

**A PROSPECTIVE CLINICAL PILOT STUDY OF FUSION RATES USING SPIRA™-C
TITANIUM 3-D PRINTED INTERBODY DEVICE FOR ANTERIOR CERVICAL DISCECTOMY
AND FUSION**

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INTRODUCTION/BACKGROUND

Anterior cervical discectomy and fusion surgery (ACDF) is a common procedure performed by spine surgeons for degenerative disc disease and spinal stenosis of the cervical spine. Typically, patients present with neck pain associated with radiculopathy or myelopathy; ACDF surgery is the treatment of choice once conservative, non-operative therapies have been exhausted. During ACDF surgery, a discectomy is performed and an interbody spacer or cage is implanted in the disc space to facilitate arthrodesis and maintain stability and intervertebral height; this is further stabilized with plate and screws fixated at the intended level. There are many material and design options for interbody cages ranging from metal, plastic, composite, and allograft to enhance bone growth and optimize fusion. Polyetheretherketone (PEEK) and titanium are two materials commonly used to manufacture interbody cages and both are routinely utilized in ACDF surgery.¹ Although both PEEK and titanium cages are biocompatible with similar fusion rates (88% vs. 93% respectively³, 100% both cages⁸, and 100% vs. 86.5% respectively⁶), PEEK cages offer a modulus of elasticity similar to cortical bone, which can contribute to a lower subsidence rate by allocating stress and load.² However, given the smooth surface and hydrophobic properties of PEEK, it may inhibit cell adhesion and osseointegration.¹ Titanium cages offer durability and enhanced osseointegration but a higher modulus elasticity.⁴ There are other factors that can influence the performance of a cage aside from material, including endplate preparation, bone density, cage placement, and cage design⁹ Ideally, an interbody cage should possess biomechanical stability and biocompatibility with a low incidence of subsidence and a high potential for osseointegration while maintaining intervertebral height and alignment. In order to obtain some of these features there have been modifications in shape and structure of cages as well as the material surface (i.e. porous, roughened, or osteoconductive treated surfaces) to promote osseointegration.¹⁰ A recent technology growing in spinal surgery is the use of 3D printed titanium cages. 3D printing allows for the fabrication of atypical cage designs that traditionally could not have been manufactured.¹ These designs may include a more open and intricate structure to allow for significant bone packing and bone ingrowth. Another feature of 3D printing is the ability to modify the material surface to create an osteoconductive foundation.¹ 3D printed cages can incorporate these biomechanical factors to maximize the potential for fusion and stable fixation. In a preclinical study by McGilvray et al (2018), it was found that there was a significantly greater total bone volume within the 3D porous titanium device compared to PEEK at 8-weeks and 16-weeks as demonstrated on micro-CT as well as a significant decrease in flexion-extension range of motion for the 3D porous titanium device.¹ There are prior studies comparing traditionally manufactured titanium alloy cages to PEEK as cited in the previously mentioned fusion rates.^{3,6,8} In this pilot study proposal, a prospective, single-arm treatment group using a 3D printed porous titanium alloy cage (Spira™-C; Camber Spine Technologies, Wayne PA) will be compared to historical data based on literature review of fusion rates and patient reported outcomes of PEEK interbody cages .

OBJECTIVE

The objective of this study is to perform a prospective, single-arm clinical evaluation utilizing the Spira™-C 3-D printed titanium interbody device for treatment of degenerative disc disease and spinal stenosis of the cervical spine to evaluate fusion status and patient reported outcomes. The primary objective is fusion status; this will be measured using dynamic (flexion and extension) X-rays and CT scan at 12 months. Secondary objectives include evaluation of patient reported outcomes, VAS score (pain), NDI (neck disability index; pain and function), SF-36 (quality of life), and EAT-10 (dysphagia). Also, radiographs will be evaluated for the occurrence of device-related adverse events or complications, such as revision surgery at the index level, subsidence, migration, and failure or loosening of the interbody device. Neurological motor and sensory evaluations will be followed for improvement or worsening over the course of the study. Data collected from subjects treated with the Spira™-C Interbody Device will be compared to historical data based on literature review of fusion rates and patient reported outcomes of traditional PEEK interbody cages.

DESCRIPTION OF SPIRA™-C OPEN MATRIX CERVICAL INTERBODY DEVICE

The Spira™-C Open Matrix Cervical Interbody Device, manufactured by Camber Spine Technologies, was 510(k) cleared by the FDA on October 17, 2017. The Spira™-C device is a 3-D printed titanium alloy cage designed with open spiral supports to allow for a hollow chamber to facilitate the packing of bone graft to optimize fusion. Spira™-C is indicated for use at one or two contiguous levels from C3-C7 for degenerative disc disease (DDD) with up to grade I spondylolisthesis. It is intended to be used with a supplementary FDA-cleared plate fixation system. Spira™-C must be used with autograft or cancellous or cortico-cancellous allograft.

METHODOLOGY

Study Design

This is a post-market, single-arm, prospective clinical study to evaluate fusion status and patient reported outcomes using the Spira-C titanium interbody cage for degenerative disc disease where single-level ACDF surgery is indicated. The treatment group will consist of 40 subjects treated with the Spira™-C Interbody Device at one level. Patients with a diagnosis of cervical degenerative disc disease and/or spinal stenosis, radiculopathy or myelopathy and planning to undergo a 1-level ACDF surgery between C3-C7 will be screened. If the subject meets all of the inclusion criteria and none of the exclusion criteria, the patient will be approached regarding study participation by the surgeon or study coordinator. If the subject wishes to participate, the study coordinator will initiate the consent process. Once the consent process has been completed and the subject has signed an IRB approved informed consent form the medical history, cervical spine examination (motor/sensory), and baseline subject questionnaires (VAS, NDI, SF-36, and EAT-10) will be collected. Once the ACDF surgery has taken place as planned; data will be regarding the surgery performed, operative time, bone graft used, plate and screw fixation system used,

length of stay, and adverse events or complications related to the procedure, device, or cervical spine.

Subjects will be followed up postoperatively at 6-weeks, 3-months, 6-months, and 12-months as per standard of care, at the private practice or clinic. During these visits, subjects will complete the questionnaires, cervical spine (motor/sensory) examination completed by the investigator, and cervical spine x-rays done per standard of care. Adverse events related to the device and/or procedure and/or cervical spine will be assessed at each visit.

Radiographic assessments will be performed at all postoperative visits; fusion status will be measured using dynamic (flexion and extension) X-rays and CT scan at 12 months. Fusion status at 12-months will be evaluated by an independent spine surgeon. Radiographs, including a cervical spine CT at 12-months, will also be utilized to assess for device-related complications, including implant failure. Any clinically significant complications related to the device will be recorded as an adverse event. Specifically, subsidence, migration, and loosening of the device that result in non-union or pseudoarthrosis and/or clinically significant neurological symptomology will be considered a device failure and reported as an adverse event. Also, any incidental findings on the CT scan will be discussed with patient and a referral to primary care physician will be made for further evaluation if necessary.

Data collected from subjects treated with the Spira™-C Interbody Device will be compared to historical data based on literature review of PEEK cage fusion rates and patient reported outcomes.

This study design reflects the current standard of care for cervical degenerative disc disease and spinal stenosis with symptoms of radiculopathy or myelopathy. Anterior cervical discectomy and fusion using an interbody device with plate and screw fixation is the treatment of choice after conservative therapies (non-surgical, i.e., physical therapy, epidural steroid injections, pain medications) have been exhausted.

Study Population – Inclusion/Exclusion Criteria

Patients scheduled to undergo a primary single-level ACDF surgery between C3-C7 will be approached about potential study participation. If the patient wishes to proceed with study participation, the study coordinator will perform the informed consent process. After the consent process has been completed and study details have been discussed, the subject will be further screened for eligibility and given the subject questionnaires to complete.

Inclusion Criteria

1. ≥ 18 years of age and skeletally mature
2. Able to provide consent
3. Undergoing a primary, single-level ACDF between C3-C7
4. Diagnosis of symptomatic degenerative disc disease
5. Neck pain and/or radicular symptoms with a baseline Visual Analog Scale score of ≥ 4cm (0-10cm scale)
6. Baseline Neck Disability Index score of ≥ 20

7. Attempted at least 6-weeks of conservative non-operative treatment

Exclusion Criteria

1. Any prior history of cervical fusion
2. Requires cervical fusion of more than one level
3. Acute cervical spine trauma requiring immediate intervention
4. BMI > 40
5. Active systemic bacterial or fungal infection or infection at the operative site
6. History of vertebral fracture or osteoporotic fracture
7. Current treatment with chemotherapy, radiation, immunosuppression or chronic steroid therapy
8. History of osteoporosis, osteopenia, or osteomalacia that would contraindicate spinal surgery
9. Psychological or physical condition in the opinion of the investigator that would interfere with completing study participation including completion of patient reported outcomes
10. History of neurological condition in the opinion of the investigator that may affect cervical spine function and pain assessments
11. Subjects with a history of cancer must be disease free for at least 3 years; with the exception of squamous cell skin carcinoma
12. Pregnant, or plans on becoming pregnant
13. History of allergy to titanium

Intervention

The intervention will consist of 40 patients undergoing an anterior cervical discectomy and fusion surgery where the Spira™-C Open Matrix Cervical Interbody cage with autograft and allograft will be utilized for interbody fusion at a single-level between C3-C7.

Statistical Analysis

The primary objective of this pilot study is to evaluate fusion status using the Spira™-C titanium interbody device at the 12-months postoperative time point. Results obtained in this study will be compared to historical data based on literature review. Based on previous literature review, a sample size of 40 patients was determined to be adequate for this study. The Wilson Score method was used to calculate two-sided confidence intervals for a single proportion (fusion rate) from .70 to 1.00. A sample size of 40 produces a two-sided 95% confidence interval with a width equal to 0.274 when the sample proportion is 0.70 and 0.088 when the sample proportion is 1.00. The intervals may be wider based on dropout rate at the 12-month endpoint. Due to the pilot nature of this study, the dropout rate will help to provide an estimate for similar future studies.

Data and Safety Monitoring

The PI and study team (including sub-investigators, clinical research manager) will be responsible for data and safety monitoring. All adverse events will be reviewed to determine relatedness to the product and reported to sponsor as necessary (if related to product and unanticipated according to risk profile). The data will be reviewed for maintenance of confidentiality and integrity as well as the data collection process. The data and safety review will take place every six months from the date of the first patient enrolled into the study or after ten patients have been enrolled whichever comes first.

Adverse Events

Relevant adverse events (those related to the study device, the surgical procedure, or cervical spine) or complications will be recorded in this study; including revision surgery at the index level, pseudoarthrosis, subsidence, migration, and failure or loosening of the device. Subsidence, migration, or loosening of the device that result in non-union or pseudoarthrosis and/or clinically significant neurological symptomology will be considered a device failure and reported as an adverse event. Any unanticipated serious adverse events related to the device will be reported to the IRB as well as the manufacturer. Per Medical Device Reporting (MDR) regulation (21 CFR 803), manufacturers and facilities are required to report to the FDA when it is known that any of their devices have caused or contributed to a death or serious injury.

Protocol Deviations

The investigators are responsible for documenting all protocol deviations, including an explanation for why the deviation occurred. All protocol deviations will be recorded and submitted to the IRB per policy.

OUTCOMES

Primary Endpoint

- Successful cervical spinal fusion as measured by dynamic (flexion and extension) X-rays and CT scan at 12 months as evidence by the following three criteria: bony bridging, no development of pseudoarthrosis, and no presence of radiolucency

Secondary Endpoints

- Improvement in patient-reported outcomes as measured by VAS (≥ 2 -point improvement), NDI (≥ 15 -point improvement), SF-36 (≥ 15 -point improvement and EAT-10 (score of < 3) from baseline to 12-months.
- No occurrence of adverse events or complications related to the device by month 12; including revision surgery at the index level, subsidence, migration, and failure or loosening of the interbody device. Subsidence, migration, and failure that results

in non-union or pseudoarthrosis and/or clinically significant neurological symptomology will be considered a device failure and reported as an adverse event.

- No new or worsening neurological (motor and sensory of the cervical spine) deficit as compared to baseline through 12-months.

SUBJECT SCREENING AND ENROLLMENT

Patients scheduled to undergo a primary single-level ACDF surgery between C3-C7 will be approached about potential study participation. If the patient wishes to proceed with study participation, the study coordinator will perform the informed consent process. After the consent process has been completed and study details have been discussed, the subject will be further screened for eligibility and given the subject questionnaires to complete.

Screen Failures

If the subject does not meet all inclusion criteria or meets one of the exclusion criteria after signing consent, then the subject will be considered a screen failure and therefore, not enrolled into the study. The subject will also be considered a screen failure and not enrolled in the study if there is a change in surgical treatment based on the surgeon's observations and best practice intraoperatively.

Withdrawals

A subject who withdraws consent prior to study completion will be removed from the study and no longer followed. The surgery, instrumentation, and bone grafts are FDA approved and cleared and considered standard of care. The subjects may follow-up as needed and per standard of care at their own discretion if they decide to no longer participate in the study. The reasons for voluntary withdrawal or discontinuation of study subjects will be documented. If during the course of the clinical study, a study subject is non-responsive to attempts to schedule follow-up visits, communication methods such as phone calls, emails, mail, or other means as appropriate in an attempt schedule an appointment or determine if the subject has moved, died, or otherwise become lost to follow-up.

Study Synopsis

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| <i>Sponsor</i> | Camber Spine Technologies 418 E. Lancaster Ave. Wayne, PA 19087 |
| <i>Protocol Version</i> | Version 1.2 Date: 11.01.18 |
| <i>Study Title</i> | A PROSPECTIVE CLINICAL PILOT STUDY OF FUSION RATES USING SPIRA™-C TITANIUM 3D PRINTED INTERBODY DEVICE FOR ANTERIOR CERVICAL DISCECTOMY AND FUSION (ACDF) |
| <i>Site/ PI</i> | Beaumont Health – Royal Oak (William Beaumont Hospital) Principal Investigator: Jad Khalil, MD |
| <i>Study Design</i> | Post-market, single-arm, prospective clinical pilot outcomes study |
| <i>Study Duration</i> | Approximately 3 years (enrollment of first subject to the last follow-up visit) |
| <i>Enrollment Number</i> | Total: 40 Treatment: 40 Spira™-C Open Matrix Titanium interbody cage (on-label use) |
| <i>Treatment Arm</i> | 40 patients undergoing an anterior cervical discectomy and fusion surgery where the Spira™-C Open Matrix Cervical Interbody cage with autograft and allograft will be utilized on-label for interbody fusion at a single-level between C3-C7. |
| | Data collected from subjects treated with the Spira™-C Interbody Device will be compared to historical data based on literature review of fusion rates and patient reported outcomes of traditional PEEK interbody cages. |
| <i>Study Objectives</i> | <p><i>Primary Objective:</i></p> <ul style="list-style-type: none"> • To evaluate fusion status using the Spira™-C titanium interbody device for treatment of degenerative disc disease of the cervical spine at a single-level between C3-C7 at 12-months. <p><i>Secondary Objectives:</i></p> <ul style="list-style-type: none"> • To evaluate VAS, ODI, SF-36 and EAT-10 scores postoperatively compared to baseline/preoperative • To evaluate the occurrence of device-related or procedure related adverse events or complications including subsidence and pseudoarthrosis. |

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| Study Endpoints | <p><i>Primary Endpoint:</i></p> <ul style="list-style-type: none"> • Successful cervical spinal fusion as measured by dynamic (flexion and extension) X-rays and CT scan at 12 months and as evidenced by the following three criteria: bony bridging, no development of pseudoarthrosis, and no presence of radiolucency . <p><i>Secondary Endpoints:</i></p> <ul style="list-style-type: none"> • Improvement in patient-reported outcomes as measured by VAS (≥ 2-point improvement), NDI (≥ 15-point improvement), SF-36 (≥ 15-point improvement and EAT-10 (score of < 3) from baseline to 12-months. • No occurrence of adverse events related to the device by month 12; including revision surgery at the index level, subsidence, migration, and failure or loosening of the interbody device. Subsidence, migration, and loosening of the device that result in non-union or pseudoarthrosis and/or clinically significant neurological symptomology will be considered a device failure and reported as an adverse event. • No new or worsening neurological (motor and sensory of the cervical spine) deficit as compared to baseline through 12-months. |
| Inclusion Criteria | <p>A subject may be included if the following criteria are met:</p> <ol style="list-style-type: none"> 1. ≥ 18 years of age and skeletally mature 2. Able to provide consent 3. Undergoing a primary, single-level ACDF between C3-C7 4. Diagnosis of symptomatic degenerative disc disease 5. Neck pain and/or radicular symptoms with a baseline Visual Analog Scale score of ≥ 4 (0-10cm scale) for neck or arm pain 6. Baseline Neck Disability score ≥ 20 7. Attempted at least 6-weeks of conservative non-operative treatment |
| Exclusion Criteria | <p>A subject will be excluded if any of the following criteria are met:</p> <ol style="list-style-type: none"> 1. Any prior cervical fusion surgery 2. Requires cervical fusion of greater than one level 3. Acute cervical spine trauma requiring immediate intervention 4. BMI > 40 5. Active systemic bacterial or fungal infection or infection at operative site 6. History of an osteoporotic fracture and/or vertebral body fracture 7. Current treatment with chemotherapy, radiation, immunosuppression or chronic steroid therapy |

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| | <ol style="list-style-type: none"> 8. History of osteoporosis, osteopenia, or osteomalacia that would contraindicate spinal surgery 9. Psychological or physical condition in the opinion of the investigator that would interfere with study participation, including completion of patient reported outcomes 10. History of neurological condition in the opinion of the investigator that may affect cervical spine function and pain assessments 11. Subjects with a history of cancer must be disease free for at least 3 years; with the exception of squamous cell skin carcinoma 12. Pregnant, or plans on becoming pregnant 13. History of allergy to titanium |
| <p><i>Study Schedule of Events</i></p> | <p>All subjects who sign an IRB approved consent form are considered in active screening to determine eligibility. Once a subject is consented, the following visits will take place:</p> <p>Baseline Visit:</p> <ul style="list-style-type: none"> • Medical history • Cervical Spine Exam • Demographics • VAS, NDI, SF-36, EAT 10 questionnaires • Cervical spine x-rays AP/lateral, flexion/extension or as done per standard of care <p>Surgical Visit (\leq 60 days of baseline visit):</p> <ul style="list-style-type: none"> • Surgery performed • Amount of Bone Graft, both local bone autograft/allograft used • Cervical plate and screw fixation system used • Adverse Events/Complications <p>6-week Visit (\pm 2 weeks):</p> <ul style="list-style-type: none"> • VAS, NDI, SF-36, EAT 10 • Cervical Spine Exam • Cervical AP/Lateral x-rays • Adverse Events <p>3-month Visit (\pm 3 weeks):</p> <ul style="list-style-type: none"> • VAS, NDI, SF-36, EAT 10, patient satisfaction questionnaires • Cervical Spine Exam • Cervical AP/Lateral and flexion/extension x-rays • Adverse Events <p>6-month Visit (\pm 1 month):</p> <ul style="list-style-type: none"> • VAS, NDI, SF-36, EAT 10 • Cervical Spine Exam • Cervical AP/Lateral and flexion/extension x-rays • Adverse Events |

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| | <p>12-month Visit (\pm 2 months):</p> <ul style="list-style-type: none">• VAS, NDI, SF-36, EAT 10• Cervical Spine Exam• Cervical AP/Lateral and flexion/extension x-rays• CT scan of the cervical spine without contrast• Adverse Events |
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