A Prospective, Single Arm Study of Patients Undergoing Posterolateral Lumbar Fusion (without Interbody) Supplemented with ViviGen Cellular Bone Matrix

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1 INVESTIGATIONAL PLAN

1.1 Purpose

The purpose of this prospective study is to assess clinical and radiographic outcomes in patients who are to undergo Posterolateral Lumbar Fusion (PLF) procedures without interbody using ViviGen Cellular Bone Matrix, with pedicle screw instrumentation cleared for spinal fusion.

2 INTRODUCTION

2.1 Background

In 2012, over 727,000 spinal fusion and non-fusion procedures were performed in the US.[1] This included treatment for various conditions such as DDD, spinal stenosis, spondylosis, spinal deformities, tumors, and traumatic spinal injuries. Over time, intervertebral discs wear down and lose water and then disc height. The degeneration of these discs can impact the spine in several ways, including spinal canal stenosis, spondylolisthesis, and osteophyte formation. These changes can impinge on the nerve roots, causing chronic pain. Consequently, as the population of elderly in the US expands, demand for treatments that address back pain will rise accordingly. The correlation between age and the incidence of DDD has been well-documented; for example, one study concluded that there was a direct relationship between age and the grade of degeneration caused by DDD.[2] Increasing rates of obesity in the US will also contribute to growth in spinal fusion and non-fusion volumes because obesity represents a risk factor for DDD.[3]

The premise behind fusion surgery for lower back pain (LBP) is that a degenerated and mobile lumbar segment acts as a pain generator. Consequently, if motion is prohibited through a fusion, it is expected that the patient will experience improvement in both pain and disability which will increase their ability to function. Currently, there is no way to be certain which structure or structures actually are causing the pain, but the main interest has been focused on the facet joints, the disc, or a combination of both.[4]

Lumbar spine fusion rates can vary according to the surgical technique. Although many studies on spinal fusion have been conducted and reported, the heterogeneity of the study designs and data handling make it difficult to identify which approach yields the highest fusion rate. Traditional posterolateral intertransverse fusion (PLF) still remains a good procedure with acceptable fusion rates for most degenerative conditions. For solid fusion, PLF can be combined with interbody fusion to circumferentially stabilize the relevant segment, even though it is unclear whether this improves fusion rates.[5]

A bone graft or bone graft substitute is required to produce the fusion and can be implanted on its own, in the posterolateral gutters, or contained with an interbody device using either a posterior or anterior approach. Spinal laminectomy is most often the largest generator of bone graft product due to the nature of the procedure. The current gold standard is autograft bone, in which tissue is harvested locally or from the iliac crest and is then placed at the

site. However, local bone graft may be relatively limited and harvesting at the iliac crest can easily lead to significant morbidity [6-9]. Complications such as inflammation, infection, and chronic pain may outlast the pain of the original surgical procedure.[10]

Autograft is the gold standard because it possesses all of the characteristics necessary for new bone growth—namely, osteoconductivity, osteogenicity, and osteoinductivity. Allograft tissues are alternatives to autografts and are taken from donors or cadavers, circumventing some of the shortcomings of autografts by eliminating donor-site morbidity and issues of limited supply.[10] Osteoconductivity refers to the situation in which the graft supports the attachment of new osteoblasts and osteoprogenitor cells, providing an interconnected structure through which new cells can migrate and new vessels can form. Osteogenicity refers to the situation when the osteoblasts that are at the site of new bone formation are able to produce minerals to calcify the collagen matrix that forms the substrate for new bone. Osteoinductivity refers to the ability of a graft to induce nondifferentiated stem cells or osteoprogenitor cells to differentiate into osteoblasts.[10] Using the 2 basic criteria of a successful graft, osteoconduction and osteoinduction, investigators have developed several alternatives, some of which are available for clinical use and others of which are still in the developmental stage. Many of these alternatives use a variety of materials, including natural and synthetic polymers, ceramics, and composites, whereas others have incorporated factor- and cell-based strategies that are used either alone or in combination with other materials.[10]

2.2 Device Description

All subjects enrolled in this study will be implanted with ViviGen Cellular bone matrix in the posterolateral gutters along with a pedicle screw system cleared for lumbar fusion.

2.2.1 ViviGen

ViviGen is a Human Cells, Tissues, and Cellular and Tissue-based Product (HCT/P) as defined by the U.S. FDA in 21 CFR 1271.3(d). ViviGen meets the criteria set out in 21 CFR 1271.10 for regulation solely under section 361 of the Public Health Service Act. In Canada, ViviGen and the allograft spacers are Human Cells, Tissue and Organs (CTO) products per SOR/2007-118. ViviGen is processed by LifeNet Health and is available through DePuy Synthes Spine as a formulation of cryopreserved, viable, cortical cancellous bone matrix, and demineralized bone.

ViviGen is osteogenic, osteoinductive, and osteoconductive. It contains viable lineage committed bone cells that are able to proliferate post thawing. Demineralization of the cortical bone component exposes the natural growth factors within the bone matrix. ViviGen contains cortico-cancellous chips which provide the natural scaffold for cell attachment, migration, and proliferation.[11]
ViviGen is processed from donated human tissue and is a generous gift by an individual or his/her family.

Every donor for ViviGen must meet LifeNet Health's strict medical and behavioral risk assessment in addition to microbial and serological testing, all of which comply or are higher than those required by the AATB and the FDA. LifeNet Health utilizes aseptic techniques in ISO Class 4 (certified) clean rooms to eliminate the need to use aggressive disinfection and sterilization methods which can have adverse effects on cell viability. Each lot of final product is tested for sterility.

Indications for Use: ViviGen Cellular Bone Matrix is intended for repair or reconstruction of musculoskeletal defects. It is contraindicated in any patient who has a known or suspected allergy to any of the antibiotics and/or reagents listed under the Warnings and Precautions section of the Instructions For Use (IFU), in immune compromised patients, and as a stand-alone in load- bearing applications.

Packaging and Labeling: ViviGen is supplied in packaging designed to facilitate rapid thawing to maximize cell viability. In addition, this allograft arrives in a cryo-preservative solution containing Dimethyl Sulfoxide (DMSO) and Human Serum Albumin (HSA) formulated specifically to protect bone cell viability.

Product Storage and Accountability: After removal from the shipment container, ViviGen must be stored immediately in its original packaging at -70°C or colder until ready for use. Do not store in liquid phase of the liquid nitrogen (LN2). It is the responsibility of the end-user to document and maintain ViviGen storage at these conditions.

There is no formal accountability of ViviGen for this type of study. The Investigator, or designee, at each site is responsible for recording on the electronic Case Report Form (eCRF) (1) the product code(s), (2) lot number(s), and (3) expiration date(s) of ViviGen implanted in each study subject.

3 TRIAL DESIGN

3.1 Design

This is a prospective, single-arm post market study of patients to assess fusion in one or multiple continuous levels of the lumbosacral spine (L1-S1) using ViviGen Cellular Bone Matrix. All subjects will be followed up to 24 months for final assessment.

3.2 Inclusion Criteria

Subjects will be considered for inclusion in this trial if they satisfy the following criteria.

1. Subject is scheduled to undergo a single or multilevel posterolateral spinal fusion surgery using ViviGen Cellular Bone matrix.
2. Subject must be over the age of 18 years old.
3. Subject has been unresponsive to conservative care for a minimum of 6 months.
4. The subject must in the investigator's opinion, be psychosocially, mentally, and physically able to fully comply with this protocol including the required follow-up visits, the filling out of required forms, and have the ability to understand and give written informed consent.

3.3 Exclusion Criteria

Subjects will be excluded from this trial if they satisfy any of the following criteria.

1. Subjects requiring additional bone grafting materials other than local autograft and ViviGen Cellular Bone Matrix will be excluded from this outcomes study.
2. Subject has inadequate tissue coverage over the operative site.
3. Subject has an open wound local to the operative area, or rapid joint disease, bone absorption, or osteoporosis.
4. Subject has a condition requiring medications that may interfere with bone or soft tissue healing (i.e., oral or parenteral glucocorticoids, immunosuppressives, methotrexate, etc.).
5. Subject has an active local or systemic infection.
6. Subject has a metal sensitivity/foreign body sensitivity.
7. Subject has a body mass index (BMI) greater than 45.
8. Subject has any medical condition or extenuating circumstance that, in the opinion of the investigator, would preclude participation in the study.
9. Subject is currently involved in another investigational drug or device study that could confound study data.
10. Subject has a history (present or past) of substance abuse (recreational drugs, prescription drugs or alcohol) that in the investigator's opinion may interfere with protocol assessments and/or with the subject's ability to complete the protocol required follow-up.
11. Subjects who are pregnant or plan to become pregnant in the next 24 months or who are lactating.
12. Subject is involved in or planning to engage in litigation or receiving Worker's Compensation related to neck or back pain.
13. Osteoporosis (per the investigator's diagnosis or per a T-score > 2.5 SD below the mean for a young, healthy adult) that may prevent adequate fixation of screws and thus preclude the use of a pedicle screw system.
14. Subjects who have a known or suspected allergy to any of the following antibiotics and/or reagents: Gentamicin Sulfate, Meropenem, Vancomycin, Dimethyl Sulfoxide (DMSO), and Human Serum Albumin (HSA);
15. Immune compromised subjects
16. Known sensitivity to device materials
17. Subject is a prisoner.

4 STUDY PROCEDURE

4.1 Screening Assessments

4.1.1 Informed Consent

Subjects will be provided with an informed consent form and given ample opportunity to review the consent and ask questions. The signed informed consent form will be obtained before any study specific procedures, that are not part of the investigator's standard of care, begin. A copy of the informed consent will be given to the subject. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

All subjects who have agreed to participate in this study, have signed the informed consent and who meet the inclusion/exclusion criteria will be considered enrolled and assigned a subject ID number. Once a subject ID number has been issued, it cannot be reassigned or used for another subject.

4.1.2 Medical History and Demographic Data

Within 60 days prior to the surgery date, the following information will be collected:

- Demographic data including year of birth, gender, weight, and height
- Medical history, including a complete history of spinal disorder(s) (non-operative or operative treatments performed)
- Physical examination
- X-Rays
- Current pain medications and other drug therapies.
- Neurological status

4.1.3 Clinical Assessments

Subject study data will be collected preoperatively, intra-operatively and postoperatively at 6 weeks as well as 3, 6, 12 and when available, 24 months. The following data will be recorded on the Case Report Forms (CRFs) and in addition, electronic data entry will be employed via an Internet connection when possible using an Electronic Data Capture (EDC) system, REDCap.

Oswestry Disability Index v2.1a (ODI): Pre-operatively the subject will complete the Oswestry Disability Index v2.1a for baseline low back pain and functional assessment. The questionnaire is a combined pain and function index which will be used to assess the subject's back pain and how that pain affects the subject's ability to manage in everyday life. The questionnaire is divided into ten sections designed to assess limitations of various activities of daily living. Each section contains six statements and each statement describes a greater degree of difficulty in that activity than the preceding statement. The subject marks the one statement in each section, which describes his/her limitations most accurately. Each section is scored on a 0-5 scale, 5 representing the greatest disability. The scores for all sections are added together, giving a possible score of 50. The total is doubled and expressed as a percentage. If a subject marks two statements, the highest scoring

statement is recorded as a true indication of his disability. If a section is not completed because it is inapplicable, the final score is adjusted to obtain a percentage.

Back and Radicular Leg Pain: Preoperatively all subjects will assess their back and/or radicular leg pain in one or both legs using a visual analog scale (VAS) from 0-10 with 10 being considered most painful.

4.2 Surgical Procedure

After receiving antibiotic prophylaxis, the patient is placed under general anesthesia and positioned prone. A midline posterior approach is performed, exposing the posterior lumbar elements including the facet joints. Polyaxial pedicle screws are placed bilaterally, using fluoroscopic guidance, depending on preference of the surgeon.

In cases of neurogenic claudication related to spinal canal stenosis, the central part of the spinal canal is decompressed by laminectomy. In cases of radicular leg pain related to foraminal stenosis, partial facetectomies will be performed as needed to decompress the associated nerve roots.

Titanium rods are then positioned interconnecting the screws on each side. The posterolateral cortical bony surfaces are then fully decorticated and supplemented with milled local autograft bone on one side and an equal volume of Depuy Synthes ViviGen on the other side.

Data will be collected during and immediately after the surgery according to the parameters described by the ViviGen Lumbar study CRFs. This includes: diagnosis, duration of surgery, blood loss, OR time, length of hospital stay, instrumentation used, type of procedure, and surgical level(s). In addition, all intraoperative complications (e.g. excessive blood loss, hematoma, vascular injury, etc.) will be reported and recorded as a complication in the study CRFs.

Intra-operative (after hardware installation is completed) and immediate post-operative x-rays will be obtained. Postoperative care will follow the standard of care for subjects who undergo fusion procedures.

Postoperative care is extremely important. The subjects will be warned that noncompliance with postoperative instructions could lead to breakage of the pedicle screw system requiring revision surgery.

4.3 Schedule of Events

	Screening /Enrollment (-60 days of procedure)	Procedure	6 weeks (± 7 days)	3 months (± 14 days)	6 months (± 14 days)	12 months (± 30 days)	24 months (± 60 days)
Informed consent	X						
Medical History	X						
Demographics	X						
Concomitant medications review	X	X	X	X	X	X	X**
Oswestry Disability Index v2.1a	X		X	X	X	X	X**
Visual Analog Scale (VAS) back and leg	X		X	X	X	X	X**
Radiographic X-rays (AP/ Lateral with Flexion and Extension)	X		X	X	X	X	X**
CT Scan						X*	
Urine Pregnancy Test						X*	
AE/ SAE review	X	X	X	X	X	X	X**
*CT scan & Urine Pregnancy Test not standard of care. Cost will be covered by study sponsor. ** Optional time point (when available)_							

4.4 Follow-Up Assessments

Subjects will be asked to return postoperatively at 6 weeks (± 1 week), 3 months (± 2 weeks), 6 months (± 2 weeks), and 12 months (± 1 month) for a clinical and radiographic exam. An additional visit at 24 months (± 2 months) may be scheduled at the request of either the physician or the subject. The following data will be recorded on the Case Report Forms (CRFs) and in addition, electronic data entry will be employed via an Internet connection when using the Electronic Data Capture (EDC) program, REDCap.

Clinical assessment: The investigator will carry out a clinical examination at the 6 week as well as the 3, 6, 12 and when available, 24 month visit to assess:

- subject compliance with postoperative care instructions,
- ability to return to work and normal activity, and
- any procedure related or device related adverse events since discharge from the hospital
- review of medication usage
- progress towards fusion consolidation
- Neurological status

Subject self-assessment: Patient completed forms

- Each subject will be asked to complete a follow-up Oswestry Disability Index v2.1a (ODI) form and a Back and Leg Pain VAS form at each follow-up visit.

Radiographic assessment: Each subject will undergo AP and lateral x-rays at the 6 weeks as well as 3, 6, 12 and when available, 24 month visits and flexion/extension x-rays at the 3, 6, 12 and when available, 24 month visits. Additionally each subject will undergo a CT scan and urine pregnancy test at the 12 month visit to assess the extent of fusion.

4.5 Fusion Determination

Fusion will be assessed by an independent radiologist using the subjects' 12 month visit CT images. The extent of fusion will be determined using the Lenke classification. The scale is as follows:

- Grade A - Definitely solid with bilateral trabeculated stout fusion masses present
- Grade B - Possibly solid with a unilateral large fusion mass and a contralateral small fusion mass
- Grade C - Probably not solid with a small fusion mass bilaterally
- Grade D - Definitely not solid with bone graft resorption or obvious pseudoarthrosis bilaterally

Radiographic success: radiographic success is defined as grade A.

Partial radiographic success: partial radiographic success is defined as grade B. Images graded as "B" will be subcategorized by the location of the unilateral large fusion mass (autograft side, B-a vs. ViviGen side, B-v).

Radiographic Failure: radiographic failure is defined as grades C or D.

4.6 Success Criteria

4.6.1 Primary Objective

A subject outcome will be considered a success if fusion is graded as a Grade A. A subject outcome will be considered a partial success if fusion is graded as a Grade B. Images graded as "B" will be subcategorized by the location of the unilateral large fusion mass (autograft side, B-a vs. ViviGen side, B-v).

4.6.2 Secondary Objectives

The secondary measures of effectiveness will be determined by maintenance or improvement of pain and disability scores from completed questionnaires (VAS and ODI v2.1a)

4.7 Subject Withdrawal

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. If the subject is withdrawn for any reason at any time a final evaluation form will be completed and the Sponsor will be notified.

Other Conditions for Withdrawal:

Any subject who develops a severe concurrent medical illness during the trial should be withdrawn. This type of illness is defined as any illness that would hinder the subject's ability to return for scheduled follow-up appointments. Such a withdrawal will not be counted for the purposes of determining success or failure.

5 STATISTICAL ANALYSIS PLAN

Statistical analyses will be performed as deemed appropriate to evaluate different healing outcomes across the various patient populations.

Primary outcome analysis to assess the final fusion status of all enrolled patients will be performed prospectively by the former principal investigator, Dr. H. Francis Farhadi. Following his departure from The Ohio State University, the investigator(s) will review the 12 month CT scans to evaluate each subject for radiographic success, partial success, or failure.

In case early findings reveal a statistical difference in fusion grades comparing the sides of autograft and ViviGen Cellular Bone matrix, enrollment will cease as investigators are unlikely to maintain clinical equipoise. Similarly, if the analysis suggests it is unlikely the study will achieve statistical significance, the investigators may choose to close the trial early for futility. Currently enrolled subjects will be followed throughout the remainder of the study, up to 12 months post-surgery.

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