IRB Application for Population Health and Quality Research Study

Title of Study: rhBMP-2 versus Vivigen, a novel cellular allograft, in lumbar fusion procedures: a prospective randomized controlled study

Background and Statement of Context

Instrumented lumbar fusion procedures with bone graft are one of the most common procedures performed today. There are numerous bone graft options, including iliac crest bone graft, local autograft, allograft, extenders, and rhBMP [1]. Several studies have demonstrated the efficacy and complications associated with these bone graft options [2-6]. Iliac crest autograft, long considered the gold standard of bone graft, is associated with donor site morbidity, longer operative times, and limited availability [7]. Recombinant human bone morphonogenetic protein-2 (Infuse) has revolutionized lumbar fusion surgery. Initially approved for a single level ALIF, Infuse has been utilized in many off-label applications. Further studies of Infuse demonstrated multiple adverse effects, such as osteolysis, ectopic bone formation, retrograde ejaculation, and potentially carcinogenesis [8]. The premium cost and adverse effects of Infuse has led researchers to develop other options. A novel bone graft option is the cellular allograft, a cryopreserved mixture of viable bone cells, demineralized bone matrix, and cancellous bone chips. This product is purported to be osteogenic, osteoinductive, and osteoconductive. There is a paucity of literature evaluating these cellular allograft bone graft options in lumbar spine surgery. This study is aimed at comparing the overall efficacy (clinical and radiographic) of Vivigen, a novel cellular allograft product, and rhBMP-2 when utilized in lumbar fusion procedures.

Study Questions/Objectives and Hypothesis

The purpose of this study is to compare the overall efficacy (clinical outcome and radiographic fusion) of Vivigen (cellular allograft product) and rhBMP-2 in patients who undergo a single level lumbar instrumented fusion. Specifically, when compared to their control group counterparts treated to rhBMP-2, we hypothesize that the intervention group administered Vivigen would, following surgery, experience:

1. Comparable mean postoperative leg/back pain score, where the pain scores are obtained using the numeric rating scale of 0-no pain, to 10-worst pain possible
2. Comparable inpatient length of stay (LOS)
3. Comparable postoperative Oswestry Disability Index (ODI) score (0-no disability, to 100-maximum disability possible), two weeks, 6 weeks, 3 months, 6 months, and 1 year postoperatively
4. Comparable fusion rates, evaluated via CT scan I year postoperatively

Study Benefits to Virtua

Virtua could stand to gain some significant cost savings if the more cost-effective Vivigen is shown to be a clinically equivalent bone graft option that can replace the more expensive rhBMP-2.

Study Methodology

Patients who meet all of the following inclusion criteria may be eligible to participate in the study if:

1. Age 18 or older;
2. Diagnosed with lumbar degenerative/isthmic spondylolisthesis, degenerative disc disease with axial low back pain and neurologic symptoms, failed conservative treatment and eligible for a single level lumbar instrumented fusion;
3. Willing to provide informed consent, participate in study, and comply with study protocol.

Patients who meet any of the following criteria may not be eligible to participate:

1. Pregnant or contemplating pregnancy prior to surgery;
2. Serious spinal conditions (e.g. spinal cord compression, cauda equina syndrome, spinal infection, spinal tumor, spinal fracture, inflammatory or systemic spinal arthritis);
3. Surgery involving more than 2 vertebral levels;
4. Worker's compensation or personal injury related to lumbar spine (treatment outcomes may be affected by patient's personal interests; could also run into potential issues with reimbursement).
5. Lactating women
6. Patients who have a known or suspected allergy to Gentamicin Sulfate, Meropenem, Vancomycin, Dimethyl Sulfoxide (DMSO), and Human Serum Albumin
7. Immune compromised patients

During the preoperative office visit, the surgeon will inform patients that appear to meet study eligibility criteria, about the study, and discuss the differences between the two bone graft options, including their potential risks and benefits. The surgeon will make clear to the patient that consenting to be a part of the study means that the patient has agreed to be randomly assigned to one of the two bone graft groups.

Patients who are deemed eligible to participate in the study and are willing to participate will be asked by a trained study physician assistant (PA) to complete the research informed consent. This document will be summarized verbally by the PA and potential participants will be given the opportunity to ask questions about the protocol or their involvement prior to providing consent. Those who agree to

participate and provide research informed consent will be enrolled in the study, and given a copy of the research informed consent document. The patient's informed consent would be added to the patient's chart.

A computer generated randomization scheme will be employed and the randomization outcomes will be sealed in envelopes. On the day of surgery, in the operating room, the circulating nurse will pick an envelope from the randomized stack, unseal the envelope, and based on the outcome (even or odd), assign the patient to one of the two bone graft groups. While the study intervention group (even) will receive 5cc Vivigen and local autograft, the control group (odd) will receive small kit rhBMP-2 with local autograft. Anesthesiologists will use their usual pre-operative and intra-operative techniques for all study participants.

The surgical team, including the surgeons, will be blinded to the treatment options until decompression/instrumentation have been completed. The patients and all staff, including hospital nursing staff, case management, and physical therapists, will be blinded as to which bone graft treatment the patient received.

The primary outcome in this study will be the mean Oswestry Disability Index (ODI) score. The ODI is one of the most commonly utilized condition-specific measures of disability used in the management of spinal disorders [9]. The ODI Version 2.0 is what the Virtua Memorial Spine Center currently uses to examine patient disability preoperatively, as well as two weeks, 6 weeks, 3 months, 6 months, and 1 year postoperatively. The ODI has 10 sections of six statements with the first statement corresponding to a score of 0 indicating no disability and the last statement corresponding to a score of 5 indicating maximum possible disability. The final score which is calculated as: [total score/(5 x number of questions answered)] x 100%, could range from 0% to 100% [9].

Adopting a standard deviation of 10, which is one of the most commonly used standard deviations in ODI studies [9], and looking to detect a mean difference of 8 in ODI scores to indicate superiority of one bone graft option over the other, it is estimated that for a statistical power of 80% and significance level of 0.05, a minimum of 26 participants will be required in each study group for a total of 52 study participants. To minimize the possibility of dropouts or incomplete data impacting the analysis, a minimum of 30 participants will be enrolled in each study group, for a total of 60 study participants.

Secondary outcome measures in this study include the mean scores from the 36-Item Short Form Survey Instrument (SF-36) [10]; the mean leg/back pain scores from the numeric rating scale of 0-no pain, to 10-worst pain possible; mean LOS; incidence of ORAEs, and fusion rates examined via CT scan 1 year postoperatively by an independent radiologist.

Means will be compared between the two study groups using one-tailed 2-sample t tests, proportions will be compared using chi-square tests, and logistic regression will be used to analyze for confounding effects. All statistical analyses will be conducted in Minitab 16 Statistical Software.

Protection of Human Subjects

Throughout the study, the principal investigators (Virtua Memorial spine surgeons and PAs), will be the only ones with access to the data collection database. Following the completion of the study, all personal health information collected, including name, gender, age, significant medical comorbidities, and postoperative complications, will be de-identified as soon as possible prior to data analysis and any subsequent publications or research submissions. Patient would be told participation is purely voluntary with no monetary reimbursement and minimal risk of being assigned to one of the two pain management groups.

References

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APPENDIX 3. The Oswestry Disability Index Questionnaire

RECONSTRUCTIVE ORTHOPEDICS
FOCUSED ON YOU

Last Name: _____
First Name: _____
DOB: _____

Oswestry Disability Questionnaire

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer every section and mark in each section only the ONE box which applies to you. We realize you may consider that two of the statements in any one section relate to you, but please just mark the box which most closely describes your problem.

Section 1 – Pain Intensity

- ❑ I have no pain at the moment.
- ❑ The pain is very mild at the moment.
- ❑ The pain is moderate at the moment.
- ❑ The pain is fairly severe at the moment.
- ❑ The pain is very severe at the moment.
- ☒ The pain is the worst imaginable at the moment.

Section 2 – Personal Care (washing, dressing, etc.)

- ❑ I can look after myself normally but it is very painful.
- ❑ I can look after myself normally but it is very painful.
- ❑ It is painful to look after myself and I am slow and careful.
- ❑ I need some help but manage most of my personal care.
- ❑ I need help every day in most aspects of my personal care.
- ❑ I need help every day in most aspects of self-care.
- ☒ I do not get dressed, wash with difficulty, and stay in bed.

Section 3 - Lifting

- ❑ I can lift heavy weights without extra pain.
- ❑ I can lift heavy weights but it gives extra pain.
- ❑ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned (i.e. on a table).
- ❑ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned.
- ❑ I can lift only very light weights.
- ☒ I cannot lift or carry anything at all.

Section 4 – Walking

- ❑ Pain does not prevent me walking any distance.
- ❑ Pain prevents me walking more than 1mile.
- ❑ Pain prevents me walking more than ¼ of a mile.
- ❑ Pain prevents me walking more than 100 yards.
- ❑ I can only walk using a stick or crutches.
- ❑ I am in bed most of the time and have to crawl to the toilet.

Section 5 – Sitting

- ❑ I can sit in any chair as long as I like.
- ❑ I can sit in my favorite chair as long as I like.
- ❑ Pain prevents me from sitting for more than 1 hour.
- ❑ Pain prevents me from sitting for more than ½ hour.
- ❑ Pain prevents me from sitting for more than 10 minutes.
- ❑ Pain prevents me from sitting at all.

Section 6 – Standing

- ❑ I can stand as long as I want without extra pain.
- ❑ I can stand as long as I want but it gives me extra pain.
- ❑ Pain prevents me from standing more than 1 hour.
- ❑ Pain prevents me from standing for more than ½ an hour.
- ❑ Pain prevents me from standing for more than 10 minutes.
- ❑ Pain prevents me from standing at all.

Section 7 – Sleeping

- ❑ My sleep is never disturbed by pain.
- ❑ My sleep is occasionally disturbed by pain.
- ❑ Because of pain, I have less than 6 hours sleep.
- ❑ Because of pain, I have less than 4 hours sleep.
- ❑ Because of pain, I have less than 2 hours sleep.
- ❑ Pain prevents me from sleeping at all.

Section 8 – Sex life (if applicable)

- ❑ My sex life is normal and causes no extra pain.
- ❑ My sex life is normal but causes some extra pain.
- ❑ My sex life is nearly normal but is very painful.
- ❑ My sex life is severely restricted by pain.
- ❑ My sex life is nearly absent because of pain.
- ❑ Pain prevents any sex life at all.

Section 9 – Social Life

- ❑ My social life is normal and cause me no extra pain.
- ❑ My social life is normal but increases the degree of pain.
- ❑ Pain has no significant effect on my social life apart from limitingmy more energetic interests, i.e. sports.
- ❑ Pain has restricted my social life and I do not go out as often.
- ❑ Pain has restricted social life to my home.
- ❑ I have no social life because of pain.

Section 10 – Traveling

- ❑ I can travel anywhere without pain.
- ❑ I can travel anywhere but it gives extra pain.
- ❑ Pain is bad but I manage journeys of over two hours.
- ❑ Pain restricts me to short necessary journeys under 30 minutes.
- ❑ Pain prevents me from traveling except to receive treatment