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Clinical Study

Porous titanium cervical interbody fusion device in the treatment of degenerative cervical radiculopathy; 1-year results of a prospective controlled trial

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Abstract

BACKGROUND CONTEXT: Anterior cervical discectomy with an interbody cage (ACDF) to obtain fusion is a common procedure in cervical spine surgery. Presently, polyetheretherketone (PEEK) with (auto) graft is frequently used for interbody fusion although alternative implant technology like 3-D printing titanium has been introduced recently.

PURPOSE: Reporting the clinical and quantitative radiological outcome of a prospective cohort of 3-D printed porous titanium implants.

STUDY DESIGN/SETTING: Prospective study of patients with single level ACDF using 3-D printed porous titanium cervical implants. These data were compared with 48 patients from the PEEK with autograft group of the previously performed CAncellous Structured Ceramic Arthrodesis DEvice trial.

PATIENT SAMPLE: Fourty-nine patients were included.

OUTCOME MEASURES: Neck disability index (NDI), visual analog scale (VAS), self-reported perceived recovery, and fusion status.

METHODS: The clinical outcomes and fusion rates were documented at 3, 6, and 12 months. Dynamic X-rays were analyzed to determine range of motion (ROM) of the operated level. Fusion was defined as rotation ≤4° and ≤1.25 mm translation on flexion-extension films.

RESULTS: The mean NDI improved from 41.2 preoperatively to 19.4 at 12 months postoperatively. Both VAS arm and VAS neck improved significantly after surgery and 77.1% of the patients reported complete or nearly complete recovery at 12 months. The mean ROM of the affected disc level decreased from 8.7° (range 2.6–21.4) before surgery to 1.6° (0.0–4.6°) after 12 months. The fusion rate at 3, 6, and 12 months was 84%, 89%, and 91% respectively, compared with 67%, 72%, and 90%, in the PEEK group.

CONCLUSIONS: 3-D printed porous titanium cervical implants resulted in significant clinical improvement after surgery. The fusion rate of porous titanium compared with PEEK with autograft at 12 months was similar, although porous titanium resulted in faster consolidation. In addition, one level anterior cervical fusion can be successfully achieved without additional plating.

Keywords: 3-D printing; Anterior cervical discectomy; Fusion, Implant; PEEK, Surgery; Titanium

Introduction

Anterior cervical discectomy is the standard surgical treatment of patients with radicular pain caused by cervical disc herniation unresponsive to conservative treatment. In 1958, Cloward first described anterior cervical decompression with the use of autologous iliac crest interbody graft

FDA device/drug status: Not applicable.

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anterior cervical discectomy with fusion (ACDF) to maintain disc height [1]. Smith and Robinson developed a technique using iliac crest bone blocks which was the standard for many years [2]. There is still controversy about the benefits of adding interbody fusion to the cervical discectomy technique [3−5]. Frequently, surgeons perform ACDF to maintain disc height and cervical alignment, and promote bony fusion to prevent instability [6]. At present, ACDF with a polyetheretherketone (PEEK) plastic cage is frequently used by many surgeons [7−10]. The PEEK cage can be filled with iliac crest bone graft, local bone obtained during the decompression procedure, cadaver bone (allograft), or a bone graft substitute [11]. PEEK, however, is a hydrophobic material, that has no bone-incorporative qualities compared with other cage material (titanium) as shown in an in vitro study of Olivares-Navarrete [12]. In a recently published study, the ACDF procedure that include the PEEK cage filled with local bone has been compared with a more biocompatible ceramic cage in the randomized controlled CAncellous Structured Ceramic Arthrodesis DEvice (CASCADE) trial [13]. However, both groups reported similar recovery with no significant difference in clinical outcome.

New production methods like additive manufacturing, also known as 3-D printing, allow to create complex implant design features and controlled microstructural architectures leveraging the bone-incorporative qualities of titanium material. A laser-based powder bed fusion process, also called selective laser melting, using titanium alloy powder is used to manufacture the porous titanium cage. The 3-D printed porous titanium cage design includes a solid framework with an internal porous structure Emerging Implant Technologies (EIT) Cellular Titanium® throughout the cage. The interconnected porous structure is designed for optimized porosity (80%) and pore size (700 μm) to enable bone incorporative qualities. The proprietary 3D printing technology leads to cellular titanium structure that offers a modulus of elasticity similar to PEEK (3.84 GPa) [14]

In vivo studies demonstrated extensive and quick bone ingrowth in porous titanium implants. Animal models documented the optimal pore size of around 500 μm to 700 μm with fast bone incorporation in the absence of a fibrous tissue bone-implant interface revealing the promising capacities of this material [15,16]. The 3-D printed porous titanium cage is a new product which has been used in humans in a small number of recent cases. Although the clinical application of 3-D printed titanium implants in orthopaedic reconstructive surgery has excellent clinical results, no clinical trial of the spinal application of this material has been conducted yet. Whether porous titanium cervical cages have more favourable clinical and radiological results as compared with PEEK, has to be determined by this trial. In the present study, a consecutive group of patients receiving porous titanium cervical cages were prospectively followed for clinical and radiological parameters and ultimately were compared with the PEEK group of the CASCADE trial, which served as an historical control.

Materials and methods

The study has been registered in The Netherlands Trial Register (NTR1289). All patients gave written informed consent before enrolment into the study. Patients (age 18 −75 years) with monoradicular symptoms in one or both arms lasting more than 8 weeks due to disc herniation and/or osteophytes, and unresponsive to conservative treatment were eligible for the trial (Table 1). Exclusion criteria included previous cervical surgery, severe kyphosis at the involved level, neck pain only without radicular or medullary symptoms, metabolic disease, neoplasms, cervical trauma, spinal anomalies, severe mental or psychiatric disease, and inadequate Dutch language.

The Examination of Fast Fusion with EIT Cellular Titanium (EFFECT) study was designed as a prospective consecutive cohort trial with a follow-up period of 1 year. Based on the sample size analysis of the recently performed CASCADE trial, a cohort of 50 patients was applicable [17]. Patients were followed up at 3 months, 6 months, and 1 year with patient reported outcome measures and plain radiographs. The analysis was conducted at 1-year follow-up and was compared with the before mentioned historical CASCADE trial which, unfortunately, did not have baseline visual analog scale (VAS) arm and VAS neck pain. All patients were operated by the authors MA and JW.

Surgical procedure

All patients were positioned prone with their neck in neutral position or slightly extended under general anesthesia. The affected cervical disc level was verified with fluoroscopy. A small transverse incision was made on the right side. Medial to the carotid sheath, the prevertebral space was opened and the anterior cervical spine was exposed. Caspar spreader and 2 distraction pins were placed in the affected segment. A standard anterior discectomy with the aid of loupe magnification or microscope (depending on the surgeon's preference) was performed in all cases. The posterior longitudinal ligament was opened and the nerve root and dura were decompressed adequately. Once the anterior discectomy was performed, the porous titanium cage (without additional bone graft) was placed within the intervertebral space under fluoroscopic guidance. The implant was smeared with blood obtained by scratching the end plate after the disc space is prepared. No supplemental fixation (eg, cervical plate) was used in the procedure. If required, a vacuum drain was placed. The porous titanium cage was available in two footprints, 16 × 12 mm (small) and 18 × 14 mm (large), and each footprint was available in 4, 5, 6, 7, and 8 mm height. All implants had 4° of lordosis. After surgery, all patients were mobilized as soon as possible without a collar.

Table 1
The EFFECT trial inclusion and exclusion criteria

Inclusion criteria:
- Age 18–75 years
- Radicular signs and symptoms in one or both arms (ie, pain, paresthesia, or paresis in a specific nerve root distribution) or symptoms and signs of acute or chronic myelopathy.
- At least 8 weeks prior conservative treatment (ie, physical therapy, pain medication)
- Radiographic diagnosis of cervical disc herniation and/or osteophyte at 1 level (C3–C4 to C7–T1) in accordance with clinical signs and symptoms
- Ability and willingness to comply with project requirements
- Written informed consent given by the subject or the subject's legally authorized representative

Exclusion criteria:
- Previous cervical surgery (either anterior or posterior)
- Increased motion on dynamic studies (> 3 mm)
- Severe segmental kyphosis of the involved disc level (> 7°)
- Patient cannot be imaged with MRI
- Neck pain only (without radicular or medullary symptoms)
- Infection
- Metabolic and bone diseases (osteoporosis, severe osteopenia)
- Neoplasm or trauma of the cervical spine
- Spinal anomaly (Klippel-Feil, ankylosing spondylitis, ossification of posterior longitudinal ligament)
- Severe mental or psychiatric disorder
- Inadequate Dutch language
- Planned (e)migration abroad in the year after inclusion

Primary noninferiority hypothesis

The primary effectiveness hypothesis was defined as no difference in neck disability index (NDI) improvement between the porous titanium group and PEEK group. This hypothesis was formulated for testing clinical noninferiority based on the Blackwelder approach [18]. In the Blackwelder approach, the null hypothesis is that the investigational device is clinically significantly worse than control by an amount (at least) equal to an a priori selected noninferiority margin. The minimal clinically important difference for the NDI is 7.5 points out of 50, or 15% when the scale is standardized to a range from 0 to 100 [19]. Therefore, the primary null hypothesis is that the mean improvement for the investigational device is smaller (ie, less negative) than the mean improvement for the control device by an amount equal to or exceeding 15 out of the 100-point scale.

Sample size determination

As the CASCADE trial will serve as the historical control for this study, similar statistical requirements were considered for this trial [17]. For power analysis, they used the NDI improvement rate cited in the literature for ACDF with carbon fiber reinforced PEEK cages: 10% improvement with a standard deviation of 22% [19,20]. In the CASCADE study, calculating 8% loss to follow up, 15% improvement of NDI with 90% power and alpha margin 5%, a total of 100 patients were enrolled, leading to 50 patients in every arm.

To state the treatment with porous titanium cage is clinical successful, a minimal difference in NDI of 15% or 7.5 points is defined. To be able to use the outcome of the CASCADE trial as a historical control, also a group of 50 patients need to be included in the EFFECT trial.

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 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).

Outcome measures

The primary outcome measure was improvement in the NDI which has been translated into Dutch and validated for the population of the Netherlands [21,22]. Secondary outcome measures were the 100-mm VAS for arm pain and neck pain [23], the 7-point Likert self-rating scale for

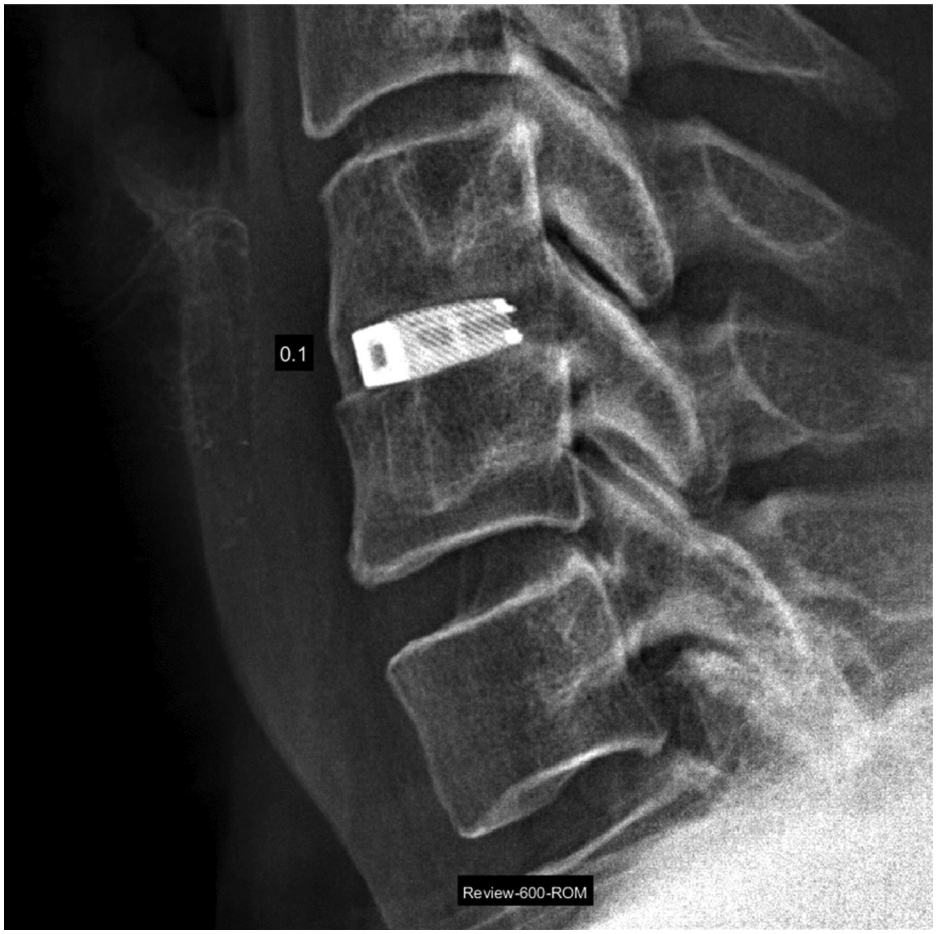

Fig. 1. Flexion-extension motion analysis allowed measurement of rotation on flexion-extension films with an accuracy of ±1°; solid fusion of 3-D printed porous titanium is documented.

perceived recovery in which ''complete recovery'' and ''almost complete recovery'' are defined as good outcome [24], and the EuroQol-5D [25,26]. Perioperative variables including operating time, blood loss, length of hospital stay in addition to adverse events, reoperations, and surgical complications were also recorded.

Radiological assessment

At each follow-up time point, four plane films were collected (standing anterior-posterior, lateral, flexion and extension radiographs). In addition, quantitative and qualitative motion analysis using Functional X-Ray Analysis of Aces (GmbH, Filderstadt Germany) allowed measurement of rotation on flexion-extension films with an accuracy of ±1° (Fig. 1). Fusion for this study was defined as rotation ≤4° 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 <2° and <1°.

Results

Between September 2015 and November 2016, a total of 54 patients were enrolled in the study. Five patients were excluded from primary analysis for various reasons; two patients were randomized but not operated because of improvements of symptoms, one patient received additional plating and therefore protocol violation, one patient died of an unrelated cause, and one patient refused to continue the

Table 2
Baseline characteristics of 49 patients receiving porous titanium cages, compared with the PEEK group of the previously performed CASCADE trial [13]

Demographics	Porous titanium (N=49)	PEEK (N=48)
Female gender (%)	26 (53%)	23 (48%)
Mean age in years (range)	50.3 (31−-69)	49.4 (28−67)
Symptoms		
Radicular pain only	43	39
Medullary only	6	7
Combined	0	2
Symptomatic level		
C3C4	6 (1%)	1 (2%)
C4C5	2 (0.4%)	6 (13%)
C5C6	21 (43%)	30 (63%)
C6C7	19 (18%)	10 (21%)
C7T1	1 (0.2%)	1 (2%)
Smoking	17 (35%)	19 (40%)
Mean BMI (range)	27.1 (20.6−45.1)	28.6 (20.6−75)
NDI	41.2±20.6	42.8±14.9

PEEK, polyetheretherketone; NDI, neck disability index.

study follow-up. Of the 49 patients included patients, 26 were female (54%). The mean age was 50.3 years and 17 patients (35%) did smoke. All patients presented with radicular arm pain or medullary symptoms. The majority of the cervical disc herniation and/or osteophyte were at the level C5C6 and C6C7. All baseline characteristics are shown in Table 2.

Primary outcome measure

Patients treated with porous titanium cages showed large improvement of NDI from 41.2 preoperatively, to 24.2 at 3 months, 21.6 at 6 months, and 19.4 at 12 months postoperatively. The improvement of NDI in patients treated with porous titanium and PEEK with autograft were similar and there was no statistically significant difference between both groups (Fig. 2).

Other outcome measures

The mean VAS arm pain improved significantly from 56.1 mm before surgery, to 18.9 mm at 3 months, 21.3 mm at 6 months, and 22.2 mm at 12 months. Similar improvement was documented for VAS neck pain. At 3 months, 63.3% of the patients reported good outcome which improved to 72.9% at 6 months, and 77.1% at 12 months. These results were comparable with the historical PEEK control group (Table 3).

Surgical parameters and complication

The surgical procedure was uneventful in all patients. The average operation time was 40.6±10.8 minutes. The majority of the patients received a large cage 5 mm or 6 mm in height. Ten patients reported complications (10%); five patients experienced transient dysphagia, two patients had increased sensory deficit of the arm, one patient documented cage rotation on X-ray without clinical consequence, one patient had an infection requiring removal of the cage, and one patient had symptomatic adjacent level disease during follow-up. All perioperative data are presented in Table 4.

Radiographic outcome

The mean RoM of the affected disc level at baseline was 8.7° (range 2.6–21.4) which decreased to 2.5° (0.2–7.0°) at

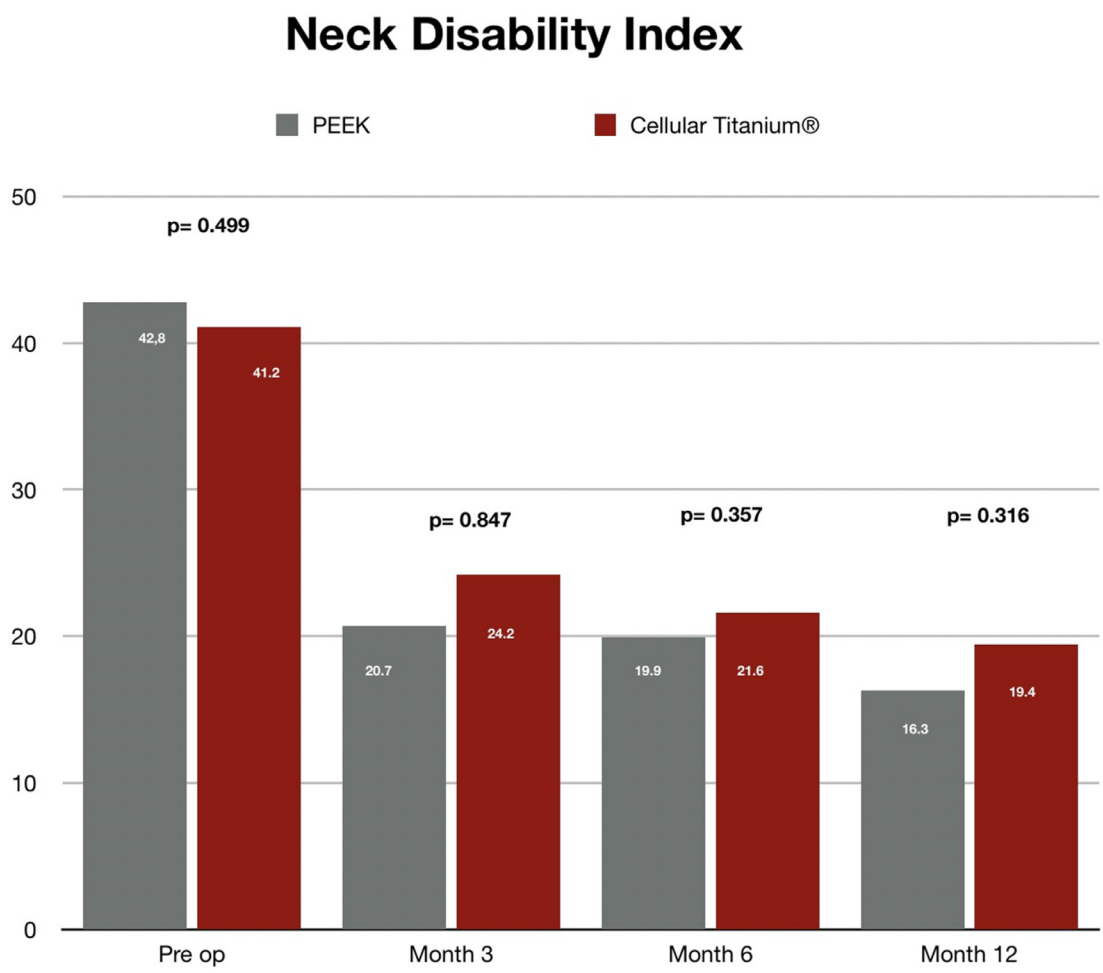

Fig. 2. Neck and disability index scores of patients treated with porous titanium cages compared with PEEK with autograft during the follow-up of 12 months. PEEK, Polyetheretherketone.

Table 3
Treatment effect of primary and secondary outcome during follow-up period

	Porous titanium (N=49)	PEEK (N=48)
Neck disability index		
Preop	41.2±20.6	42.8±14.9
3 months	24.2±8.8	20.7±14.5
6 months	21.6±8.8	19.9±17.8
12 months	19.4±8.4	16.3±16.4
VAS arm		
Preop	56.1±25.1	-
3 months	18.9±25.1	28.7±31.7
6 months	21.3±21.5	21.5±28.5
12 months	22.2±24.3	20.5±26.3
VAS neck		
Preop	53.2±25.5	-
3 months	28.3±23.3	29.5±26.3
6 months	28.8±22.6	20.4±23.2
12 months	23.8±22.4	22.4±26.8
EuroQol		
Preop	0.56±0.29	-
3 months	0.74±0.24	-
6 months	0.77±0.25	-
12 months	0.73±0.24	-
Patient perceived recovery		
3 months	63.3%	65.2%
6 months	72.9%	70.5%
12 months	77.1%	76.1%

PEEK, polyetheretherketone; VAS, visual analog scale.

3 months, to 2.3° (0.1–5.7°) at 6 months, and 1.6° (0.0–4.6°) at 12 months. The mean subsidence after 12 months was 1.2 mm. The fusion rate (defined as less than 4° of ROM) at 3, 6 and 12 months was 84%, 89%, and 91% respectively, compared with 67%, 72%, and 90%, in the PEEK group. The difference in fusion rate at 6 months was slightly significant in favor of porous titanium (p=.048) (Fig. 3).

Discussion

Advances in implant materials have rapidly evolved over the years. Additive manufacturing enables the construction of 3-D printed porous titanium implants to potentially facilitate bony ingrowth throughout the cage instead of just surrounding the cage such as in PEEK and solid titanium implants. Due to lacking clinical data on 3-D printed titanium cervical cages, the EFFECT trial was able to study and evaluate single level ACDF clinical and radiological outcomes compared with a historic control group of PEEK cages with autograft. This study on patients receiving 3-D porous titanium cervical cages has shown that the implants are safe and result in similar clinical improvement compared with patients receiving PEEK cages with autograft. Both groups showed significant improvement of NDI from preoperative to 3, 6, and 12 months postoperatively.

Table 4
Operative and implant characteristics with complications during follow-up

Operative characteristics	Porous titanium (N=49)
Operation time in minutes (range)	40.6 (28–75)
Blood loss, ml (range)	50 (0–2500)
Implant characteristics	
Small	6
Large	43
5 mm height	25
6 mm height	22
7 mm height	2
Complications	10 (20%)
Transient dysphagia	5
Increased sensory deficit arm	2
Cage malposition without consequence	1
Infection (reoperation and cage removal)	1
Adjacent segment spondylosis (requiring surgery)	1

In addition to clinical improvement comparison, this study was able to demonstrate an increase rate of fusion, at earlier timepoints. According to the literature, bony fusion is achieved in approximately 70% to 90% of the patients, although 30% of spinal fusion surgeries may result in nonunion [27]. In the 3-D printed titanium cages, fusion was achieved in 84% of the patients at 3 months and 89% of the patients at 6 months, over the PEEK control group in 67% and 72%, respectively, with fusion defined as rotation ≤4° and ≤1.25 mm translation on flexion-extension films at the index level. Although there is no statistical difference between the groups for fusion at 1 year, the speed of solid fusion in 3-D printed porous titanium cage is faster.

Surgical exploration has traditionally been accepted as the standard method for determining nonunion. Given the invasive nature, noninvasive diagnostic tools such as flexion-extension radiographs and computer tomography (CT) are required to assess fusion and non-fusion. At present, trabecular bridging bone visible on CT scan is defined as the gold standard for fusion [28]. Moreover, the amount of intervertebral motion measured at the adjacent endplates or the distance between the spinous process at the index level, has also been addressed. Ghiselli et al. defined a cutoff of 4° of angular motion as pseudarthrosis [29]. However, the cutoff of 4° is quite arbitrary because solid fusion in fact is complete absence of segmental motion. Therefore, in our study, we also examined fusion criteria as less than 2° and less than 1° of segmental motion. Results showed that at 12 months, the 90% fusion rate when defining fusion less than 4°, dropped to 70% when defining fusion less than 2°, and to 45% when defining fusion less than 1° of segmental motion. Therefore, fusion seems to be a matter of definition and clinical data should be criticized for this. In the EFFECT and CASCADE trials, our data has shown improvement of fusion rates in patients undergoing anterior cervical discectomy up to 1 year after surgery, regardless the type of implant. Fusion seems to be an ongoing process and the fusion status is dependent on the time interval after surgery.

The EFFECT trial was able to evaluate fusion on single level ACDF without a plate utilizing a 3-D printed titanium cage when compared with a historic PEEK group, also without anterior plating. In accordance to the Cochrane

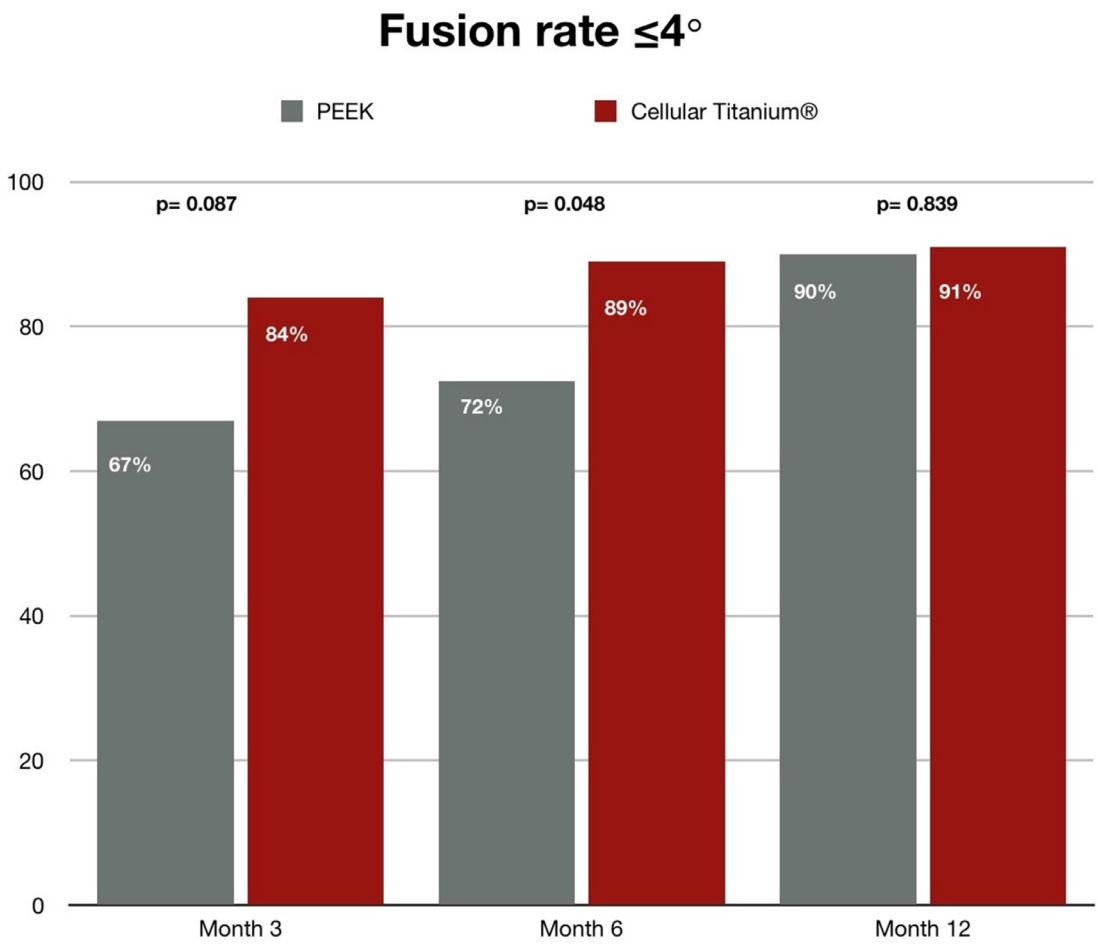

Fig. 3. The fusion rate (defined as less than 4˚ of ROM) at 3, 6 and 12 months of porous titanium compared with PEEK with autograft. The fusion rate of porous titanium is faster but there was no significant difference at 12 months. ROM, range of motion; PEEK, Polyetheretherketone.

review of Jacobs et al., general surgical practice in the Netherlands and other European countries is to perform a one level ACDF without additional plating [4]. In the United States however, nearly all surgeons perform additional plating although there is no evidence supporting the benefit of this surgical strategy; the operation time is longer, patients may experience more dysphagia, and the procedure is more expensive. A recently performed meta-analysis by Cheung et al., confirmed this criticism [30].

The design of the EFFECT trial had several limitations. First, we did not randomize the patients but solely compared them to the PEEK group with autologous bone of a previously performed randomized controlled trial. Second, we did not have postoperative CT to document bony bridges and compare these with dynamic radiographs for analyzing fusion. Third, the number of included patients is relatively small. And finally, the authors MA and JW have financial conflict of interest based on their royalties.

In conclusion, 3-D printed porous titanium implant devices are safe and effective and will result in similar clinical outcomes compared with patients receiving PEEK with autograft. The fusion rate in 3-D printed porous titanium cages is faster and there is no need for autologous bone or additional plating. These results are quite unique and may possibly change the daily care of patients requiring cervical surgery. Future research involving larger sample size population and longer-term follow-up will help to support these initial findings.

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