Radiographic and Clinical Outcomes Following Unilateral or Bilateral Posterior Fixation in Minimally Invasive Transforaminal Lumbar Interbody Fusions

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TABLE OF CONTENTS

Abbreviations
TLIF: Transforaminal Lumbar Interbody Fusion
MI-TLIF: Minimally Invasive Transforaminal Lumbar Interbody Fusion
PLIF: Posterolateral Lumbar Interbody Fusion
ALIF: Anterior Lumbar Interbody Fusion
X/DLIF: Lateral Lumbar Interbody Fusion
ODI V2: Oswestry Disability Index
VAS: Visual Analog Scale
CT: Computed tomography

1. INTRODUCTION

1.1 Background

Since its original description in 1982, transforaminal lumbar interbody fusion (TLIF) has grown in popularity as a means for achieving arthrodesis in the lumbar spine. As with PLIF, ALIF or X/DLIF procedures, TLIF surgery achieves high fusion rates with minimal complications. Minimally invasive TLIF (MI-TLIF) in particular has emerged as a valid alternative to standard or mini-open TLIF with equivalent clinical and radiographic outcomes (Foley et al., 2003; Karikari and Isaacs, 2010, Mummaneni and Rodts, 2005). Surgeons usually combine open or MI-TLIF with pedicle screw instrumentation in an attempt to achieve circumferential (i.e., anterior and posterior) fusion. Although bilateral pedicle screw placement is often performed in MI-TLIF procedures, only a single small study to date has been reported evaluating comparative radiologic and clinical outcomes with unilateral (ipsilateral) pedicle screws (Xue and Cai, 2012).

1.2 Rationale

Several retrospective reports have confirmed that unilateral pedicle screw instrumentation is equally as effective as bilateral pedicle screw instrumentation when used solely without any other devices (Fernandez-Fairen et al., 2007; Kabins et al., 1992; Suk et al., 2000). Based on these results, a number of subsequent reports have evaluated unilateral pedicle screw instrumentation following MI-TLIF surgery and also reported good outcomes with no significant untoward effects (Beringer and Mobasser, 2006; Deutsch and Musacchio, 2006; Tuttle et al, 2006).

Despite these reassuring findings, biomechanical studies using cadaveric specimens have shown that placing unilateral posterior instrumentation allows for significantly increased segmental range of motion, less stiffness, and produces off-axis movement (Harris et al., 2204; Schleicher et al., 2008; Slucky et al., 2006). It remains unknown at this time whether this observed increased flexibility in cadaveric specimens has any clinical correlations in terms of either radiologic fusion rates or pain/functional outcome measures. A unilateral construct has the benefit of avoiding soft-tissue disruption on the contralateral side, decreasing

operative time, and is associated with lower implant costs. This study will assess radiologic interbody fusion rates and clinical outcomes between the following arms following MI-TLIF surgery: stand-alone unilateral pedicle screw instrumentation, unilateral pedicle screw instrumentation with contralateral facet screw fixation, bilateral pedicle screw instrumentation.

2. OBJECTIVES

Primary Outcome: To compare bony fusion rates at one year between the three study arms, using the Brantigan, Steffee and Fraser scale. Post-operative CT scans will be evaluated at 12 months for evidence of new solid osseous trabeculations bridging across the interspaces.

Secondary Outcomes: To compare clinical outcomes between the three study arms utilizing the VAS, ODI V2, and SF-36V2™ serially. Additionally, immediate and delayed medical and surgical (including neurological) complications between the three study arms will be compared.

Exploratory outcomes: Bony fusion rates at 12 and 24 months between the three study arms, using an X-ray based classification scale (see appendix 2).

3. INVESTIGATIONAL PLAN

Study Design

All patients will undergo the following preoperative procedures: lumbar CT, lumbar MRI, lumbar x-rays, and medical evaluation including clinical history and physical examination. Patients will be randomized to MI-TLIF followed by either stand-alone unilateral pedicle screw instrumentation, unilateral pedicle screw instrumentation with contralateral facet screw fixation, or bilateral pedicle screw instrumentation using Redcap (Research Electronic Data Capture), a web-based randomization process. Post-operative follow-up will occur at 6 weeks and 3, 6, 12, and 24 months. CT scans will occur at the 12 month visit.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1 Anticipated number of available subjects

Based on our current case numbers, we estimate approximately 100-120 MI-TLIF surgeries over approximately 24 months, corresponding to approximately 35-40 cases for each arm of the study.

The target population includes patients with degenerative lumbar spine disease (e.g. spondylolisthesis, facet arthropathy with foraminal stenosis, recurrent disc herniation, far lateral disc herniation) who have failed non-operative management and require lumbar fusion surgery.

4.2 Inclusion criteria

1. Age 18-80 years.
2. Symptomatic single-level lumbar disease including lumbosacral junction.
3. Unilateral leg-dominant pain non-responsive to conservative management with concordant imaging findings. These include degenerative spondylolisthesis (grade 1 or 2), facet arthropathy +/- lateral disc herniation, recurrent disc herniation, or large central disc herniation OR back pain of confirmed discogenic origin (single level disease only).
5. Failed conservative management for a minimum of 3 months.
6. Negative serum pregnancy test for women of childbearing potential.

4.3 Exclusion criteria

1. Severe bilateral leg symptoms.
2. Prior instrumented arthrodesis at any lumbar level.
3. History of osteoporosis.
4. Co-morbidity requiring medication that may interfere with bone or soft tissue healing (i.e., oral or parenteral glucocorticoids, immunosuppressive agents, methotrexate).
5. Severe co-morbidities (e.g., heart, respiratory, or renal disease).
6. Recent (<3 yrs) or co-incident spinal tumor or infection.
7. Greater than single level symptomatic involvement.
8. Associated thoracolumbar kyphotic or scoliotic deformity (> 10°).
9. Morbid obesity (BMI > 40).
10. History of metal sensitivity/foreign body sensitivity.
11. Concurrent involvement in another investigational drug or device study that could confound study data.
12. History of substance abuse (recreational drugs, prescription drugs or alcohol) that could interfere with protocol assessments and/or with the subject's ability to complete the protocol required follow-up.
13. Subjects who are pregnant or plan to become pregnant in the next 24 months.
14. Prisoner.

4.4 Subject completion and Withdrawal

Every attempt will be made to maintain patient participation in the study. However, patients have the option of withdrawing consent at any time. Patients who do not receive assigned treatment (those who refuse treatment after randomization or who decide to have other treatment after randomization) or those who have subsequent treatment, will still be followed and analyzed as randomized for the primary analysis. Should a patient be lost to follow-up (after 3 attempts), all data will be included during the period of participation.

5. STUDY DESIGN

All patients will undergo unilateral approach MI-TLIF. All patients will be randomized into one of the following treatment groups using Redcap, a web-based randomization process: Group 1 will also have unilateral percutaneous pedicle screws placed. Group 2 will have unilateral (ipsilateral) percutaneous pedicle screws placed along with a contralateral facet screw through a minimally-invasive approach. Finally, Group 3 will have bilateral percutaneous pedicle screws placed. This web-based randomization process will be managed by the study statisticians within the OSU Center for Biostatistics. Randomization will be stratified by patient age (<60 vs. 60+) and will be generated with varying block sizes.

Patients will be randomized to one of the following three groups and will be followed and asked to return at 6 weeks, 3 months, 6 months, 12 months and 24 months for assessment (See study calendar in 6.4).

Group	Interbody fusion	Posterolateral fusion
1	**MI-TLIF**	**Unilateral pedicle screws**
2	**MI-TLIF**	**Ipsilateral pedicle screws, contralateral facet screw**
3	**MI-TLIF**	**Bilateral pedicle screws**

6. STUDY ASSESSMENTS AND PROCEDURES

All patients randomized in the trial will be followed according to the schedule. Surgical outcome will be evaluated by pre-operative and post-operative VAS back and leg scales (Attachment 1), ODI V2 (Attachment 2) and SF-36V2^{TM} (Attachment 3). If a patient is unable to follow-up in person at 6 months, he/she will be asked to fill out the forms via mail or over the telephone. Fusion rates will be evaluated based on CT scans at 12 months follow-up after surgery using a CT interbody fusion rating scale. Each CT scan will be interpreted by the same independent radiologist. Interbody fusion rates will be graded by the method of Brantigan, Steffee and Fraser (BSF scale) (Santos et al., 2003; Appendix 1). Solid osseous trabeculations bridging across the interspaces will be considered as a fusion. All pseudoarthroses, heterotopic ossifications or migration/malposition of implants will also be evaluated separately. Pre-operative and post-operative clinical outcomes will be evaluated at 3 months, 6 months, 12 months and 24 months using VAS (back and leg), ODI V2 and SF-36V2^{TM} index measures.

6.1. Demographic and baseline assessments

A signed, written, informed consent form will be obtained before surgery. The following will be obtained at the first visit.

- Demographic data: date of birth, race, gender, height, body weight
- Medical and surgical history
- Physical exam, vital signs, VAS back and leg, ODI V2, SF-36V2™
- Serum pregnancy test (only required for Women of childbearing potential)
- Lumbar CT
- Lumbar MRI
- Lumbar x-rays

6.2. Intra/perioperative Assessments

The following assessments will be performed during the patient's hospitalization:

- Demographic data: height, body weight, Index Level(s)
- Operative Time
- Blood Loss
- Length of stay
- Infection rate
- Use of opiates

6.3. Assessments during follow-up

The following assessments are to be performed as close as possible to the schedule:

- Follow-up visits at 6 weeks (+/- 7 days), 3 months (+/- 30 days), 6 months(+/- 30 days) , 12 months (+/- 30 days) and 24 months(+/- 60 days) following surgery
- Note: if 6 month follow-up visit is not completed in person, study teams will follow up via phone and mail
- History and physical exam, including vital signs
- VAS back and leg, ODI V 2, and SF-36V2™ (these questionnaires will be collected by mail or completed over the phone should patients not return to clinic at the designated follow-up time points)
- X-rays of lumbar spine at 6weeks, 3months, 12 months, and 24 months
- Lumbar CT scan at 12 months
- Infection rate
- Return to work

6.4 Study Calendar

	Pre-Study	6 wk. F/U	3 mo. F/U	6 mo. F/U	12 mo F/U	24 mo F/U
Test and Observations						
H&P	X	X	X	X[a]	X[a]	X
Height	X	X	X	X[a]	X[a]	X
Weight	X	X	X	X[a]	X[a]	X
Vital Signs	X	X	X	X[a]	X[a]	X
Serum Pregnancy Test	X[b]					
Consent	X					
Procedures						
Lumbar MRI	X					
Lumbar CT	X				X	
Lumbar X-Rays	X	X	X		X	X
Surgical Outcome Measures						
VAS back and leg	X		X	X	X	X
ODI V 2	X		X	X	X	X
SF-36V2™	X		X	X	X	X

a. Optional

b. Only Women of childbearing potential will undergo a serum pregnancy test prior to enrollment in the study to confirm that they are not pregnant.

Findings from any additional imaging studies deemed necessary (as per standard of care) by the principal investigator will be recorded and reported with study results.

7. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

7.1 Data Management Clinical data management will be performed by the Integrated Healthcare Information System (IHIS) program. In all cases, subject names will not be collected or transmitted to the instrumentation company. Subject data necessary for analysis and reporting will be entered and transmitted into Redcap.

7.2 Outcome Measures

Primary Outcome:

- Bony fusion at 12 months is being measured using the Brantigan, Steffee and Fraser scale which is a three-point scale, used to measure interbody fusion success. Possible values range from 1-3 with higher scores indicating more fusion (a better outcome). The scores will be dichotomized in the following categories: BFS-1 or 2 and BFS-3 where fusion is defined as BFS-3.

Secondary Outcomes:

- Visual analog scales will be used to assess neck, back, arm and leg pain. Scores can range from 0 to 10 with higher scores indicating higher levels of pain.
- The Oswestry Disability Index (version 2) will be used to assess how back pain affects patients' ability to function in everyday life. Scores can range from 0% to 100% with higher scores indicating higher levels of disturbance in everyday life.
- The Short Form (36) Health Survey (version 2) will be used to assess patients' physical and mental health. Scores range from 0 to 100 with higher scores indicating better physical and mental health.

Safety Outcomes: Comparison of immediate and delayed medical and surgical (including neurological) complications between the three study arms will be compared.
Exploratory Outcomes: Comparison of bony fusion rates at 12 and 24 months between the three study arms, using an X-ray based classification scale (see appendix).

7.3 Sample size/Power Calculation

Assuming an average proportion of 0.7 and estimated variance of proportions of 0.027, a sample size of 90 patients (30/group) gives the study over 80% power to detect significant differences for the overall test comparing proportions across groups (α=0.05). It is anticipated that the attrition rate will be approximately 10% therefore 102 patients will be accrued to the study (34/group). Every effort will be made to reduce attrition; consent documents will emphasize the importance of complete data and encourage patients to return for follow-up visits.

7.4 Statistical Analyses

Primary Analysis:
To compare the overall effect of treatment, the proportion of patients with BFS-3 will be compared across groups using Cochran-Mantel-Haenszel statistic. Given a statistically significant result for this overall test, all possible pair-wise comparisons between the study arms will be evaluated. Details of multiple comparisons adjustments and modeling details will be provided in the Statistical Analysis Plan (SAP).
We will employ generalized linear models (specifically Poisson regression) to estimate the relative risk of bony fusion between each study arm. We prefer to estimate adjusted risks, rather than adjusted odds ratios and will employ a '*Poisson working model'* within the survey framework.

Primary Analysis will be performed according to the intention-to-treat principle. Using this approach, patients will be included in the analysis as they were randomly assigned to treatment, regardless of the procedure actually performed. Methods to address missing data will be considered and detailed in the SAP.

Secondary and Exploratory Analyses:
Descriptive statistics, overall and by study arm for each secondary outcome. Generalized linear models will be used to compare secondary outcomes between study arms. Details will be provided in the SAP.

7.5 Quality Assurance

Our team has substantial experience in all elements necessary to successfully conduct high-quality RCTs: representative samples, adequate random assignment, outcome assessment blinding, high follow-up rate, and attention to preventing potential errors.

8. STUDY CONDUCT CONSIDERATIONS

8.1. Regulatory and ethical considerations, including the informed consent process

This study will be conducted in accordance with all applicable regulatory requirements. The study will also be conducted in accordance with "good clinical practice (GCP), all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki. This process includes, but is not limited to, the following:

- IRB review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Subject informed consent
- Investigator reporting requirements

Written informed consent will be obtained for each subject before he or she can participate in the study.

8.2. Publication policy

Publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for the study.

9. Adverse Events

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal, or
- Is associated with a serious adverse event, or
- Leads to additional treatment or to further diagnostic tests, or
- Is considered by the investigator to be of clinical significance.

For this study, all AE's rather reported, observed, or elicited by direct or indirect questioning will be recorded from the time of study enrollment through study completion. Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study intervention, action taken, and outcome.

All unresolved AE's will be followed, whenever possible, until the events are resolved or stabilized, the subject is lost to follow up, and/or it has been determined that the study treatment or participation in the study is not the cause. At the last scheduled assessment, the investigator should instruct each subject to

report any subsequent event(s) that the subject or the subject's personal physician believes might reasonably be related to participation in this study.

Information on AE's should be recorded in the patient research record, and also in the appropriate AE page on the REDCap database.

10. Serious Adverse Event Reporting

A serious adverse event is an AE that is:

- Fatal, or
- Life-threatening, or
- Requires or prolongs hospital stay, or
- Results in persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or
- An important medical event. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Information on SAE;s should be recorded in the patients research record, and also in the appropriate SAE page on the REDCap database.

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APPENDIX 1

BSF scale

Classification of interbody fusion success: Brantigan, Steffee, Fraser (BSF)

BSF-1	Radiographical pseudoarthrosis is indicated by collapse of the construct, loss of disc height, vertebral slip, broken screws, displacement of the carbon cage, or significant resorption of the bone graft, or lucency visible around the periphery of the cage or graft.
BSF-2	Radiographical locked pseudoarthrosis is indicated by lucency visible in the middle of the cages with solid bone growing into the cage from each vertebral endplate.
BSF-3	Radiographical fusion: bone bridges at least half of the fusion area with at least density the originally achieved at surgery. Radiographical fusion through one cage (half of the fusion area) is considered to be mechanically solid fusion even if there is lucency on the opposite side.

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APPENDIX 2:

X-Ray Based Classification Scale

- Grade 1 - No graft incorporation
- Grade 2 - Incomplete graft incorporation
- Grade 3 - Graft Incorporation
- Grade 4 - Solid fusion with graft incorporation

Radiographic Success: Radiographic success (Grades 3 or 4) is defined by graft incorporation or solid fusion with graft incorporation