

Research Article

Interbody Fusion Device in the Treatment of Cervicobrachial Syndrome: A Prospective 5-Year Follow-Up Extension Study of Porous Titanium Cervical Cages

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Abstract

Background: To assess long-term clinical and radiological data of porous titanium cervical interbody cages.

Methods: We recruited 34 out of 49 patients previously enrolled in the EFFECT trial on 3D printed titanium cages, for 5 years follow-up. Objectives were the evaluation of Neck Disability Index, Visual Analog Scale of arm pain and neck pain, Likert self-reported perceived recovery, EQ-5D, fusion status and subsidence. Fusion was defined as rotation $\leq 4^\circ$ and ≤ 1.25 mm translation at the index level, using flexion-extension radiograph.

Results: All patients had good outcomes in terms of NDI (12.5 ± 15.4), VAS neck pain (23.5 ± 24.1), VAS arm pain (18.7 ± 20.2) and EuroQol (0.77 ± 0.24). 88.6% of the patients experienced complete or nearly complete recovery. NDI improved significantly at 5 years compared to 1 year, all other outcome measures did not significantly differ from the 12 months results. The fusion rate at the index level increased from 91.5% at 12 months to 100% at 5 years.

Conclusion: 3D printed stand-alone porous titanium cervical implants are effective in terms of clinical and radiological outcome with 88.6% complete or nearly complete recovery and fusion rate of 100% at 5 years follow-up. Moreover, solid single level anterior cervical fusion can be achieved without additional plating.

Trial Registration: The study has been registered in The Netherlands Trial Register (NTR 1289) and approved by the Medical Ethical Committee (NL76079.058.20).

Keywords: Cervical Cage; Titanium; Surgery; Fusion; Pain

Introduction

Anterior Cervical Discectomy (ACD) is the basic surgical treatment of patients with radicular pain caused by cervical disc herniation or spondylosis unresponsive to conservative treatment. Most surgeons, however, perform Anterior Cervical Discectomy with Fusion (ACDF) to maintain disc height and cervical alignment and promote bony fusion to prevent instability [1]. Although there has been some debate on the necessity of interbody fusion, recent studies have shown that patients treated with ACD alone fare worse [2-4].

At present, ACDF with a Polyetheretherketone (PEEK) plastic cage is considered as the gold standard for cervical disc herniation for many surgeons [5-7]. The PEEK cage can be filled with iliac crest bone graft, local bone obtained during the decompression procedure, cadaver bone or a bone graft substitute [8]. PEEK, however, is a hydrophobic material, which has no bone incorporative qualities compared to other cage material (titanium) as shown in an *in-vitro* study of Olivares-Navarrete [9]. Our previously performed randomized controlled trial on ACDF patients (CASCADE trial), consisted of PEEK cages filled with local bone compared to ceramic cages. There was no difference in outcome between the two types of implants [10]. New methods of production allow for the manufacturing of 3D printed porous titanium cages that combine the biocompatibility of titanium

material with improved biomechanical and bone incorporative qualities. Our recently performed EFFECT trial involved patients who had implanted 3D printed porous titanium cervical cages (CONDUIT™, DePuy Synthes, Raynham, MA). Forty-nine patients were included and compared with the historic control of the PEEK cage group from the CASCADE trial. At 1 year, there was significant clinical improvement in both groups and the fusion rate was similar, although porous titanium resulted in faster consolidation [11]. However, long term clinical and radiological results of porous titanium implants are lacking.

In this extension study of the EFFECT trial, we have reconsented all original 49 patients for a prospective 5-year follow-up visit for clinical and radiological parameters to assess long term safety and performance of 3D printed porous titanium cervical implants.

Methods

The study was designed as a prospective consecutive follow-up of subjects, previously enrolled in the EFFECT trial, to evaluate safety and efficacy of the implanted device 5 years after surgery. All 49 subjects were contacted to participate in the EFFECT follow-up extension study. The study has been registered in The Netherlands Trial Register (NTR 1289) and approved by the Medical Ethical Committee (NL76079.058.20) on 10-06-2021.

Outcome Measures

The primary outcome measure was improvement in the Neck Disability Index (NDI) which has been translated into Dutch and validated for the population of the Netherlands [12]. Secondary outcome measures were the 100-mm Visual Analog Scale (VAS) for arm pain and neck pain, the 7-point Likert self-rating scale for perceived recovery in which “complete recovery” and “almost complete recovery” were defined as good outcome and the EuroQol-5D. All outcome measures were documented at 5 years and compared with the 1-year data. Safety and complications were not assessed at the 5-year follow-up visit [13].

Radiological Assessment

At 5 years, four plane films were collected (standing anterior and posterior, lateral flexion and lateral extension radiographs). In addition, independent quantitative analysis using Functional X-Ray Analysis of RAYLYTIC GmbH (Leipzig, Germany) allowed measurement of rotation on flexion-extension films with a mean error of 0.04° (standard deviation: 0.13°). Fusion for this study was defined as rotation $\leq 4^\circ$ and ≤ 1.25 mm translation on flexion-extension films at the index level. For comparison, we also calculated fusion status when Range of Motion (RoM) was $\leq 2^\circ$. Non-fusion was defined as $> 2^\circ$ angular motion during flexion/extension. Absence of RoM at the index disc level was documented as indicator of fusion. Migration or subsidence of the device was assessed by using a standard lateral radiograph in reference to discharge imaging. Only a change of >3 mm was considered clinically significant due to the margin of error in radiographic determination of displacement distances. Qualitative assessment of continuous bridging bone between involved endplates adjacent to the device and of the radiolucency around the device was additionally done by an independent radiologist. Radiolucency at the cage-bone interface was assessed as either present or absent by the investigator using a standard lateral radiograph. The presence of radiolucency of more than 50% of the inferior or superior surface of the implant was considered clinically significant, an indication that the fusion is not complete.

Data Capture and Statistical Analyses

All data was collected in a data management system (Castor EDC, Amsterdam, The Netherlands; <https://www.castoredc.com>) and performed according to Good Clinical Practice guidelines. For analyses we used descriptive statistics and inferential statistics. Continuous normally distributed variables were expressed by their mean and standard deviation, not normally distributed data by their median and min-max range for skewed distributions. To test groups, categorical variables were tested using the Pearson chi-square test or Fisher exact test, when appropriate. Normally distributed continuous unpaired data were tested with the independent samples Student t-test and in case of skewed data, with the independent samples Mann-Whitney U-test. Normally distributed continuous paired data were tested with the dependent samples Student t-test or a repeated-measure Analysis of Variance (ANOVA) and in case of skewed data, with the Wilcoxon signed rank test. Significance level was set at p-value $< .05$. Statistical analysis was performed using R studio statistical software (Version 1.0.153).

Results

Forty-nine patients were initially operated in the EFFECT trial, of which 34 subjects (70%) were identified and available at the 5-year time point. Baseline characteristics are shown in Table 1.

Clinical Outcome Measure

The primary outcome measure NDI significantly improved from 19.4 ± 8.4 at 12 months to 12.5 ± 15.4 at 5 years ($p=0.02$). The improvement of NDI during the complete follow-up is shown in Fig. 1. The VAS neck and VAS arm was 23.5 ± 24.1 and 18.7 ± 20.2 , respectively, compared to 23.8 ± 22.6 and 22.2 ± 24.3 at 12 months ($p=0.953$ and $p=0.489$). The EQ-5D at 5 years was 0.77 ± 0.24 versus 0.73 ± 0.24 at 12 months ($p=0.455$). All outcome measures improved significantly at 12 months and maintained during the 5-year follow-up. According to the patient, 88.6% experienced complete or nearly complete recovery at 5 years, compared to 77.1% at 1 year. All outcome measures are presented in Table 2.

Radiological Outcome

The preoperative mean RoM at the index level was 8.7° . The RoM significantly decreased at 12 months to 1.6° ($p(\text{PreOP} - 12 \text{ Months}) < 0.001$; range $0.0^\circ - 4.6^\circ$) and to 0.8° (range: $0.0^\circ - 3.4^\circ$) at 5 years ($p(\text{PreOP} - 5 \text{ Years}) < 0.001$; Fig. 2). At 5 years, no patient demonstrated a translational motion during flexion-extension of more than 0.6 mm at the index level (mean: 0.1 mm). Patients demonstrated on average a C2-C7 RoM of the cervical spine of 41.1° , indicating a sufficient and physiological overall motion during flexion-extension [14]. The fusion rate, defining fusion as less than 4° RoM, was 91.5% at 12 months, which increased to 100% at 5 years. When defining fusion as less than 2° RoM, the fusion rate at 5 years was 88% compared to 68% at 12 months (Table 3.). Consistently at 5 years, bone bridging anterior, posterior or lateral to the cage was documented in 85% of the patients. Only one case (3% of all evaluations) showed radiolucency around the cage of more than 50%.

At 5 years, the mean segmental lordosis at the index level was 3.2° and the mean subsidence was 1.4 mm, compared to 1.2 mm at 1 year. The average anterior-posterior migration at 5 years was determined to 0.2 mm, with no patient showing an AP-migration of more than 2 mm (Table 3).

An example of a study subject is shown in Fig. 3. During the five years of follow-up, fusion status and range of motion clearly increased and decreased, respectively.

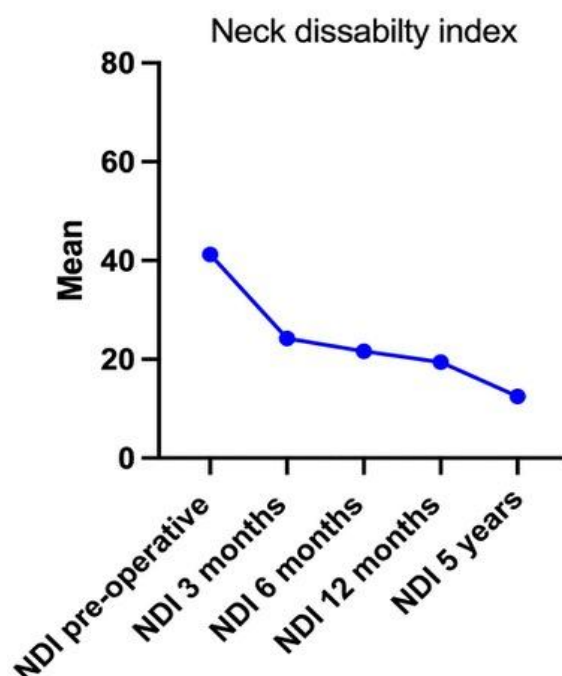


Figure 1: Neck Disability Index (NDI) as primary outcome measure during the complete follow-up of the study. The postoperative improvement was significant, as well as 5 years compared to 1 year.

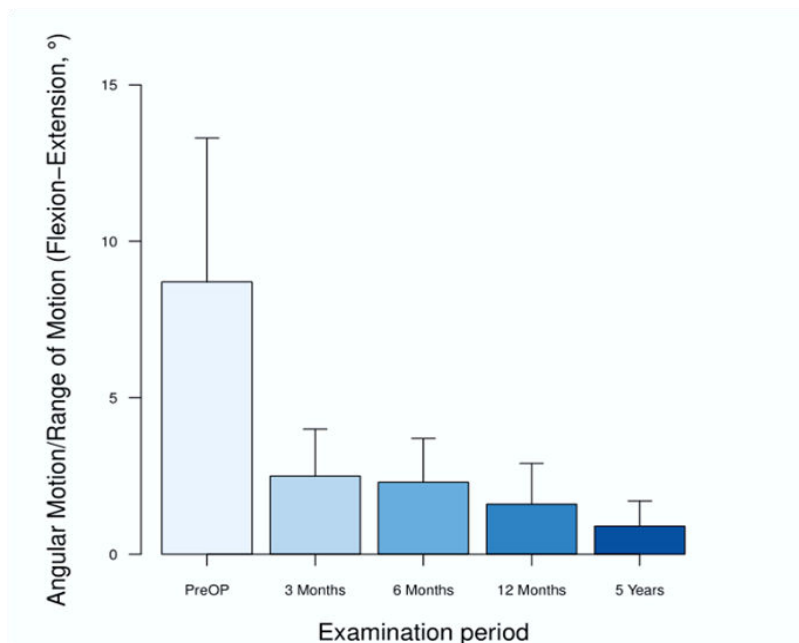


Figure 2: Average Range of Motion at the index level over all study follow-ups. Error-bars indicate the standard deviation.



Figure 3: During follow-up, the fusion status and Range of Motion (RoM) of the index level increased and decreased, respectively.

Demographics	Porous titanium (N=49)
Female gender (%)	26 (54%)
Mean age in yrs (range)	50.3 (31 - 69)
Symptoms	
Radicular pain only	43
Medullary only	6
Combined	0
Symptomatic level	
C3C4	6 (1%)
C4C5	2 (0.4%)
C5C6	21 (43%)
C6C7	19 (18%)
C7T1	1 (0.2%)
Smoking	17 (35%)
Mean BMI (range)	27.1 (20.6 - 45.1)

Table 1: Baseline characteristics of the initial 49 patients receiving porous titanium cages, 34 (70%) were included for long-term follow-up. NDI: Neck Disability Index, BMI: Body Mass Index.

	Porous Titanium	P-value *
NDI		
Pre-op	41.2 ± 20.6	
3 months	24.2 ± 8.8	
6 months	21.6 ± 8.8	
12 months	19.4 ± 8.4	
5 years	12.5 ± 15.4	0.02
VAS arm		
Pre-op	56.1 ± 25.1	
3 months	18.9 ± 25.1	
6 months	21.3 ± 21.5	
12 months	22.2 ± 24.3	
5 years	18.7 ± 20.2	0.489
VAS neck		
Pre-op	53.2 ± 25.5	
3 months	28.3 ± 23.3	
6 months	28.8 ± 22.6	
12 months	23.8 ± 22.4	
5 years	23.5 ± 24.1	0.953
EuroQol		
Pre-op	0.56 ± 0.29	
3 months	0.74 ± 0.24	
6 months	0.77 ± 0.25	
12 months	0.73 ± 0.24	
5 years	0.77 ± 0.24	0.455
Patient perceived recovery		
3 months	63.3%	
6 months	72.9%	
12 months	77.1%	
5 years	88.6%	0.251

Table 2: Treatment effect of primary and secondary outcome during 5 years of follow-up.

* represents p-value 1 year versus 5 years postoperative.

	Mean	Standard Deviation	Max Value	Min Value
Range of Motion (°)	0.8	0.8	3.4	0.0
Translational Motion (°)	0.1	0.1	0.6	0.0
C2-C7-Range of Motion (°)	41.1	11.7	63.5	19.2
AP-Migration (mm)	-0.2	0.5	0.6	-1.8
Subsidence (mm)	1.4	0.9	3.8	0.2
Segmental Lordosis (°)	3.2	5.5	16.7	-7.7

Table 3: Descriptive statistical analysis of quantitative radiographic parameters at 5 years.

Discussion

The presented study showed long term clinical and radiological results of stand-alone 3D printed porous titanium cages in patients receiving anterior discectomy with fusion. At 5 years, the clinical and radiological results were comparable to the initially published 1 year data, although the NDI, patients' perceived recovery and the fusion rate further improved over time.

Titanium cages have been used for many years although long term results are scarce. Jin, et al., presented mid-term and long-term data on titanium cages and documented a fusion rate of 100%, when defining fusion as $< 5^\circ$ of motion on dynamic radiographs. In contrast to our study, all of their cages were filled with central bone graft and additional plates were used [15]. Hida, et al., published data on 146 patients treated with cylindrical titanium stand-alone cages and documented solid fusion in 96% of the cases at 6 years follow-up [16].

Fusion or non-fusion, can be determined traditionally by bony formation during surgery exploration, trabecular bony bridging on computer tomography or decreased range of motion on dynamic radiographs. Ghiselli, et al., defined angular motion $\leq 4^\circ$ as being fused [17]. However, this cut off is quite arbitrary and ideally, fusion is complete absence of segmental motion. Therefore, we also examined fusion as less than 2° of range of motion. When defining fusion as $\leq 4^\circ$, the fusion rate was 91.5% at 1 year, which improved to 100% at 5 years. These rates dropped to 68% at 1 year and 88% at 5 years, when defining fusion as $\leq 2^\circ$ range of motion. Clearly, fusion is a matter of definition. Therefore, to our knowledge, a correlation between fusion rate and neck pain has never been documented because of inconsistency in the definition of fusion. Possibly, with the introduction of a consistent definition of fusion and non-fusion, there could be a relationship between radiological parameters and clinical outcome.

Subsidence is a common observation during follow-up of cervical intervertebral cages. A recently published meta-analysis on cervical cages showed three times more subsidence in titanium cages compared to PEEK, although there was no difference in functional status according to the Odom criteria [18]. However, there is always physiological subsidence due to axial load of the head and subsidence of less than 3 mm is therefore been defined as not-clinically relevant [19]. Our data showed an average subsidence of 1.2 mm at 12 months and 1.4 mm at 5 years, which is clearly in the physiological range.

Internationally, there is no uniformity to perform ACDF with or without additional plating. Plating is frequently performed to improve fusion rate and clinical outcome, but may be associated with increased blood loss, longer surgery time, postoperative dysphagia and extra costs. Cochrane review and various meta-analyses showed no difference between stand-alone cages versus additional plating in terms of functional outcome and fusion [20-22]. In accordance, our data does not support the benefit of additional plating and in our opinion, should not be performed in single level ACDF. One of the advantages of porous titanium is maximal bony ingrowth due to its optimized porosity (80%) and pore size (700µm). The porosity characteristics warrant an elasticity modulus close to bone and *in-vivo* studies demonstrated extensive and quick bone ingrowth [23]. Also in humans, an extracted porous titanium cage retrieved during revision surgery, demonstrated complete osteointegration at two years after the initial surgery [24]. Another advantage of the significant porosity is reduced distortion on MRI and CT scans, which is frequently seen in massive titanium or trabecular metal implants.

The EFFECT follow-up trial has several limitations. First, the study involved a relatively small cohort of subjects undergoing cervical discectomy with porous titanium implants, without a case-control randomization with PEEK or other material. Second, there was only long-term data available of 34 out of the initial 49 operated patients. And finally, the authors MA and JW have financial conflict of interests based on their royalties.

In conclusion, porous titanium cages are safe and effective during long-term follow-up of patients with single level anterior cervical fusion. The stand-alone implant, without additional plating, facilitates spinal fusion in the vast majority of the patients and will further increase over time.

Conclusion

3D printed stand-alone porous titanium cervical implants are effective in terms of clinical and radiological outcome with 88.6% complete or nearly complete recovery and fusion rate of 100% at 5 years follow-up. Moreover, solid single level anterior cervical fusion can be achieved without additional plating.

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Financial Interests

The authors MA and JW receive royalties from Johnson and Johnson based on revenues outside their own hospital.

Availability of Data and Material

All data and materials as well as software application or custom code are supported their published claims and comply with field standards.

Code Availability

Not applicable.

Author's Contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Mark Arts and Jasper Wolfs, analysis was performed by Bart Torensma. The first draft of the manuscript was written by Mark Arts and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

The study was approved by Medical Ethical Committee South West Holland (NL 51781.098.14).

Consent to Participate

All study subjects gave informed consent to participate.

Consent for Publication

All study subjects gave informed consent to publication.

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