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Registry Based, Randomized Controlled Trial comparing Long-Term Results of Heavyweight versus Medium Weight Mesh in Ventral Hernia Repair

P.I.: Michael J. Rosen, MD FACS

Director, Cleveland Clinic Comprehensive Hernia Center

INTRODUCTION

Approximately five million laparotomies are performed annually in the United States with upwards of 25% of these patients developing a ventral hernia postoperatively.[1] Despite the prevalence of ventral hernias, the surgical approach to these procedures lacks standardization. In fact, nearly 20%-50% of patients undergoing ventral hernia repair (VHR) will experience a hernia recurrence.[2]

There are several factors that can contribute to ventral hernia recurrence. One of these is the use of prosthetic reinforcement. Although previous studies have shown that the use of mesh during VHR significantly decreases the risk of ventral hernia recurrence, guidelines for the ideal prosthetic material remain unknown. In terms of synthetic mesh, there are proponents that argue the value of medium weight material (40-60 g/m^2) in order to combat the risk of postoperative deep surgical site infection and minimize the risk of a "stiff abdomen" or chronic pain syndromes.[3-5] On the other hand, however, proponents of a heavier weight material (> 80 g/m^2) argue that its tensile strength leads to a long-term, durable hernia repair with decreased risk of hernia recurrence.[3-5]

To help determine if mesh weight has an impact on postoperative pain, we propose a registry-based, randomized clinical trial (RCT) through the Americas Hernia Society Quality Collaborative (AHSQC). The AHSQC is a multicenter, nationwide quality improvement effort with a mission to improve value in hernia care.[6] Data are collected prospectively in the routine care of hernia patients for quality improvement purposes. The information collected in the AHSQC offers a natural repository of information that can be used for research, in addition to its quality improvement purpose. We hypothesize that patients who undergo ventral hernia repair with medium weight mesh will have significantly less pain than those patients who undergo ventral hernia repair using heavyweight mesh one year after operation. Both the intended randomization arms of the study are accepted standard of care practices in use by surgeons.

Specific Aim #1: To determine if the use of a medium weight material leads to a decrease in pain intensity at one year following ventral hernia repair.

Specific Aim #2: To determine if there is a difference in ventral hernia recurrence at one year following surgery.

Specific Aim #3: To determine if there is a difference in the rate of deep surgical site infection at 30-days following surgery between the two mesh types.

Specific Aim #4: To determine if there is a difference in the quality of life between the two groups at one year following surgery.

STUDY DESIGN

This trial will be the first registry-based prospective study performed in the hernia disease space. Registry-based trials use the data available in a pre-existing database to increase the efficiency of performing RCTs.[7] To date, few high-quality RCTs have been performed evaluating treatments for hernia disease due to the high cost and logistical challenges associated with operationalizing this type of research. In our case, the AHSQC will serve as our platform. The exposure variables (mesh type) and outcomes of interest (pain intensity, quality of life, recurrence, and deep surgical site infection) for this trial are already captured within the AHSQC database, which will allow for long-term follow-up and data capture with minimal additional effort outside that of routine care.[7]

There will be a total of four sites participating in this study, including the Cleveland Clinic Foundation, Vanderbilt University Medical Center, Medical College of Wisconsin, and Greenville Health System. Specific patient inclusion criteria include patients aged 18 years or older, presenting for an elective, single-stage, open, retromuscular reconstruction of a clean (CDC wound class 1) midline abdominal wall defect, are able to achieve midline fascial closure, have a hernia defect

width ≤ 20 centimeters measured intraoperatively, are able to tolerate general anesthesia, and are able to give informed consent. Patients will be excluded from our analysis if they undergo laparoscopic or robotic repair of an abdominal wall defect, have CDC wound class 2, 3, or 4, are unable to undergo successful retromuscular mesh placement, are pregnant, or are unable to give informed consent.

Patients will be randomized to heavyweight (> 75 gm/m^2) versus medium weight (40-60 gm/m^2) mesh at the time of operation. Specifically, patients will be randomized precisely at the point of mesh placement during the operation. All currently available polypropylene meshes and their densities have been confirmed by their respective manufacturer as follows:

AHSQC #	Frequency Used	Mesh Name	Type	Density (g/m^2)	Source
88	**1.8**	ULTRAPRO Mesh (Ethicon Inc.)	PP	28	Ethicon
118	**0.1**	VitaMESH Blue (Atrium Medical Corp.)	PP	29	Atrium
5	**14.7**	Bard Soft Mesh (Bard/Davol Inc.)	PP	43	Bard
70	**1.9**	PROLENE Soft Mesh (Ethicon Inc.)	PP	45	Ethicon
123	**1.4**	Parietene (Covidien)	PP	46	Covidien
72	**0.6**	ProLite Ultra Mesh (Atrium Medical Corp.)	PP	50	Atrium
116	**4**	VitaMESH (Atrium Medical Corp.)	PP	50	Atrium
125	**0.2**	Freedom Octomesh (Insightra Medical)	PP	55	Insightra Medical (http://studiowebgroup.ca/liaison/files/5614/0741/6221/Insightra_-_Freedom.pdf)
69	**0.8**	PROLENE Mesh	PP	76	Ethicon
71	**0.6**	ProLite Mesh (Atrium Medical Corp.)	PP	85	Atrium
4	**2.5**	Bard Mesh (Bard/Davol Inc.)	PP	105	Bard

Yellow = Lightweight Mesh; Blue = Medium Weight Mesh; Red = Heavy Weight Mesh

Baseline patient demographics will be obtained at initial patient recruitment. Standard baseline AHSQC questionnaires will be completed following patient recruitment for baseline comparison. Operative details will be collected and stored in the AHSQC database. Patient follow-up visits will occur at 4 weeks (± 2 weeks) and 12 months (± 2 months) postoperatively. Follow-up

at 4 weeks (±2 weeks) and 12 months (±2 months) will occur either in person or using Cleveland Clinic platform for virtual visits. In the instances where a subject cannot attend to their 1-year follow-up visit in person or through a virtual visit, information will be collected through a telephone contact. Pain intensity at different time points will be assessed using the NIH PROMIS Pain Intensity 3A scale, which is collected for all patients entered into the AHSQC. Patient quality of life and functional mobility will be assessed using the Hernia Quality of Life (HerQLes), which is also collected as standard for all patients entered into the AHSQC. Patients will be required to complete these forms at each clinic visit to allow for monitoring of postoperative progression and overall effect of heavyweight versus medium weight mesh on patient quality of life. Hernia recurrence will be assessed using the Ventral Hernia Recurrence Inventory, a validated questionnaire that can be performed either in person or via email or phone correspondence.[8] At the time of the one month and one-year follow-up clinic visits, a routine physical examination will be performed on all patients. Confirmation of a recurrent hernia will occur if the patient reports recurrence of a bulge or hernia at the site of previous repair during the Ventral Hernia Recurrence Inventory questionnaire. If the surgeon's physical examination does not correlate with the patient-report hernia recurrence, an ultrasound or computed tomography scan will be ordered based on the usual practice of the surgeon. At the completion of the study protocol, patients will be informed as to the type of mesh that was used during the surgical operation. An additional question ("Do you feel your mesh?") will be asked to the subjects during the 1-year follow-up contact and this information will be stored in REDCap.

OUTCOMES TO BE INVESTIGATED

Each outcome to be investigated is based on the specific aims of the study and are listed below:

Specific Aim #1: To determine if the use of a medium weight material leads to a decrease in pain intensity at one year following surgery. This will be assessed with the use of the NIH PROMIS 3a Pain Scale. The change in scaled score one year after operation will be calculated by comparison to the scaled score obtained at baseline for each patient. The mean change at one year will be compared for each group (heavyweight mesh and medium weight mesh).

Specific Aim #2: *To determine if there is a difference in ventral hernia recurrence at one year following surgery.* Hernia recurrence will be determined using the Ventral Hernia Recurrence Inventory, a validated questionnaire using patient-reported outcomes to determine hernia recurrence after repair.[8]

Specific Aim #3: To determine if there is a difference in the rate of deep surgical site infection at 30-days following surgery between the two mesh types. Definitions of wound events are per the Centers for Disease Control and were agreed upon by all participating surgeons. These wound outcomes will be recorded in the AHSQC database at 30 days as follows:

Deep Incisional SSI

A **deep incisional SSI** must meet the following criteria:

Infection occurs within 30 days after the operative procedure AND the infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision AND patient has at least ONE of the following:

a. purulent drainage from the deep incision but not from the organ/space component of the surgical site

b. a deep incision spontaneously dehisces or is deliberately opened by a surgeon AND is culture-positive or not cultured AND the patient has at least one of the following signs or symptoms: fever (>38°C), or localized pain, or tenderness. A culture-negative finding does not meet this criterion.

c. an abscess or other evidence of infection involving the deep incision is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

d. diagnosis of a deep incisional SSI by a surgeon or attending physician.

NOTE:

a. Classify an infection that involves both superficial and deep incision sites as a deep incisional SSI.
b. Classify infection that involves superficial incisional, deep incisional, and organ/space sites as deep incisional SSI. This is considered a complication of the incision.

Specific Aim #4: To determine if there is a difference in the quality of life between the two groups at one year following surgery. Quality of life will be measured using the Hernia-Related Quality of Life Survey (HerQLes).

SURGICAL PROCEDURE

The surgical approach to repairing these defects will be standardized, as previously described. Skin preparation, hair removal, and perioperative antibiotics will be based on SCIP protocol. The midline fascia will be opened and complete adhesiolysis performed to free up the entire abdominal wall. All concomitant procedures will be performed prior to beginning the

abdominal wall reconstructive phase and documented. Intraoperative concomitant procedures will be allowed unless they change the wound classification to CDC Class 2, 3, or 4. An acceptable concomitant procedures is removing uninfected mesh. Other routine concomitant procedures, such as bowel resection or creation of a stoma, are not acceptable as these will change the wound classification. The abdominal wall is reconstructed by initially incising the posterior rectus sheath just lateral to the linea alba. The release is performed at least five centimeters above and below the fascial defect. The posterior rectus sheath is then separated off the rectus muscle to the linea semilunaris. If additional release is necessary to achieve fascial closure, the transversus abdominis muscle or the external oblique muscle may be released at the discretion of the surgeon and documented. The posterior components are then reapproximated, which can occur with the aid of biologic or Vicryl mesh, to exclude the abdominal viscera from the mesh. If the mesh cannot be placed in the retromuscular position, then the patient will be excluded from the study. Final wound classification will occur just prior to mesh placement per CDC criteria.

The allocation of the patient to either a heavyweight or medium weight mesh will be performed in the operating room based on final CDC wound classification after the posterior components are reapproximated. Randomization will be performed according to a computer-generated block randomization scheme at each participating institution. The corresponding prosthetic material will then be placed with at least 5 cm of fascial coverage on all sides of the defect. The mesh will be fixed with mechanical sutures. Drains will be placed above the mesh, when utilized, and the timing of removal will be based on the surgeon's standard practice. Skin must be closed with either suture or staples. Fascial closure and management of the wound dressings will occur based on the surgeon's standard practice.

ANTICIPATED TIME FRAME

Estimated patient accrual time is one year with data collection to occur over one year from the last enrolled patient. Data analysis and manuscript production will occur within six months of completion of data collection.

PATIENT RISKS AND DISCOMFORTS

As with any surgical procedure, there are some associated risks and they will be discussed in a separate surgical consent form. The subjects may experience some pain, bleeding and discomfort; however this is with any surgical operation. Common occurrences following hernia repair include seroma or hematoma around the hernia repair, inflammation, opening of the wound, or infection. Subjects may also experience additional therapies or treatments, including the removal of the mesh to treat any of these events.

PATIENT BENEFITS

There are no direct benefits to subjects for participating in this study. Subject participation will help us better understand the long-term outcomes of heavyweight and mediumweight mesh with respect to patient quality of life and hernia recurrence.

COSTS TO THE SUBJECTS

There are no extra costs to the subjects associated with the research. Procedures related to the preoperative evaluation and the hernia surgery are considered standard of care and will be the responsibility of the subject and the subject's insurance company.

ALTERNATIVES TO PARTICIPATION

Patients are under no obligation to participate in this study. A member of the research will discuss all available surgical options to the patients. Declining to participate in this study will not impact any patient's ability to receive care or to undergo ventral hernia repair at the Cleveland Clinic Foundation.

PAYMENTS TO THE SUBJECTS

There are no extra costs to the subjects associated with the research.

PLAN FOR OBTAINING INFORMED CONSENT

For each subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator, surgeon co-investigator, or one of the approved study coordinators must explain orally and in writing the nature, duration, and purpose of the study in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. The subjects will be informed that they may withdraw from the study at any time. Subjects will receive all information that is required by federal regulations.

After a potential study patient is identified, the investigator or the study coordinator listed in this protocol as a person who will obtain consent will be responsible for instituting the informed consent process in a face-to-face manner. Before starting any study procedures, the investigator will discuss the proposed research study in detail with the potential subject during the office visit to discuss treatment options. The subject will be allowed ample time to read and review

the informed consent document, and ask questions. The informed consent document will be reviewed with the subject in depth by the participating investigator or designated member of the research team to ensure that the potential participant has a good understanding of the study protocol, what is required of the study participants, the potential risks and benefits of study participation, and his or her rights as a study participant. The investigators will be available by phone or office visit to answer any questions that the participant may have. After consideration, the subject may return if necessary for another visit with the investigator to discuss the study, ask questions, and sign the informed consent document to participate in this study.

After the subject has read and reviewed the informed consent document and has agreed to participate, he/she will be asked to sign and date the document. The study member obtaining consent will also sign and date the form, and documentation of the informed consent process will be included in the research file (i.e., the person who obtained consent, where and when consent was obtained, and who was present during the process). A copy of the consent form will be given to the subject for their records.

PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS

The population to be studied includes adults 18 years of age or over, so children are therefore excluded. Decisionally-impaired and cognitively-impaired persons will not be approached to participate in this study as we are seeking subjects who have the capacity to understand and actively consent to the procedure independently. Pregnant women will be excluded from participating in this study.

Staff and employees at the participating institutions are considered a part of the vulnerable population. Staff and employees may be eligible to participate in this study. Since

subjects may or may not benefit from this study, we do not want to exclude this population. If an employee is a potential candidate for this study, the subject will be informed during the consent process that his/her participation or refusal to participate will in no way influence grades, employment, or subsequent recommendations. Every effort will be made to prevent coercion during this initial process and throughout study participation. According to IRB policy, students and house staff cannot be asked to participate in research conducted while under the direct supervision of the investigator, so those subjects will not be enrolled.

In those instances where potential participants cannot read the consent form because they do not speak English, we will work with the IRB to develop a language-appropriate consent form. In addition, a qualified translator will be present to assist with obtaining the informed consent of the participant and throughout the duration of the patient's participation in the study.

In addition, in the unusual situation where a subject cannot read a consent form due to illiteracy or blindness, a member of the research study staff will read and explain the consent form to the participant or to the participant's legally authorized representative. A witness, who will sign and date the consent form, must also be present during this oral presentation.

SUBJECT PRIVACY AND DATA CONFIDENTIALITY

Anonymity and confidentiality of subjects participating in this study will be maintained. The only potential identifiers on any study documents submitted to the sponsor or designee will be subject study numbers, dates of birth, and dates of procedures. Every effort will be made to maintain the confidentiality of documents that identify the subject by name (e.g., signed informed consent documents, clinic charts), except to the extent necessary to allow monitoring by the Office of Research Compliance at the Cleveland Clinic or other regulatory authorities.

All information collected, such as name or medical record number, will be stored in the AHSQC database. Randomization will occur with the use of a customized Research Electronic Data Capture (REDCap®) database program. This is in a secure network/firewall protected electronic database to which only the investigator and the designated members of the study team will have access using an individual assigned login and password. Only approved study members listed on the IRB protocol will have access to the separately-stored master list. Only the Principal Investigator, Lead Research Coordinators, and Biostatisticians will be granted access to retrieve patient data for routine data quality assessments and data analyses. All electronic records pertaining to the clinical study will be password-protected, and only approved study members listed on the IRB protocol will have password access.

Any information about the subject will be stored in the AHSQC, a secure database that is used at our institution to track clinical outcomes in patients who undergo hernia repair.

POWER CALCULATION

The primary outcome measure of this study is the change in NIH PROMIS Pain Intensity Scale 3a scaled score one year after operation. The mean scaled score change at one year will be compared for each group (heavy weight mesh versus medium weight mesh). Patient reported outcomes within the AHSQC were evaluated for patients undergoing ventral hernia repair from July 2013 through August 2016. Twenty-three patients met criteria for medium weight mesh as defined in Table 1 and six patients meeting criteria for heavy weight mesh. Scaled score changes at one year after operation are summarized as below:

	Size	Mean	SD	Min	Lower Quartile	Median	Upper Quartile	Max
Medium weight (Group 1)	23	-10.3	10.9	30.7	41.9	46.3	53.3	71.8
Heavy weight (Group 2)	6	-7.5	6.3	30.7	41.7	47.8	53.2	54.5

Using a two sample t-test allowing for unequal variance with equal sample sizes (1:1) group allocation of medium weight and heavyweight mesh, 160 patients per group will achieve a target power of 80% given an alpha of 0.05. Assuming a 10% loss to follow up at 1 year, a total of 352 patients will be recruited for this study (176 patients in each group).

STATISTICAL ANALYSIS

Categorical variables will be examined using Pearson's Chi-Square and all continuous variables will be examined using the non-parametric Wilcoxon signed rank test. The categorical variables will be reported using proportions and continuous variables will be reported using the median and the interquartile range.

Specific Aim 1: The Wilcoxon signed rank test will be performed to determine if the change from baseline to one-year follow-up is statistically significantly different between the medium weight and heavyweight mesh groups.

Specific Aim 2: The proportion of patients in each group reporting a hernia recurrence will be examined using Pearson's Chi-Square test to determine if there is a difference between the groups.

Specific Aim 3: The counts of the surgical site infections will be compared using Pearson's Chi-Square test to determine if an association exists between either type of mesh and frequency of SSI.

Specific Aim 4: The change in the HerQLes will be examined using the Wilcoxon signed rank test to determine if there is a difference in the quality of life after hernia repair for patients receiving medium weight vs heavyweight mesh.

DATA SAFETY MONITORING BOARD

A data safety monitoring board will oversee the progress of this trial. This board will be comprised of surgeons and statisticians from the Cleveland Clinic Foundation. This group of individuals will meet at regular intervals to monitor the safety and progression of this trial.

CLINICAL SIGNIFICANCE/INNOVATION

The use of prosthetic reinforcement during ventral hernia repair is well accepted. Both arms evaluated in this study represent standard of care for retromuscular ventral hernia repair. Nevertheless, previous studies have concluded that the use of heavyweight mesh does not lead to a protective benefit with regards to long-term hernia recurrence at the cost of chronic pain and/or impaired quality of life.[3] In a recent study by Burgmans et al investigating the use of heavyweight versus medium weight mesh during inguinal hernia repair, there was no statistically significant difference in chronic pain between the two types of meshes but there was a significant advantage in terms of hernia recurrence for those patients that underwent inguinal hernia repair with heavyweight mesh.[9] As previous studies looking at the same outcomes in ventral hernia repair are > 10 years old and several advances in the world of hernia surgery have occurred during this time period, we think that this is a valuable question that warrants re-addressing.

As previously mentioned, this trial will be the first registry-based prospective study performed in the hernia disease space. Registry-based clinical trials have been recently proposed as a way to achieve the scientific power of a RCT while minimizing the cumbersome nature often associated with running such a trial. In effect, the registry-based trial allows for faster accrual of

patients and secure data storage with a reduced financial burden.[6] As this is the first trial of its kind in the field of hernia surgery, we hope this trial will help to determine the feasibility and quality of registry-based trials within this field of surgery.

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