TITLE: Prospective, Single-Blinded, Randomized-Controlled Trial Comparing the Performance Profiles of Two Non-Cross-Linked Porcine Dermal Matrices in Abdominal Wall Reconstruction

Research Protocol V2
Document Date: September 24, 2024
NCT # NCT02228889

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I. Background and rationale

250,000 ventral hernia repairs are performed in the United States every year,[1] and hernia recurrence, as well as surgical site occurrences (SSOs), remain a significant problem. When hernias recur and require reoperation, the subsequent risk of recurrence increases significantly. In fact, Luijendijk *et al* have shown that the 5-year risk of hernia recurrence increases stepwise with every reoperation[2] (24% after the first reoperation, 35% after the second reoperation, 39% after the third reoperation), and this underscores the importance of performing the best possible hernia repair the first time. In order to design the operation with the best possible odds of success, high-quality level I evidence is needed. There is a scarcity of high-quality, randomized-controlled trials in the field of ventral hernia repair.[3]

One aspect of hernia repair that still contains significant uncertainty due to the scarcity of high-quality data is the ideal type of mesh. Meshes used in hernia repair fall into two broad categories: synthetic and biologic. Synthetic meshes add strength to the fascial repair, but are plagued by a high rate of infection and formation of enterocutaneous fistulas.[3] This led to the development of biologic meshes. These usually consist of human or animal dermis that has been treated to remove cells, thus leaving a collagen matrix and making the material non-immunogenic. They are less prone to fibrous encapsulation than synthetic meshes. In addition, those biologic meshes serve as scaffolds that allow ingrowth of new tissue, including new blood vessels. This makes them less prone to infection than synthetic meshes. The Ventral Hernia Working Group (VHWG) recommends using a biologic mesh rather than a synthetic mesh in patients with a VHWG hernia grade of 2 or above.[3] Although many biologic meshes exist, it is unclear which one provides optimal ventral hernia repair with the lowest rate of SSOs.

Some biologic meshes commonly used in abdominal wall reconstruction include:
-Strattice: non-cross-linked porcine acellular dermal matrix (LifeCell Corp., Branchburg, NJ)
-XenMatrix: non-cross-linked porcine acellular dermal matrix (Davol, Warwick, RI)
-SurgiMend: non-cross-linked bovine acellular dermal matrix (TEI Bioscience, Inc., Boston, MA)

-FlexHD: human acellular dermal matrix (Ethicon, Somerville, NJ)
-AlloDerm: human acellular derman matrix (LifeCell Corp., Branchburg, NJ)
-AlloMax: human acellular derman matrix (Davol, Warwick, RI)
-Permacol: cross-linked porcine acellular dermal matrix (Covidien, Mansfield, MA)

It is known that the lowest recurrence and complication rates are achieved when the fascia is closed primarily in the midline, with additional reinforcement using mesh.[2,4] Closure of the native fascia can be achieved via primary advancement and suture in the case of small hernias, or component separation (as described in Ramirez *et al*[5]) in the case of larger hernias. Meshes can be placed as an overlay (superficial to the fascial closure), underlay (deep to the fascial closure), or bridge (in cases where the fascia cannot be primarily closed)

The senior author (J.E.J) performs hernia repair using a technique similar to the Minimally-Invasive Component Separation with Inlay Bioprosthetic Mesh technique (MICSIB) described by Butler *et al*.[6] The technique involves division of the external oblique aponeurosis just lateral to the semilunar line via a narrow subcutaneous tunnel, without significant subcutaneous undermining. This can be performed unilaterally or bilaterally. This is followed by placement of biologic mesh for reinforcement, in an intraperitoneal or retro-rectus plane, with wide overlap with the native fascia (this is a departure from the MICSIB technique, where the mesh is placed in the pre-peritoneal plane). Finally, the rectus muscles are advanced medially and the fascia is primarily closed over the mesh. This technique improves skin flap vascularity by preserving the myocutaneous perforators to the abdominal skin, and by minimizing subcutaneous dissection and dead space, which can result in fluid collections. In their evaluation of 38 patients with large abdominal hernias, Butler *et al* applied the MICSIB technique, achieving primary musculofascial closure with inlay mesh in 31 patients and bridged repair with mesh in 7 patients. Mean follow-up was 12.4 months. There were no hernia recurrences. There was one bulge. There were no seromas, and there were two instances of skin necrosis (compared to a rate of 20% in the literature for standard component separation[7]). In a subsequent report comparing minimally-invasive component separation to standard open component separation, Butler *et al* found the minimally-invasive technique to result in far fewer instances of skin dehiscence and wound healing complications.[8] The same group has also found that primary repair of the fascia with mesh reinforcement results in far fewer instances of hernia recurrence than cases where the fascia cannot be primarily closed and where mesh is used as a bridge.[9]

In the MICSIB study by Butler *et al*,[6] all patients received non-cross-linked acellular porcine dermal matrix bioprosthetic mesh. There are several retrospective studies comparing various types of allogenic and xenogenic bioprosthetic meshes in abdominal wall reconstruction. Non-cross-linked porcine mesh has been shown to be superior to human acellular dermis, resulting in fewer instances of laxity/bulge.[10,11] Non-cross-linked porcine acellular dermis has also been shown to be superior to cross-linked porcine acellular dermis.[12] Non-cross-linked acellular porcine dermal matrix has been shown to result in successful hernia repair in 80% of patients with contaminated or

infected hernias in a retrospective review.[13] Janfaza *et al* retrospectively compared SurgiMend, a non-cross-linked bovine acellular dermal matrix, to Flex HD, a non-cross-linked human acellular dermal matrix.[14] They found higher rates of surgical site infections and hernia recurrence with Flex HD. Clemens *et al* conducted a prospectively collected, retrospectively analyzed study in which they compared hernia repair with Strattice, a non-cross-linked porcine acellular dermal matrix, and with SurgiMend, in 120 patients with mean follow-up of 21.0 months.[15] They found no difference in the rate of recurrent hernia or bulge, although the Strattice group had a higher rate of overall complications due to a relatively higher rate of medical complications (pneumonia, renal failure) in that group not directly related to the type of mesh used.

At the Ohio State University Wexner Medical Center, the two most commonly used biologic meshes for hernia repair in the practice of the senior author (J.E.J) are Strattice and XenMatrix. These are both non-cross-linked porcine acellular dermal matrices, manufactured by different companies using different technologies. There are some structural differences between the two. For example, according to internal reports by the companies, XenMatrix has larger pores that allows more tissue ingrowth.[16] However, there are no published reports comparing the performance profile those two meshes in the clinical setting.

II. Objectives

Our goals in this study are:

- *a.* PRIMARY OUTCOME
  - **i.** To compare the **hernia recurrence rate** between XenMatrix and Strattice at **30 days and 1 year postoperatively**
- *b.* SECONDARY OUTCOMES
  - i. To compare the **bulge rate** between XenMatrix and Strattice at **30 days and 1 year postoperatively**
  - **ii.** To compare the **rate of Surgical Site Occurrences (SSOs)** between two non-cross-linked porcine dermal matrices (XenMatrix and Strattice) in abdominal wall reconstruction at **30 days and 1 year postoperatively**
    1. Infection
    2. Seroma
    3. Hematoma
    4. Wound dehiscence
    5. Skin necrosis
    6. Formation of enterocutaneous fistula
    7. Mesh infection
  - **iii.** To compare to changes in patient pain, physical functioning and quality of life after hernia repair between XenMatrix and Strattice, **preoperatively, and at 1 year postoperatively**
    1. **Pain** assessment: PROMIS Pain Intensity survey, PROMIS Pain Interference survey

2. **Physical functioning** assessment: PROMIS Physical Function
3. **Quality of life** assessment: HerQLes survey

III. Procedures

a. Research design

This is a **prospective, randomized-controlled trial**. It is **single-blind** (patients are blinded to the type of mesh used while surgeons are not).

b. Sample

Inclusion criteria:

-Age > 18
-Patients presenting for elective hernia repair, with VHWG grade 2 or above
-Patients deemed to be good surgical candidates, with **no active life-threatening** cardiac disease, pulmonary disease, renal disease, hematologic disease
-Patients presenting for resection of large abdominal wall tumors who are expected to undergo have tumor extirpative defect that would require biologic mesh for closure

Exclusion criteria:

-Known allergy to porcine products
-Active smokers (within the past 4 weeks) presenting for elective hernia repair
-Patients with active life-threatening cardiac disease, pulmonary disease, renal disease, hematologic disease presenting for elective hernia repair
-Patients presenting for emergent hernia repair (in the setting of bowel strangulation, necrosis, penetrating trauma) as it will be difficult to consent those patients for the study preoperatively
-Patients with severe systemic sepsis
-Patients with frank purulence in the wound

Sample size (power analysis)

Our primary outcome is hernia recurrence rate at 30 days and 1 year postoperatively. According to two industry-sponsored studies, the rate of hernia recurrence with XenMatrix is approximately 7%.[17,18]
According to the large series by Clemens *et al*, the rate of hernia recurrence with Strattice is approximately 2.9%.[15]
Assuming an alpha error of 5%, a power of 80%, and assuming a large standard deviation (3), the number of patients in each group that is needed to demonstrate a significant difference is 5.

In order to adequately power the study to analyzethe secondary outcomes, **we plan to enroll 35 patients in each group (70 patients total**)

a. Detailed study procedures

When a patient with a ventral hernia or an abdominal wall tumor presents to the senior author for evaluation for abdominal wall reconstruction, a full history and physical examination will be performed. Patient who satisfy the study inclusion and exclusion criteria will be offered the opportunity to participate in the study. If they agree to participate, informed consent and HIPAA forms will be filled out and signed.

Patients will then be randomized to group A (Strattice) or group B (XenMatrix) using a random number generator made in Microsoft Excel. They will not be told which group they are in, and only the principal investigator, co-investigators and operating room staff will be aware of which mesh is being used.

The patients will be asked to fill out 4 surveys preoperatively: PROMIS Pain Intensity survey, PROMIS Pain Interference survey, PROMIS physical function survey and HerQLes survey.

They will then undergo surgery, and will be followed weekly for a month, then every 3 months for a year, and as needed. They will be evaluated for hernia recurrence, bulge, or other SSOs throughout the follow-up period.

They will be asked to fill out the PROMIS Pain Intensity survey, PROMIS Pain Interference survey, PROMIS physical function survey and HerQLes survey at 1 year.

c. Measurements

The patient characteristics that will be collected will include:

1) Age
2) Comorbidities
    a. Diabetes
        i. Hemoglobin A1c
    b. Current tobacco use (defined as <4 weeks prior to surgery)
    c. Former tobacco use (defined as >4 weeks prior to surgery)
    d. Chronic Obstructive Pulmonary Disease
    e. Coronary Artery Disease
    f. Malnutrition (defined as prealbumin < 18 or albumin < 3.5)
    g. Corticosteroid use
    h. Use of other immunosuppressants
    i. BMI
    j. History of chemotherapy
    k. History of radiation to abdomen
3) Hernia characteristics
    a. Size on abdominal CT scan in cm^2
    b. Ventral Hernia Working Group (VHWG) grade[3]

i. Grade 1 (low risk): no comorbidities, no history of wound infection, no contamination
ii. Grade 2 (comorbid): smoker/obese/diabetic/immunosuppressed/COPD
iii. Grade 3 (potentially contaminated): previous wound infection, stoma present, GI tract violated
iv. Grade 4 (infected): infected mesh, septic dehiscence

c. Number of prior hernia repairs

The surgical details that will be collected will include

1) Surgeon
2) Date of surgery
3) Wound class
    a. Class I = clean
    b. Class II = clean-contaminated
    c. Class III = contaminated
    d. Class IV = dirty
4) Whether bowel resection performed
5) Whether component separation technique (CST) performed
    a. If yes, standard CST versus minimally-invasive CST
6) Whether fascia able to be primarily closed
7) Type of mesh used
8) Location of mesh
    a. Overlay (superficial to the primary fascial repair)
    b. Underlay (deep to the primary fascial repair)
        i. Sub-rectus
        ii. Intraperitoneal

The outcome data that will be collected will include

a. Hernia recurrence
b. Bulge
c. SSOs
    a. Infection
    b. Seroma
    c. Hematoma
    d. Wound dehiscence
    e. Skin necrosis
    f. Formation of enterocutaneous fistula
    g. Mesh infection
d. Score on PROMIS Pain Intensity survey
e. Score on PROMIS Pain Interference survey
f. Score on PROMIS Physical Function
g. Score on HerQLes survey

d. Internal validity

Since this is a randomized-controlled trial, we expect the baseline demographics and patient characteristics to be similar between the two groups, and we expect out results to be internally valid.

e. External validity

The study results will reflect the outcomes within our study population at the Ohio State University Medical Center, and may not be generalizable to other institutions.

f. Data analysis

Baseline patient characteristics will be compared between the two groups to ensure that the two groups are similar and that there are no confounders

Multiple binary logistic regression will be performed to detect predictors of hernia recurrence, bulge and other SSOs. It will also be used to determine whether one mesh has a higher rate of complications compared to the other.

IV. Regulatory & Continuing Review Completion Plan

Step-by-Step Communication Plan

The primary additional contact (department regulatory officer) listed on the IRB study team will be responsible for initiating the CR. when the CR notification is automatically sent by the IRB system 90 days prior to study expiration. Department contact will email study team notifying them that CR has been opened and set a timeline that is 8 weeks prior to study expiration for CR submission.

A study team member, in the key personnel, co-investigator, or principal investigator role, will be asked to complete the details of the CR to include participant numbers, status of project, or any events that require reporting. This ensures that all "engaged" study team members participate in the CR and may serve in completing the CR.

The department additional contact will follow-up with the study team via email 2x before setting up a meeting with PI to complete the CR.

The PI will submit the ready CR at least 48hrs prior to the 8 week deadline.

The 8 week deadline insures that at least 4 IRB board meetings occur prior to study expiration to account for request for modifications, delays from IRB, or other unforeseen circumstances that may cause a lapse in study.

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