Preliminary results of quantitative functional X-ray analysis of stand-alone EIT cervical implants in comparison to PEEK implants at 3 and 12 months follow up.

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Methods
A prospective cohort study of 50 patients with single level ACDF using a 3-D printed titanium cervical cage (EFFECT trial) was performed. The fusion rates were compared to 50 patients treated with PEEK cages from a previous randomized controlled trial (CASCADE trial.) The results of the first 10 patients of the EFFECT trial are shown in this abstract. Flexion and extension X-ray data on 3 (N=10) and 12 months (N=9) were analyzed using FXA (Aces GmbH, Leipzig) to determine RoM (in °) of the operated level and subsidence (in mm). The results were compared to historical quantitative motion analysis and subsidence data from the CASCADE Trial.

Results
The mean RoM of the EIT implants after 3 months was 2.8° (SD 1.9°), decreasing to 1.5° (SD 1.7°) after 12 months. Subsidence was < 2 mm in all patients. Depending on the threshold of the RoM, the fusion rate was 70% in the PEEK group and 89% in the EIT group after 12 months with a set point of <4°. This lowered to 63% in the PEEK group and to 78% in the EIT group with a set point of <2°. At every time frame, the lack of motion was more prominent in the porous titanium cage compared to the PEEK implants from the CASCADE Trial. Moreover, the subsidence rate was less in the porous titanium implants.

Conclusion
These preliminary functional X-ray results of the porous titanium cervical implants are very promising regarding RoM, fusion and subsidence rate. The results of the complete EFFECT trial are needed to support the superiority of porous titanium implants.
Anterior cervical discectomy (ACD) is the basic 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 (ACDF) to maintain disc height (Cloward 1958). Smith and Robinson developed a technique using iliac crest bone blocks which was the standard for many years (Smith & Robinson 1958). There is still controversy about the benefits of adding interbody fusion to the cervical discectomy technique (Barlocher et al. 2002; Hirsch 1960; Jacobs et al. 2004; Nandoe et al. 2007). Frequently surgeons perform ACDF to maintain disc height and cervical alignment, and promote bony fusion to prevent instability (Hee & Kundnani 2010).

At present, ACDF with a Polyetheretherketone (PEEK) plastic cage is considered as the golden standard for cervical disc herniation for many surgeons (Celik et al. 2007; Cho et al. 2002; Kulkarni et al. 2007; Lied et al. 2010; Park et al. 2009). The PEEK cage can be filled with iliac crest bone graft (ICBG), local bone obtained during the decompression procedure, cadaver bone (allograft) or a bone graft substitute (Chau & Mobbs 2009). PEEK is however a hydrophobic material, that has no bone-incorporative qualities compared to other cage material (titanium) as shown in an in-vitro study of Olivarres-Navarrete (Olivares-Navarrete et al. 2012). Additive manufacturing allows to produce porous titanium cages, that combine the biocompatibility of titanium material with improved biomechanical and bone incorporative qualities. EIT has cervical and lumbar implants that are produced using the Selective Laser Melting technique.

Literature describes a wide range in fusion percentages related to material and design of cages and presently, there is no golden standard for the measurement of fusion in spine surgery (Jacobs et al. 2004 & 2011). Analysis of dynamic X-rays of the cervical spine result in a very accurate and reliable measurement of fusion and is seemingly less subjective than CT (Ghiselli et al. 2011).

In the EFFECT Trial a cohort of 50 patients, that received either a single or double level EIT cervical implant, is prospectively being studied for clinical outcome and radiological fusion results. The present report describes the preliminary 3 and 12 months Functional X-ray Analysis (FXA) of stand-alone 3-D printed porous titanium cervical implants (EIT GmbH).

The quantitative radiological results of the first 10 patients have been compared to the outcome of the PEEK arm of the CASCADE trial (Arts et al. 2011), which served as a historical control.

A prospective cohort study of 50 patients with single level ACDF using the EIT cervical implant (EFFECT trial) was performed. The EFFECT Trial prospectively studies clinical (NDI) and radiological parameters (FXA). Initial analysis was performed on the first 10 patients of which 9 had reached 1 year follow-up. Final analysis will be conducted when all patients have 1 year follow-up. The study was approved by the Medical Ethics Committee of Southwest Holland. Informed consent was obtained from all individual participants included in the study. The patients were treated by two neurosurgeons of Haaglanden Medical Center, The Hague, Netherlands (MA and JW). In this preliminary evaluation, the radiological fusion rates of the EIT cervical implants in the first 10 patients were compared to the quantitative motion analysis and subsidence data from 41 patients treated with PEEK cages filled with local autograft (part of a previous randomized controlled trial: CASCADE trial) (Arts et al. 2013, 2017).

Flexion and extension X-ray data on 3 (N=10) and 12 months (N=9) were analyzed using FXA (Aces GmbH, Leipzig) to determine RoM (in °) of the operated level and subsidence (in mm). FXA stands for “Functional X-Ray Analysis” and is a proprietary image analysis software, capable to analyze and quantify relative motion or dimensional changes in medical images with highest possible precision. Independent validation (Schulze et al. 2011) has shown FXA to be one of the most accurate tools for analyzing images of the spine, being able to determine RoMs > 1°. The FXA software is FDA-approved for clinical trials (510k, K110765). Fusion percentages were calculated in this study for thresholds of rotation < 4° and < 2° on flexion–extension films. Subsidence was measured in mm, calculating the difference in mean height at the various follow-up moments with respect to the preoperative state and to the postoperative state.
Between May 2015 and September 2016, 50 patients were enrolled in the EFFECT trial and by January 2017, 10 patients and 9 patients were respectively eligible for the 3 months and 12 months preliminary radiological follow up with FXA analysis.

Preoperatively the EFFECT trial patients had a RoM of approximately 7°, which declined to 0.7° RoM (median) after 12 months (table 1).

The mean RoM for the PEEK cohort was 1.8° after 12 months FU (table 2). The subsidence was 1.24 mm in the EIT group and 1.57 mm in the PEEK group. The fusion rate with a set point of <4° resulted in a fusion rate of 90% in the PEEK group and 89% in the EIT group after 12 months (fig. 1). Lowering the threshold to <2° rotation lowered the fusion rate to 63% in the PEEK group and to 78% in the EIT group (fig. 2).

Examples of flexion and extension Xrays at 12 months follow up are presented in figure 3 and 4.

### Table 1. RoM of the EIT implants

<table>
<thead>
<tr>
<th>Pre-op</th>
<th>3 Months n=10</th>
<th>12 Months n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>RoM Mean [°]</td>
<td>7.4 (2.6-14.1)</td>
<td>2.8 (0.2-6.0)</td>
</tr>
<tr>
<td>RoM Median [°]</td>
<td>6.9 (2.6-14.1)</td>
<td>2.5 (0.2-6.0)</td>
</tr>
</tbody>
</table>

RoM of the EIT implants in degree of motion at the various follow up moments.

### Table 2. RoM of the PEEK implants

<table>
<thead>
<tr>
<th>Pre-op</th>
<th>3 Months n=43</th>
<th>12 Months n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>RoM Mean [°]</td>
<td>3.4 (1.1-7.5)</td>
<td>1.8 (0.0-6.8)</td>
</tr>
</tbody>
</table>

RoM of the PEEK implants in degree of motion at the various follow up moments.
Results

Fig 3. Detail of the EIT cervical implant

Detail of the EIT cervical implant clearly showing the porous structure including the X-ray marker and demonstrating bone bridging anteriorly after 12 months.

Fig 4. The radiographic characteristics of the EIT cervical implant

The radiographic characteristics of the EIT cervical implant demonstrating Flexion-Extension X-rays 12 months’ post-operative.
Microporous materials are an attractive concept since no autograft harvest or additional expense for graft materials is needed. Trabecular metal made from porous tantalum has received extensive testing and has been applied for various orthopedic purposes. It has however not fared well as a stand-alone cage material; due to brittleness of the porous implant, fragmentation can occur. Furthermore, its high radio opacity and metallic distortion interfere with clinical imaging evaluation (Kasliwal et al. 2013). PEEK has, until recently, been regarded as biological inert. Current research however has defined its inflammatory, antiosseointegrative properties and its promotion of fibrous tissue generation instead of bone (Toth et al. 2006, Kersten et al. 2013). Several in-vitro studies demonstrated an increase in inflammatory interleukines and a lack of endogenous BMP production in the presence of PEEK material (Olivarez-Navarrete et al. 2012, Olivarez-Navarrete et al. 2015, Gittens et al. 2014). Although the preliminary EFFECT group is small, demonstrating less than 2 degree of motion in almost 80% of the patients after 12 months, could reflect the favorable bone ingrowth configuration.

Currently there is still a lack of definition of fusion in the literature. In many clinical papers, the method of measuring fusion is not described, which makes it very difficult to compare or pool data to determine a superior treatment for cervical disc herniation (Jacobs et al. 2004 and 2011). Although CT scan has long been regarded as the gold standard for determining a pseudoarthrosis in the cervical spine, the interpretation is subjective. Analysis of motion using Quantitative Motion Analysis (QMA) or Functional Motion Analysis (FXA) is less subjective and has been more predictive in confirming pseudoarthrosis (Ghiselli et al. 2011). Using QMA/FXA software, pseudoarthrosis rate is highly dependent on the threshold of motion. QMA/FXA has the advantage that it corrects for magnification and reduces the inter- and intraobserver measurement error. The adjacent level motion can be used to determine the influence of the effort of the patient in performing the dynamic movement. The accuracy of the QMA/FXA method is below an average error of 0.5° (Reitman et al. 2004, Schulze et al. 2011). A threshold level of 4° of motion is commonly used to identify pseudoarthrosis, as this is also the FDA requirement. In the study of Hipp et al. the apparent pseudoarthrosis rate varied from 6% when the intervertebral motion threshold was 4° to 64% when the intervertebral motion threshold was 1° (Hipp et al. 2005). The same pattern could be observed in our small series, where the fusion rate dropped from 90% in the <4° PEEK group to 63% in the <2° PEEK group and from 89% in the <4° EIT group to 78° in the <2° EIT group. The results in the EIT group however excel the PEEK performance, which outcome was similar to the observations in the Hipp study (Hipp et al. 2005).

Preliminary quantitative radiological results of the EFFECT Trial are very promising; the final analysis will ultimately determine similarity or superiority of the EIT implant in comparison to the current gold standard, being PEEK with autograft. End of 2017 these results will be available.

Discussion

EIT Cellular Titanium® cervical and lumbar implants have been designed to tackle the most prominent critical clinical issues related to current implant materials, being the occurrence of pseudoarthrosis (non-union), subsidence, migration and malalignment, immunological reactivity of implant material and imaging distortion. The EIT Cellular Titanium® implants are designed to fit the optimal requirements for maximized bone ingrowth. This means that the implants have an ideal pore-shape (van Bael et al 2012) and an optimal pore-size and porosity, as described in various peer-reviewed publications (Devine at al. 2012; Fukuda et al. 2011, van der Stok 2013, Wu et al. 2013, Taniguchi et al. 2016, Shah et al 2016). Due to additive manufacturing, it is possible to create this optimal fusion device by ‘printing’ this biocompatible titanium porous ingrowth scaffold.
Cage placement following anterior discectomy. after tricortical iliac graft or polyetheretherketone polymer interbody cages in the treatment of cervical disc herniation; a double-blind randomised multicenter study. BMC Musculoskelet Disord 2010; 11:122

Cage placement following anterior discectomy with or without interbody fusion and arthroplasty in the treatment of cervical disc herniation; a double-blind randomised multicenter study. BMC Musculoskelet Disord 2010; 11:122

A comparison of cervical anterior discectomy with or without interbody fusion; protocol of a blinded randomized controlled trial. BMC 2013; 14:244-251.


Design of the PROCON trial: a prospective, randomized multi-center study comparing cervical anterior discectomy with-out fusion, with fusion or with arthroplasty. BMC Musculoskelet Disord 2006; 7:85


Literature


