extension) radiographs at postoperative 12th month revealed the fusion status classified as 1A, 1B, 2A and 2B. The radiological outcomes were classified as 'non-fusion' when 2B healing was observed, and as 'fusion' when 1A, 1B or 2A healing was observed at the levels subjected to surgery. According to

Odom's criteria, clinical outcomes were classified as 'excellent' or 'good' in 69 patients (success rate: 87.3%). Eight patients were graded as 'fair' and two as 'poor'. Preoperative mean ICI was 10.4 ± 3.72 and postoperative mean ICI was 10.1 ± 3.14 . The difference was statistically insignificant ($P > 0.05$); therefore, preoperative lordosis was said to be preserved at final follow-up. Final fusion rate (Types 1A, 1B, and 2A) was 91.7% (145/158 levels). Radiological imaging showed no cage failure or dislodgement and reoperation due to non-fusion was not needed.

Keywords ACDF · Two-level cervical disc disease · Demineralized bone matrix · Long-term follow-up · PEEK cage

Introduction

Anterior cervical discectomy and interbody fusion (ACDF) has become a standard and a highly successful surgical procedure for degenerative cervical disc disease associated with radiculopathy or myelopathy [10, 20]. The success rates decline in multilevel discectomies as the number of operated levels increase [10].

The literature have supported a 20–27% consistent rate of nonfusion (pseudoarthrosis) for two-level anterior discectomy and autogenous bone fusion [3, 12, 40]. Non-fusion accounts for 80% of spinal surgery failures and graft collapse with autogenous bone is also reported in 20–30% of multilevel fusion operations [18, 30]. There has been an advent of various types of cages to avoid the problems associated with autologous bone grafting. These problems include persistent donor-site pain, infection, hematoma formation, iliac crest fracture and meralgia parasthetica [21]. The use of cages obviates these complications.

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Many new interbody fusion cages have been developed, but long-term clinical studies with the use of these material are still scarce [7, 16, 31, 34]. An ideal cage should provide immediate stability, maintain spinal alignment and foraminal height, achieve higher or comparable fusion success rates with autografts [21]. To date, no perfect cage has been produced. Subsidence, migration, and structural failure of the present products [36] have been experienced [6].

Polyetheretherketone (PEEK) is a non-absorbable biopolymer that has been used in a variety of medical devices. It is biocompatible, radiolucent and has modulus of elasticity similar to the bone [21]. PEEK cages are commercially available, but clinically reliable reports of the PEEK cages are rare in the literature [6].

To the authors' knowledge, a similar study about the long-term clinical and radiological outcome of the two-level contiguous ACDF operations with the use of PEEK cages has not been reported previously [10, 20, 24]. The purpose of this prospective study is to evaluate the effectiveness of ACDF using PEEK cages packed with demineralized bone matrix and autologous blood for two-level degenerative cervical disc disease and to present the long-term clinical and radiological outcomes.

Materials and methods

This prospective study was performed with 79 patients (42 women and 37 men) with a mean age of 51 years (range, 37–72 years), who underwent two-level contiguous ACDF operations between January 2000 and December 2005, with the use of PEEK cages (Spine Next, Bordeaux-France and Eurospine, L'Hay-Les-Roses, France) packed with demineralized bone matrix (DBM) (Grafton, Osteotech, Eatontown, NJ, USA) mixed with autologous blood.

Patients with tumors, fractures, or infections were excluded. Only patients operated for degenerative cervical disc disease and spondylosis associated with radiculopathy or myelopathy were included. Conforming to international ethical standards, all patients were given detailed information on the operation, the follow-up protocol and radiological investigations, and signed consent was obtained from every patient. Indications for operation were intractable radiculopathy and/or myelopathy due to compression proven with the preoperative radiographs (anteroposterior and lateral) and magnetic resonance images (MRI).

Surgical procedure was standard anterior Smith–Robinson approach. The disc, posterior longitudinal ligament, and osteophytes, including the posterior part of the uncinate process were removed microsurgically. The upper and lower endplates were prepared by removing the overlying

cartilage preserving the hardest subchondral bone. Vertebral bodies were distracted with a Caspar distractor and an optimal PEEK cage was selected. The inner cavity of the PEEK cage was filled with DBM mixed with 1 ml of autologous venous blood supplied by anesthesiology team during the operation. Eventually PEEK cages were inserted into the disc space. All patients used Philadelphia collar for 6 weeks postoperatively. Neck exercises were initiated 6 weeks after surgery and a normal activity level was progressively resumed.

Odom's criteria was used to evaluate the clinical outcomes. The results were classified as 'excellent' (no complaints related to the cervical lesion with a smooth return to daily activities and work); 'good' (intermittent complaints related to the cervical lesion without any serious difficulties in performing daily activities and work); 'fair' (patient satisfied with the postoperative improvement of the subjective symptoms but with difficulties in performing daily activities and work); or 'poor' (deterioration or no improvement of the symptoms after the surgery) [21, 33].

Spinal curves, mobility and fusion status were assessed with anterior–posterior and lateral (neutral, flexion and extension) radiographs. Spine radiographs were obtained before surgery and at 3, 12, 24 and 36 months postoperatively. An independent radiologist evaluated these radiographs without the knowledge of clinical outcome.

Lateral X-rays were used to evaluate the spinal curve pre and post-operatively. The Ishihara curvature index (ICI) was used for this evaluation [17]. A straight line was drawn from the posterior border of the dens to the posterior border of C7. Another line was drawn from the posterior border of C4 perpendicular to the first line, in which the intersected length was measured in millimeters as the degree of spinal curvature. A positive intersected length indicates the degree of lordosis. If the intersected length is negative, it indicates kyphosis. When the intersected length is zero, the spinal curve is referred to as straight.

Statistical analysis was performed to compare preoperative and postoperative ICI scores with dependent *t* tests using SPSS V.12.0 (SPSS Inc., Chicago, IL, USA).

Lateral dynamic (flexion and extension) radiographs obtained at postoperative 12th month were used to evaluate fusion at the operated levels. The operative levels were deemed to be fused if there were no movement on dynamic views. Additionally, the radiological images were evaluated using the classification of anterior fusion proposed by Vavrukh et al. [38]. In this classification Type 1A is defined as bridging bone anterior and through the disc space; 1B as bridging bone anterior but not through the disc space; 2A as bridging bone not anterior but through the disc space; and 2B as no bridging bone at all. The radiological outcomes were classified as 'non-fusion' when 2B healing was

observed, and as ‘fusion’ when 1A, 1B or 2A healing was observed at the levels subjected to surgery.

Results

Mean follow-up period was 31.3 months (ranged from 15 to 36 months). 87% of the beginning population (79 cases) completed the 36-month follow-up and these formed the study population. C5–6 and C6–7 were the most common operated levels. Details of the treated levels are shown in Table 1.

None of the patients suffered neurological deterioration due to operation. There were no complications during the immediate postoperative period, and the radiographs confirmed the appropriate positioning of the cages.

Cages used had all same depth (12 mm) and width (12 mm). Cage heights varied due to the presence of spondylosis and mobility of the vertebral bodies during retraction. Details are given in Table 2.

According to Odom’s criteria, clinical outcomes were classified as ‘excellent’ or ‘good’ in 69 patients (success rate: 87.30%). Eight patients were graded as ‘fair’ and two as ‘poor’ though these ten patients achieved solid fusion at the final follow-up. Analysis of radiographic data of these ten patients showed that the post-operative segmental lordosis and the post-operative disc height were the same after surgery. The clinical results are given in Table 3. ‘Excellent’ and ‘good’ results are called as satisfactory outcomes. Patients were significantly better after the operation clinically ($P < 0.05$).

Table 1 Details of treated levels with fusion rates when both levels are fused

Levels	Number of cases	Rate to total (%)	Number of fusions	Rate of fusion (%)
C3–4/4–5	8	10.10	8	100
C4–5/5–6	17	21.50	15	88.20
C5–6/6–7	52	65.80	45	86.50
C6–7/C7–Th1	2	2.50	2	100
Total/mean	79	100	70	88.60

Table 2 Cage heights for levels

	Mean cage heights and ranges (mm)
C3–4	4.75 (4–5)
C4–5	5.11 (4–6)
C5–6	4.91 (4–6)
C6–7	5.07 (4–6)
C7–Th1	5.00 (5)

Table 3 Clinical outcomes regarding Odom’s criteria

Clinical outcomes due to Odom’s criteria	Number and rate of patients
Excellent	27 (34.17%)
Good	42 (53.16%)
Fair	8 (10.12%)
Poor	2 (2.53%)
Total	79

Preoperative mean ICI was 10.40 ± 3.72 and postoperative mean ICI was 10.10 ± 3.14 . The difference was statistically insignificant ($P > 0.05$); therefore, preoperative lordosis was said to be preserved at final follow-up.

At the final follow-up, the fusion rate (Types 1A, 1B, and 2A) was 91.70% for levels (145/158 levels) and 88.60% for cases (70/79 cases). The rate of Type 1A fusion was 37.30% (59/158 levels) (Fig. 1), the rate of Type 1B fusion was 40.50% (64/158 levels), the rate of Type 2A fusion was 13.90% (22/158 levels), and the rate of Type 2B non-fusion was 8.20% (13/158 levels) (Fig. 2). There were nine patients with non-fused levels: two non-fused levels in four patients (C5–6 and C6–7 levels) and one non-fused level in five patients (C4–5, C5–6 or C6–7 level). Development of fusion rates in the follow-up period is denoted in Table 4. In long-term follow-up, imaging showed no cage failure or subsiding. Reoperation for non-fusion was not needed. In addition, no cage mobility was observed on dynamic radiographs.

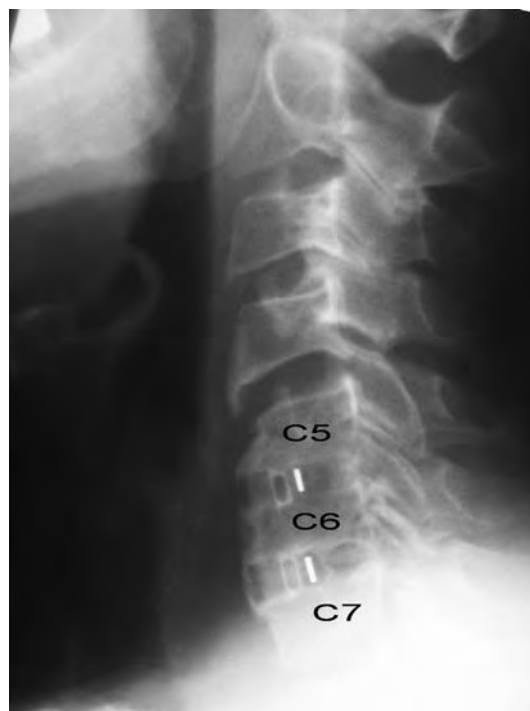


Fig. 1 Solid fusion in both C5–6 and C6–7 levels

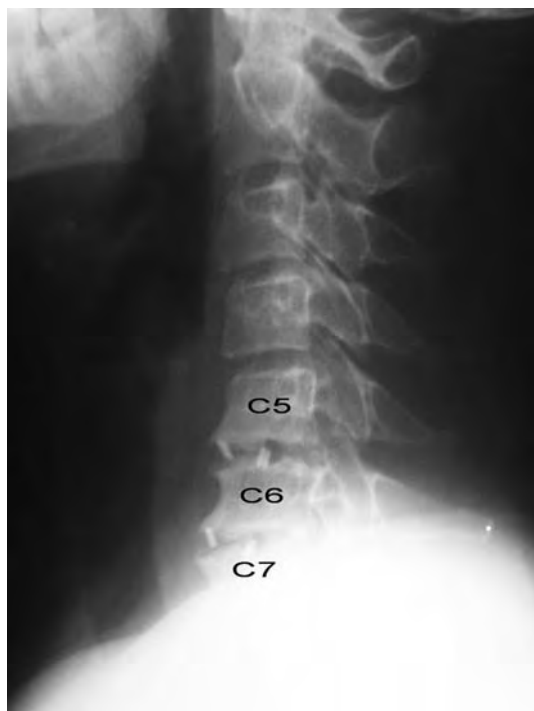


Fig. 2 Clear bone development in both levels but no bridging at all. Patient still suffered neck pain at postoperative third year

Table 4 Development of fusion rates (for individual levels)

	Months			
	3	12	24	36
Fusion rates (%)	53.79	69.62	91.70	91.70

Discussion

ACDF has become a well-established operative procedure used to treat a variety of cervical spinal disorders. The success of this procedure relies on thorough decompression and development of a solid osseous fusion [26, 38]. But a few issues, of which the optimal graft material and the necessity for additional stabilization compose the majority are still controversial [20].

Traditionally, cervical stabilization biomechanics have been investigated in three topics: single level, two levels, multi (more than two) levels. Due to the different structural behaviour of the above mentioned, particularly in regard to adjacent segment mobility and the need of additional instrumentation (plates), in this study only contiguous two level ACDF cases were included [8].

Although tricortical autograft harvested from iliac crest as interbody fusion material can provide satisfactory clinical results and fusion rates, donor-site complications are around 20% [1, 21]. Brown and Savolainen reported 97–98% fusion rate in patients who underwent fusion

procedures with autografts [10, 28]. In their series Sampath et al. denoted 92–100% fusion rate and 70–90% neurological and symptomatic improvement for single-level discectomy with autogenous bone fusion [26, 27].

The morbidity of the iliac bone harvest can often tarnish these results [25, 32, 35]. The literature also reports a consistent rate of 10–12% non-fusion for single-level anterior discectomy and autogenous bone fusion, 20–27% for two-level, and approximately 30–56% for three-level fusions [12, 38]. It is clear that the success rates decline as the number of operated levels increase. A similar comparison study found a 25% or greater graft collapse in 40% of patients treated with autografts, but no graft collapse was found in patients who received an anterior plate [15].

To eliminate autograft-related problems, interbody cages were developed for fusion operations. Use of cages resulted in a high fusion rate but there were no statistically significant differences in operation time, length of hospitalization, pain reduction or clinical results. Ludek et al. compared a historical group of patients receiving tricortical iliac autografts to those with cages packed with smaller autografts [22]. The cage group had less donor site pain and a better fusion rate with better preservation of postoperative lordosis and increase in disc space. Savolainen et al. also reported that these radiological differences were not related to the clinical results [2]. In our study, no cage failure or migration even in patients with non-fused levels, was encountered. Cages were found to preserve the spinal lordosis and the foraminal height [5, 6, 11].

Cervical interbody cages have been developed to provide immediate stability and high fusion rates with and without supplemental fixation [20]. In the light of the literature, in multilevel ACDF procedures, augmentation with plate fixation, may seem to be preferable due to higher fusion and lower reoperation rates, and better pain relief [4, 29]. In spite of these benefits, anterior fixation plates have the potential for morbidity. Plate complication rate varies from 2.2 to 24.0% and includes screw pullout, screw breakage, injury of the laryngeal nerve, injury of oesophagus, prolonged dysphagia, injury of spinal cord or root, injury of vertebral artery, and wound infection [9, 10]. Additionally, the operative time is usually longer.

Titanium, carbon fiber, and PEEK are most commonly used material for cage production [2, 13, 31]. The use of a titanium cage may lead to vertebral body collapse if the end plate is over degraded during discectomy. In addition, radiological metallic artifacts may complicate imaging. Furthermore, radiotransparent carbon fiber cages have been used widely, but synovitis and the lymphatic spread of fiber debris may be found after intra-articular procedures [6, 23].

In the present study, PEEK cages were applied in all operations. PEEK is a semicrystalline polyaromatic linear polymer that provides a good combination of strength,

stiffness, toughness, and environmental resistance with biocompatible, non-absorbable, and corrosion-resistant abilities [10, 19, 39, 40]. Furthermore, the cage structure (two titanium spikes on the upper and bottom frame, in addition to the retention teeth on the surface of the upper and bottom frame) offers a fixation mechanism, which is similar to the functions of a plate and screws [10]. Volume-related stiffness of the PEEK cage was shown to be higher than that of iliac bone in all directions. [14]. In addition, the PEEK cage is radiolucent and does not produce artefacts, it is easy to evaluate fusion status on radiographs and CT scans.

Cage-assisted ACDF has proven to be a safe and effective procedure for the treatment of degenerative cervical disc disease. In our series, the fusion rate was 91.7% which is comparable with the literature. There were nine patients with non-fusion. Despite the radiological failure, no clinical signs were observed in these patients during the follow-up period.

Usually, cages used in ACDF are packed with bone grafts, demineralized bone matrix, bone morphogenetic protein or acrylate to reach early and solid fusion. If the autologous bone graft is obtained not from the operation site, donor-site complications are still unavoidable. However, in most of these studies, cages packed with cancellous bone were used. Recent reports about the use of bone morphogenetic protein emphasize the high complication rates [37]. Studies about acrylate packing are scarce. To minimize the extent of surgery, and to avoid donor-site complications, we packed the cages with DBM mixed with autologous blood.

The purpose of this study was to evaluate the long-term outcomes of ACDF with PEEK cages. Most studies have presented short-term results and have demonstrated an improvement in pain, neurological deficit and functional disability [24]. In the literature, long-term follow-up studies are mostly retrospective with no assessment of functional disability and therefore of limited potential for firm conclusions on the effectiveness of the treatment [24]. In our study, clinical outcomes were rated as excellent or good in 69 out of 79 patients (success rate: 87.3%). Analysis of radiographic data of these unsatisfied ten patients showed that the post-operative segmental lordosis and the post-operative disc height were kept after surgery. All these cases suffered radiculopathy without neck pain giving rise to the thought that dissatisfaction might have been obviated with the implantation of higher cages to achieve a better foraminal space.

To the authors' knowledge, long-term clinical and radiological results of two-level ACDF with the use of PEEK cages and DBM have not been reported in the literature.

Conclusion

The results obtained in this study are encouraging and provide an impetus to the use of interbody cage in the treatment of two-level degenerative cervical disc disease.

In the light of our findings, we conclude that interbody fusion with PEEK cages packed with DBM is a safe and a good option for the treatment of patients with contiguous two-level cervical disc disease. It creates cervical lordosis, provides space for cord and root decompression, facilitates radiological follow-up, obviates the complications of graft harvest and leads to satisfactory outcomes without the need of any additional device. The controversies about the effect of packing material to the fusion status need to be elaborated with further studies.

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