Study Comparing the Efficacy, Safety, and Cost of a Permanent, Synthetic Prosthetic Versus a Biologic Prosthetic in the One-stage Repair of Ventral Hernias in Clean and Contaminated Wounds.

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STUDY PROTOCOL. The specific hypothesis driving the research application is that the use of a permanent synthetic prosthetic for the one-stage repair of complex ventral hernias will result in superior outcomes compared to a biologic prosthetic.

General study design. We propose a prospective, randomized, single-blind study in 330 patients with complex ventral hernias. A permanent synthetic prosthetic will be compared to a biologic prosthetic for clinical superiority. The primary endpoint is ventral hernia recurrence rate.

Eligible patients will be randomized to undergo open ventral hernia repair using either a permanent synthetic or a biologic prosthetic. Patients will be randomized while in the operating room using a technique of stratified randomization with permuted blocks to insure a balance between the two treatment groups at study entry. Patients assigned the synthetic code will be treated using the permanent synthetic prosthetic (Ventralight®, Bard, Murray Hill, NJ), whereas those patients assigned the biologic code will be treated with the biologic prosthetic (Strattice®, LifeCell Corp., Branchburg, N.J.). The selection of the synthetic and biologic prosthetics was based on a combination of established clinical experience and our best analysis of the available preclinical data. [33-39] Ventralight is a composite product that combines a synthetic mesh with a proven absorbable hydrogel barrier to minimize tissue attachment (adhesions) to the mesh. Strattice is a non-crosslinked, terminally sterilized, porcine dermal product recently introduced in 2007. While there is limited human data available, a multi-institutional trial evaluating its outcomes during the repair of infected and contaminated hernias was recently published. [6] Prior to the random assignment to receive either a permanent synthetic or a biologic prosthetic, patients will be stratified according to 3 factors;

a) *Charlson Index score, to ensure a balance of severity in chronic illnesses of the two patient groups;*
b) *Wound contamination, to ensure a balance between clean versus contaminated repairs in the two patient groups; and*
c) *Surgical technique, to ensure a balance between hernia repairs where the prosthetic bridges the fascial defect versus reinforces a primary fascial closure*

Patients will be enrolled only once.

Patients will undergo daily evaluations during their index hospitalization. Follow-up will consist of evaluations by the investigator-surgeon before and at 1 month after surgery. The study team will perform follow-up evaluations at 3, 6, 12, 18, and 24 months after surgery or until the patient's hernia recurs. (Table 1) Due to the scheduling challenges involved, we will allow for a two-week window around the patients' targeted post-operative evaluation times. Patients will be followed for a total of 24 months since there is good evidence that the majority of hernia recurrences will take place within the first 18-24 months after surgery. [19, 20, 40, 41] Each evaluation will include a brief clinical examination, laboratory analyses, (complete cell count and differential, serum electrolytes, creatinine, urea nitrogen, albumin, prealbumin, C-reative protein, Hgb $A1_C$, liver function tests, urinalysis), anterior and lateral photographs of the abdomen, and ultrasound examinations of the anterior abdominal wall. During the scheduled visits wherein blood draws will occur, plasma will be banked for possible future research, considering the future potential of using antibodies as biomarkers. Evaluations of patient well-being, including a visual pain survey, Activities Assessment Score, and SF36 and HerQLes quality- of-life questionnaires (Appendices 1-4) will be performed at enrollment and 1, 6, 12 and 24 months following surgery. In addition, this panel of well-being assessments will also be administered when a patient develops a wound occurrence and/or hernia recurrence. An abdominal CT scan with intravenous contrast and volumetric analysis of the hernia will be obtained before surgery and 24 months after the hernia repair or when the patient's hernia recurs. The patient-related factors of gender, ethnicity, age, body-mass index (BMI, with obesity defined as a BMI≥30), chronic obstructive pulmonary disease, cough, constipation, prostatism, diabetes mellitus, glucocorticoid therapy, chronic immunosuppression, smoking status (current activity and pack-years), location of the hernia and abdominal surgery history (including prior ventral or inguinal hernia repairs) will be recorded. Perioperative factors including the patient's ASA score, size of the fascial defect (area in cm^2 = craniocaudal x transverse dimensions in cm), use of component separation repair techniques, duration of the operation, estimated blood loss, blood transfusion, maximum and minimum body temperature, maximum and minimum systolic blood pressure, vasopressor administration, perioperative antibiotics (including antibiotic regimen, timing of first dose and duration of therapy), postoperative complications, hospital length of stay, total hospital and professional charges and mortality will also be recorded.

Clinical trial item or procedure	Screen / Initiation	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
history, physical exam & consent	X						
brief clinical evaluation		X	X	X	X	X	X
pain, activity & QoL assessments	X	X		X	X		X
clinical photographs	X	X	X	X	X	X	X
chemistry panel	X		X		X		X
CBC	X		X		X		X
PT/PTT	X						
liver function tests	X		X		X		X
albumin, prealbumin & CRP	X		X	X	X		X
urinalysis	X						
urine pregnancy	X						
hepatitis panel	X						
ECG	X						
chest x-ray	X						
abdominopelvic CT	X						X
abdominal ultrasound				X	X	X	X
patient expenses reimbursement			X	X	X	X	X

Table 1. Clinical trial protocol for comparing a permanent, synthetic prosthetic (Ventralight) versus a biologic prosthetic (Strattice®) for repair of a complex ventral hernia.

Before anesthesia is induced, measures to reduce the patient's perioperative risks for deep venous thrombosis/pulmonary embolism and gastrointestinal ulceration will be instituted according to institutional, risk-reduction protocols.

When anesthesia is induced, a first-generation cephalosporin will be given intravenously within thirty (30) minutes, prior to the incision, unless the patient has a clinically significant allergy to penicillin, in which case either clindamycin or vancomycin will be substituted. An alternative antibiotic can be given if needed to provide appropriate prophylaxis for patients with previous abdominal wound infections. Ceftriaxone and clindamycin will be given to patients whose procedure is expected to involve repair of the large intestine, unless the patient has a clinically significant allergy to penicillin, in which case either ciprofloxacin or ertapenem will be substituted for the cephalosporin. Quantitative wound cultures will be obtained in those patients with perioperatively identified wound contamination specific to the source, e.g., colostomy, infected ventral hernia mesh, incidental enterotomy, etc. For example, duplicate culture swab samples will be obtained from infected prosthetic mesh and abscesses, whereas duplicate tissue biopsies will be obtained from chronic wounds and fistula tracts.

Surgical techniques. The complex ventral hernias will be repaired according to one of two standardized techniques with the randomly selected prosthetic either bridging the fascial defect with mesh versus reinforcing a reconstituted linea alba.

Bridging the fascial defect. The standard surgical technique in these patients consists of identifying healthy fascial edges circumferentially around the hernia defect so as to allow placement of the prosthetic in a retrofascial (underlay) position, tailored to the size of the defect so that at least 4 cm of the prosthetic overlaps with the fascial edges. The prosthetic is then sutured to the back of the anterior abdominal wall with #1 polypropylene (Prolene) suture, using stitch widths (tissue bites) and intervals of approximately 1-1.5 cm with either a continuous or interrupted technique. The repair can include a unilateral or bilateral rectus myofascial advancement flap (component separation) at the discretion of the surgeon. Importantly, the rectus muscles remain separated with the prosthetic bridging the distance between the two sides.

Reinforcing a reconstituted linea alba. The standard surgical technique in these patients consists of identifying healthy fascial edges circumferentially around the hernia defect that can be re-approximated in the midline so as to reconstitute the linea alba using #1 polypropylene (Prolene) suture, using stitch widths (tissue bites) and intervals of approximately 1-1.5 cm with either a continuous or interrupted technique. Subsequently, the fascial closure is reinforced through placement of the prosthetic in an overlay position (anterior to fascia). The prosthetic is secured to the anterior abdominal wall with 2-0 silk or Prolene suture using either a

continuous or interrupted technique. The repair can include a unilateral or bilateral rectus myofascial advancement flap (component separation) at the discretion of the surgeon. Importantly, the rectus muscles are re-approximated with the prosthetic reinforcing the fascial closure.

All patients will have closed suction, channel drains placed during surgery; these will be removed when the output is <30cc/day/drain for two consecutive days or after 6 weeks or at the discretion of the surgeon. At the end of the procedure, the surgeon will record the surgical wound classification including the source of contamination (Appendix 5), and the surgical technique used to repair the hernia, including the suture type(s) and suturing technique(s).

The following postoperative complications will be recorded;

- ***Superficial incisional surgical site infection (SSI)*** [42, 43]: an infection that occurs at the incision site within 30 days after surgery AND involves only skin or subcutaneous tissue located at or above the fascial layer/prosthesis AND at least one of the following:
  1. Purulent drainage from the incision or drain located at or above the fascial layer/prosthesis.
  2. Organism isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
  3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and the superficial incision is deliberately opened by the surgeon, unless the incision is culture-negative.
  4. Surgeon makes a clinical diagnosis of a superficial SSI.
- ***Deep incisional SSI*** [42, 43]: an infection that occurs at the operative site within 30 or 90 days, depending on the procedure, after surgery AND the infection appears to be related to the hernia surgery AND the infection involves deep soft tissues (e.g., fascial and muscle layers) AND at least one of the following:
  1. Purulent drainage from drain located beneath the fascial layer/prosthesis.
  2. A deep incision spontaneously dehisces or is deliberately opened by the surgeon when patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness, unless the site is culture-negative.
  3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
  4. Surgeon makes a clinical diagnosis of a deep incisional SSI.
- ***Organ/Space SSI*** [42, 43]: an infection that occurs at the operative site within 30 or 90 days, depending on the procedure, after surgery AND the infection appears related to the hernia surgery AND the infection involves any part of the anatomy (e.g., organs or spaces) other than the incision, which was opened or manipulated during the hernia operation, AND at least one of the following:
  1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
  2. Organism isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
  3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
  4. Surgeon makes a clinical diagnosis of an organ/space SSI.
- ***Soft tissue infection:***
  Soft tissue infections must meet at least 1 of the following criteria:
  1. Patient has organisms cultured from tissue or drainage from affected site.
  2. Patient has purulent drainage at affected site.
  3. Patient has an abscess or other evidence of infection seen during an invasive procedure or histopathologic examination.
  4. Patient has at least 2 of the following signs or symptoms at the affected site with no other recognized cause: localized pain or tenderness, redness, swelling, or heat and at least 1 of the following:
  a. organisms cultured from blood
  b. positive laboratory test performed on blood or urine (e.g., antigen tests for H influenzae, S pneumoniae, N meningitidis, Group B Streptococcus, or Candida spp)
  c. diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen.

- ***Ventral hernia recurrence***: Any fascial defect that is palpable or detected by ultrasound or abdominal CT examination and is located within 6 cm of the site of hernia repair. Examination for hernia recurrence will include palpation of the surgical site while the patient is standing and while they are in the supine position with legs extended and raised.
- ***Wound seroma***: a palpable, aspirated or spontaneously draining fluid collection consisting of serous fluid that is associated with a non-infected surgical incision. The physical dimensions of all wound seromas will be measured and the volume of any aspirate recorded and sampled for biochemical analysis, including a complete cell count and differential, glucose, LDH, amylase and triglyceride concentrations. The red blood cell count of the fluid must be <10% of the patient's current red blood cell count to be considered a seroma rather than a hematoma.
- ***Wound hematoma*****:** a palpable, aspirated or spontaneously draining fluid collection consisting of bloody fluid that is associated with a non-infected surgical incision. The physical dimensions of all wound hematomas will be measured and the volume of any aspirate recorded and sampled for biochemical analysis, including a complete cell count and differential, glucose, LDH, amylase and triglyceride concentrations. The red blood cell count of the fluid must be ≥10% of the patient's current red blood cell count to be considered a hematoma rather than a seroma.
- ***Urinary tract infection*** [42]:

  Asymptomatic – an indwelling catheter is present within 7 days before urine is cultured AND patient has no fever (>38ºC), urgency, frequency, dysuria, or suprapubic tenderness AND has a urine culture of ≥10^5 organisms/ml urine with no more than two species or organisms.

  Symptomatic – fever (>38ºC), urgency, frequency, dysuria or suprapubic tenderness AND a urine culture of ≥10^5 organisms/ml urine with no more than two species or organisms
- ***Sepsis*** [42]: One of the following clinical signs or symptoms without another recognized cause: fever (>38ºC), hypotension (systolic pressure ≤90 mm Hg) or oliguria (<20 ml/h) AND all of the following:
  1. Blood culture not done or no organism detected in the blood
  2. No apparent infection at another site
  3. Physician institutes appropriate antimicrobial therapy for sepsis

The potential postoperative complications listed are superficial wound infection, deep wound infection, deep space/organ infection, wound seroma, wound hematoma, urinary tract infection, and sepsis. The peri- and postoperative risk mitigation plan for all of these potential complications involves standard clinical management procedures. Specifically, the risk mitigation plan for the surgical site infections, seromas, hematomas and sepsis entails the application of sterile technique throughout the immediate perioperative period, including clipping hair, antimicrobial skin preparation, minimal handling of repair prosthetics, meticulous surgical technique (including minimizing soft tissue dissection, careful hemostasis, use of closed suction drains and use of abdominal wall binders after surgery), perioperative intravenous antibiotics administered less than 1 hour before the incision and the avoidance of intraoperative hypothermia. In the event of a surgical site occurrence, accumulated fluid or pus will be drained, and the incision opened and antibiotic therapy instituted as per clinical judgment. Urinary tract infections will be mitigated by the placement of urinary catheters in the operating room using sterile technique and removing the catheters on the second postoperative day. Appropriate antibiotic therapy will be instituted in the event of a urinary tract infection.

To evaluate perioperative pain we will use the visual analog scale (VAS) and quality of life using the Rand Short Form 36 (SF36), Activities Assessment Scale (AAS) and HerQLes questionnaires. The VAS and SF36 have been used to evaluate pain and quality of life outcomes in several studies of ventral hernia patients over the past several years. [7-10] Using these instruments will facilitate comparison of our results with those of other investigators. Importantly, the AAS and HerQLes quality of life tools were specifically designed and have been prospectively validated for use in patients undergoing ventral hernia repair. [11-13]

Data and Safety Monitoring Plan

Review of Safety Information. The PI, Designated Safety Officer and Internal Review Committee (IRC) will review safety data on an ongoing basis. The IRC will be composed of the PI, specialists in Infectious Diseases, Critical Care Medicine, Plastic Surgery and Biostatistics. The Designated Safety Officer will be a nurse or

research assistant with experience in clinical trial operations and safety. The IRC will prepare study data reports for review by the Data and Safety Monitoring Board.

An independent Data and Safety Monitoring Board (DSMB) will review safety data on an ongoing basis. The DSMB will be comprised of UCSF faculty and will be independent of the study team. The composition of the DSMB, as well as the schedule of activities will be made available to the NIDDK for its review. All DSMB members will review the protocol and ensure its understanding. In addition, all DSMB members will be presented with the DSMB charter and will sign a conflict of interest form.

Study Stopping Rules.
Enrollment and initiation of study treatment may be suspended at any time if any of these reviews conclude that there are significant safety concerns. If the trial is put on hold, all screening, enrollment, and initiation of any new study subjects will cease pending DSMB review.
The trial will be placed on hold based on the occurrence of the following serious adverse events: Death or Serious Infections, defined as any infection Grade ≥3 (as defined below). The DSMB shall review safety data once every nine to 12 months during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported adverse and serious adverse events. The DSMB will be informed of an Expedited Safety Report in a timely manner. In consultation with Dr. Glidden's we are planning that the DSMB will meet at least yearly to review study progress, accrual, data quality, and safety. Further, we plan a single interim analysis for efficacy and possible futility. This will be at the time the primary outcome can be assessed on half of the planned participants (50% information). Efficacy information will be presented between the arms in a semi-blinded fashion (e.g., arm A v. arm B). Efficacy will be based on a Lan DeMets continuous alpha spending approach with an O'Brien Fleming use function. Futility will use conditional power to assess the ability to reach a definitive conclusion. If the conditional power at 50% information to reject the original alternative hypothesis falls below 0.25, the board should consider the study futile.
In addition, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the PI or Designated Safety Officer. If the DSMB or the PI determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, they shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after this determination is made by the DSMB or the PI and not later than 15 working days after the DSMB and the PI first received notice of the effect.

The DSMB will report to the sponsor-investigator (in this case, the PI) any noncompliance with the signed Investigator's Agreement, conditions imposed by the IRB or FDA, and the requirements of the IDE.

The PI shall immediately conduct an evaluation of any unanticipated adverse device effects. Adverse effects will be graded by the PI and the attribution will ultimately be determined by the IRC.

The PI may not resume a terminated investigation without IRB and FDA approval.

Study Stopping Rules. The trial will be placed on hold based on the occurrence of the following serious adverse events: Death or Serious Infections, defined as any infection Grade ≥3 (as defined below). The IRC shall review safety data at least bi-annually during planned IRC Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported adverse and serious adverse events. The IRC will be informed of an Expedited Safety Report in a timely manner. In addition, the IRC may be called upon for *ad hoc* reviews. The IRC will review any event that potentially impacts safety at the request of the PI or Designated Safety Officer.

Classification, Reporting and Attribution of Adverse Events. Classification Criteria. The study site will classify the adverse events experienced by study subjects according to the criteria set forth by the Food and Drug Administration (FDA) for all adverse events. This document provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be classified and reported according to the following FDA standards:

Death

Report if you suspect that the death was an outcome of the adverse event, and include the date if known.

Life-threatening

Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (initial or prolonged)

Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage

Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events)

Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Reporting of Adverse Events. The PI will report all serious adverse events, regardless of relationship or expectedness within 24 hours of discovering the event to the IRB with all IDE Safety Reports directed to the FDA. For serious adverse events, all requested information on the AE/SAE form will be provided.

Attribution Definitions. The relationship, or attribution, of an adverse event to the study regimen will initially be determined by the Principle Investigator and recorded on the appropriate adverse event/serious adverse event form. Final determination of attribution for safety reporting will be determined by the IRC. The relationship of an adverse event to study will be determined as Unrelated, Unlikely, Possible, Probable, or Definite via NCI-CTEP definitions.