Tissue Reinforcement of Incisional Closure Among High Risk Patients

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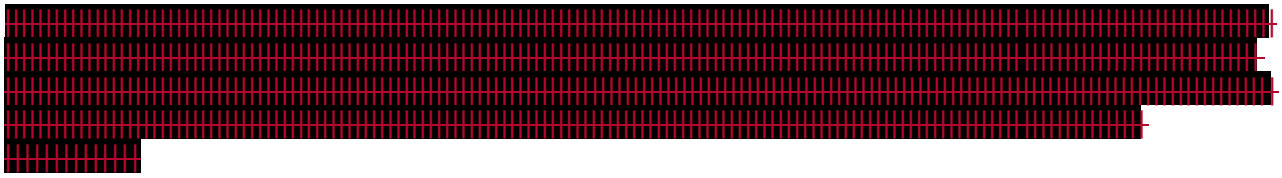

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Background

One-third of all individuals will undergo abdominal surgery in their lifetime. [1,2] Following abdominal surgery, 30% of patients will suffer a major chronic complication with their wound closure in the first post-operative year. This may include significant wound infections, open wounds, fluid collections, fascial dehiscence, or incisional hernia. These complications not only have a substantial impact on the health care system (cost and chronic disease) and the hospital (cost and space), but most importantly have a substantial impact on the patient. Major chronic wound complications adversely impact patient quality of life and function. [3-6]

Patients at greatest risk for major wound complications include comorbid patients such those who are overweight or obese, currently smoke or have COPD, are immunosuppressed, are malnourished, or who have evidence of contamination (wound classes 2-4). Among these patients, the risk of developing a major wound complication ranges from 30%-80%. [1,2,7,8,9]

Potential methods to reduce major wound complications include utilizing specific suturing techniques or reinforcing the incision line. Suturing technique of small-bites (0.5x0.5 cm bites) as opposed to large bites (1.0x1.0 cm bites) has been shown to be efficacious in European populations with a typical body mass index of 20-25 kg/m2. [10-12] Tissue reinforcement has been shown to decrease rates of major wound complications in small randomized controlled trials. [13-18]

However, the lack of widespread adoption of these practices may be due to issues of generalizability including strict inclusion criteria, careful patient selection, and small study size. For example, the generalizability of small bites to an overweight population (mean BMI in the United States is 28 kg/m2) as opposed to a normal-weight population are unclear. [10-12] The use of synthetic materials in comorbid patients or complex settings may risk major wound complications such as prosthetic infection. Biologic materials have been shown to be effective in decreasing major wound complications but in different settings. [13-19]

Specific Aims

Assess the effectiveness of different efficacious strategies to decrease the rate of major wound complications following abdominal surgery among high-risk individuals.

Hypotheses

1. Among high-risk patients undergoing abdominal surgery, the use of “small-bites” closure as opposed to “large-bites” closure will increase the proportion of patients who are free of major, chronic wound complications at 1-year post-operative.
2. Among high-risk patients undergoing abdominal surgery, the biologic tissue reinforcement of the suture line as opposed to no reinforcement will increase the proportion of patients who are free of major, chronic wound complications at 1-year post-operative.

Methods

This is a single-institution, 2x2 factorial randomized controlled trial assessing the effectiveness of known efficacious treatments (“small-bites” and tissue reinforcement) among high-risk patients undergoing midline laparotomy or laparoscopic-assisted surgery. [19] Laparoscopic-assisted abdominal surgery is defined as any surgery requiring an open incision in addition to laparoscopy to insert a hand (hand-assisted laparoscopy) or specimen extraction site ≥3 cm in

length. This length is chosen because any smaller incision will likely be closed with interrupted sutures rather than running sutures.

Table 1: 2x2 Factorial Design for Prevention of Major, Chronic Wound Complication [19]

		Randomization 1	
		Small-Bites	***(Current Care) Large-Bites***
Randomization 2	***Mesh***	Small-Bites Mesh	Large-Bites Mesh
	(Current Care) No Mesh	Small-Bites No Mesh	Large-Bites No Mesh

A 2x2 factorial trial design is utilized because it is more efficient (can assess two interventions simultaneously) and mimics real-world practice (e.g. adoption bundle therapies, adoption of multi-faceted interventions). In addition, the 2x2 factorial design remains novel, particularly among surgical literature that can improve profile of studies performed with this approach.

Inclusion criteria will include all high-risk patients undergoing laparotomy or laparoscopic-assisted abdominal surgery. High-risk patients will include (1) all overweight patients, (2) current smokers, (3) those who are immunosuppressed, (4) those who are malnourished, or (5) those who are undergoing a contaminated case. Overweight is defined as BMI ≥25 kg/m2. Current smoker is any patient who routinely smokes within the past month. Immunosuppressed is any patient who has or will receive immunosuppressive medications or drugs within 3 months of surgery. Malnourished is defined as albumin <3.5g/dL. Contamination is defined as Center for Disease Control wound classification 2 or 3. [20]

Exclusion criteria include (1) patients unlikely to follow-up in a year (e.g. no phone or lives out of state), (2) patients unlikely to survive more than 2 years based upon surgeon judgment (e.g. metastatic cancer, end-stage cirrhosis), (3) patients where the clinician would not place prosthetic (e.g. pregnant patient, pediatric patient during growth stage), (4) patients on full anticoagulation treatment or (54) patient has a planned second surgery within the next year (e.g. ostomy reversal).

Current care for wound closure includes a 1x1 cm closure using a slowly absorbable, running suture (0 polydioxanone). Surveys among surgeons have identified that the vast majority of United States surgeons and surgeons at our institution perform abdominal closure in this technique. “Small-bites” will be performed using a 0.5x0.5 cm closure using a slowly absorbable running suture (2-0 polydioxanone). Mesh placed will be a biologic mesh, (porcine acellular dermal matrix) and will be fenestrated with a scalpel. Preperitoneal space will be chosen for all midline incisions where preperitoneal space can be safely and easily developed (open, lower midline incisions). Underlay will be chosen for all off midline (e.g. stoma site incision) where laparoscopic fixation will be more efficient.

Primary outcome will be proportion of patients at one year with a major chronic wound complication. Major chronic wound complications will include any persistent wound or infection at 1-year post-operative, fascial dehiscence, or fascial defect. Persistent wound or infection will include any enterocutaneous fistula, open wound, or symptomatic fluid collection. Fascial dehiscence or fascial defect will be defined as any defect noted on clinical assessment. Clinical assessment is clinical examination and demand-driven CT scan ordered based upon signs or symptoms including patient complaint of pain, bulge by patient report or physical exam, or wound complication. This represents current practice.[21] In addition, all patients will undergo

an ultrasound performed by a trained clinician to assess for any chronic, major wound complications at one year post-operative. Patients will also be followed for up to three years post-operative.

Secondary outcomes will include any Dindo-Clavien complications, surgical site infections, reoperations, operative duration, patient centered outcomes, surgeon perceptions, and cost analyses. Dindo-Clavien and surgical site infections have been defined.[20,22] Reoperation will be defined as any unplanned invasive procedure involving the fascia, mesh, or peritoneal cavity. Patient centered outcome based upon the modified Activities Assessment Scale and Euroqol-5D will be measured at 1 year and 3 years. Surgeon perceptions will include Likert type and open-ended questions assessing perception, barriers, and likelihood of utilizing the interventions outside of the trial. Cost will be calculated from the hospital's perspective by assessing charges for all patient visits, admissions, and procedures. These charges will be adjusted utilizing department-specific cost-to-charge ratios (CCR). The CCR are the ratios at the cost center level that hospitals are required to submit to Centers for Medicare and Medicaid Services annually (under the hospital's annual Medicare cost report). This will allow charges to be converted to cost by applying these CCRs to charges. Following state-of-the-art guidelines, cost will be discounted at an annual rate of 3%. The robustness of the results will be assessed by performing sensitivity analyses of plausible ranges for the project parameters and probabilistic sensitivity analysis. Follow-up schedule is provided in Table 2.

Table 2: Follow-up Schedule

Timing	Level of Care	Assessments	Reimbursements
1 month	Routine care	Routine care Clinical exam Assessing: Hernia (clinical) Dindo-clavien complications Surgical site infections Patient centered outcomes (modified Activities Assessment Scale and Euroqol-5D	$0
1 year	Research follow-up	Clinical exam Assessing: Hernia (clinical and ultrasound) Dindo-clavien complications Patient centered outcomes (modified Activities Assessment Scale and Euroqol-5D	$10 gift card $10 parking
3 years	Research follow-up	Clinical exam Assessing: Hernia (clinical and ultrasound) Dindo-clavien complications Patient centered outcomes (modified Activities Assessment Scale and Euroqol-5D	$20 gift card $10 parking

A trained surgical clinician blinded to the treatment arms will collect outcomes. A blinded outcomes adjudication committee (non-participating members of the Ventral Hernia Outcomes Collaborative) will verify the primary outcome.

A Data Safety Monitoring Board of the Ventral Hernia Outcomes Collaborative will be developed. All major complications (Dindo-Clavien 3-5) including deaths, reoperations, mesh explantations, and enterocutaneous fistulas will be reviewed. No interim analysis will be planned as analysis of the primary outcome will weaken the strength of the results. Safety and stopping points will be determined based upon clinical judgment or greater than 50% rate of major complications.

Enrollment will occur prior to the operation either in the clinic (for elective cases) or on the day of surgery (for urgent or emergent cases). The randomization schema will be variable block randomization with blocks stratified by surgical approach (laparoscopic versus open): this is chosen not because there is belief that there will be a difference in outcomes, but because it is a different surgical approach and should be balanced. Allocation will occur at the time of abdominal closure by phone call to the study office.
Statistical analysis

Based upon prior studies, it is estimated that the risk of a major, chronic wound complication in this population is at least 30% while either intervention would result in a decrease in relative risk by 30% (i.e. absolute risk reduction from 30% to 20%). The risk of complication at 1 year is the same with open or laparoscopic assisted surgery as shown in multiple prior studies. [1,2,26] Assuming an alpha of 0.05, beta of 0.20, and a dropout rate of 20%, a total of ~~192~~ 300 patients would need to be enrolled and 154 patients randomized. Based upon our current surgical volume of nearly 6000 general surgical procedures performed each year and our track record of enrolling over 400 surgical patients in the past year for three other trials, we anticipate completing enrollment within one year. To encourage patient follow-up, all patients will be provided with up to a $10 gift card at the one-year follow-up and $20 at the three-year follow-up along with payments for their parking ($10) at both one- and three-year visits. [23]

The primary outcome will be assessed as a categorical variable using a chi square test. In addition, analysis will be performed using a Cochran-Mantel-Haenszel method as well as a multivariate regression analysis accounting for the 2 randomizations and the stratification. Secondary outcomes will be assessed either chi-square or Kruskal-Wallis test.
Based upon traditional Frequentist assessment, if the effect size does not achieve “statistical significance” the conclusions risk being reported as a false negative. To address this potential risk, a more real-world, realistic analysis will be performed using a Bayesian analysis will also be performed. [24,25] The Bayesian models will take the same form as the Frequentist models and include the same covariates. Posterior point estimates, credible intervals, and probability of increase in proportion of patients without hernias or complications will be calculated. Similar models will be used for secondary outcomes. If interactions or modifiers are identified, then this study will be underpowered and should be considered a pilot study to appropriately power future multi-center randomized controlled trials.

Cost will be calculated by assessing charges for all patient visits, admissions, and procedures. These charges will be adjusted utilizing department-specific cost-to-charge ratio (CCR). The CCR are the ratios at the cost center level that hospitals are required to submit to Centers for Medicare and Medicaid Services annually (under the hospital’s annual Medicare cost report). This will allow charges to be converted to cost by applying these CCRs to charges. Following state-of-the-art guidelines, cost will be discounted at an annual rate of 3% for charges over 1 year. The robustness of the results will be assessed by performing sensitivity analyses of plausible ranges for the project parameters and probabilistic sensitivity analysis.

Feasibility and Significance

Our group has performed three prospective trials (2 randomized trial and one non-randomized trials), have completed enrollment for 2, and am on track to complete enrollment for the final study by Mach 2017. We have a strong track record of completing all projects that we have initiated ahead of schedule. This study will provide effectiveness data on the role of small bites

and biologic tissue reinforcement on the impact of patient satisfaction, quality of life, and function.

Budget

This study represents an effectiveness study of current practices and recommendations. At present, multiple societies recommend the use of mesh reinforcement and small-bites as best practices. [26] In addition, CMS has established a Current Procedural Code for tissue reinforcement for these cases.

The costs above our group's current practice are (1) ultrasounds performed at 1-year and (2) mesh. The department of surgery owns an ultrasound and the outcomes assessors will be trained on ultrasound of the abdominal wall course with the American College of Surgeons. [27] These cost of mesh have been offset by an investigator-initiated grant (all meshes will be donated by a biologic mesh company). The concerns for conflict of interest will be curbed by (1) the study will be overseen and performed by individuals with no direct benefit from this grant; an individual blinded to the allocations will assess the outcomes that also will receive no direct benefit from this grant.

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