RINSE Study Protocol

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Title: Reducing INfection at the Surgical SitE with Antibiotic Irrigation during Ventral Hernia Repair (RINSE Trial)

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Abstract:
Surgical site infection (SSI) is common after open ventral hernia repair. Numerous factors contribute, including patient comorbidities, operative technique, and degree of contamination of the case. SSI often requires prolonged hospital length of stay (LOS), readmission, or other procedural intervention. One potential intervention to reduce SSI is the use of antibiotic irrigation, which has been shown to reduce SSI in colorectal surgery in a recent randomized control trial. We retrospectively evaluated our use of dual antibiotic irrigation at the time of mesh placement during open ventral hernia repair (OVHR), demonstrating a significant reduction in SSI (16.5 vs 5.4%) using a combination of gentamicin and clindamycin irrigation when compared to saline alone.

We plan to complete a registry-based, randomized clinical trial (RCT) through the Americas Hernia Society Quality Collaborative (AHSQC) to further assess the impact of dual antibiotic irrigation on SSI after OVHR with mesh. This will include patients undergoing open retromuscular (RM) repair with or without transversus abdominis myofascial advancement flap (TAR) with placement of permanent synthetic mesh (mid-weight, large-pore polypropylene). Power analysis based on only this subset of patients from our initial study indicates a total of 210 patients are needed to demonstrate a significant reduction in SSI using antibiotic irrigation vs saline irrigation alone.

Background and Significance:
Surgical site infections (SSI) are common complications following open ventral hernia repair (OVHR), occurring in 10-60% of cases (1). The frequency of SSIs varies greatly based on operative approach, patient co-morbidities, hernia characteristics, and degree of contamination. This may result in readmission, increased hospital length of stay (LOS), procedural or operative interventions for infection management, or mesh removal, all of which lead to significant patient morbidity and health care spending. With over 350,000 ventral hernias repaired annually, reducing the incidence of SSI could have a substantial impact on patients and health systems (1, 2). Preoperative patient optimization, including preoperative weight loss, smoking cessation, and adequate glucose control, are widely regarded as important in minimizing the risk of SSI. Minimally invasive hernia repair also significantly reduces the risk of SSI, but not all patients are candidates for this approach.

Interventions performed at the time of surgery, or in selection of materials used for repair are less understood. Antimicrobial mesh has shown enhanced bacterial clearance in laboratory testing, but little

clinical data exists (3-6). Other experimental studies have evaluated pre-soaking or dipping mesh in antibiotic solution prior to implantation, but again, clinical data is lacking (7, 8). Antibiotic irrigation of the peritoneal cavity was recently shown to have a significant impact on development of SSI in a randomized control trial in colorectal surgery. Ruiz-Tovar et al randomized 103 patients to intraperitoneal lavage with saline versus clindamycin + gentamicin lavage, demonstrating a significant reduction in postoperative SSI from 14% to 4% (9). Historically, we have used simple saline irrigation or gentamicin irrigation alone. We adopted the use of clindamycin + gentamicin soon after this report. Our initial retrospective analysis of this protocol demonstrates significant benefit of dual-antibiotic irrigation at the time of mesh placement in OVHR. We aim to more thoroughly evaluate this outcome with a prospective randomized trial.

Preliminary Data:

We recently published a retrospective evaluation of the impact of antibiotic irrigation at the time of OVHR at our institution. Irrigation with dual-antibiotic solution was performed just after mesh placement using 600 mg clindamycin + 240 mg gentamicin in 500 ml saline and was left to stand for a total of three minutes as described by Ruiz-Tovar. We analyzed 825 patients undergoing open ventral hernia repair with mesh who received either no antibiotic irrigation (Group 1, n=260), gentamicin irrigation (Group 2, n=266), or dual antibiotic irrigation with gentamicin + clincamycin (Group 3, n=299). Group 3 contained fewer smokers and patients with chronic obstructive pulmonary disease (COPD), but a significantly higher proportion of patients with clean-contaminated, contaminated, or dirty cases. Other patient characteristics were similar. Retromuscular (RM) repair with or without transversus abdominis release (TAR) was performed in 73.2% (n=624), preperitoneal repair in 21.2% (n=181), onlay in 5.1% (n=43) and intraperitoneal in 0.5% (n=4). Permanent synthetic mesh was placed in 84.7% of cases, barrier coated permanent synthetic in 5.5%, absorbable synthetic in 6.0%, and biologic in 3.8%. Hernias in Group 3 were larger, with the highest percentage RM and RM+TAR repairs.

Analysis of our primary endpoint demonstrated a significant reduction in the incidence of SSI in patients receiving both gentamicin + clindamycin irrigation. Only 5.02% of patients in Group 3 developed an SSI, compared to 16.54% in Group 1 and 15.41% in Group 2 ($p<0.001$). Distribution of infection between superficial, deep, and organ space was similar across groups. There was also a significant reduction in SSO in with dual antibiotic irrigation, occurring in 19.06% of patients in Group 3, 35.71% of patients in Group 2, and 28.08% of patients in Group 1 ($p<0.001$). The majority of these were simple seromas or serous wound drainage, followed by cellulitis, skin separation without infection, and hematoma. Rate of SSO/I requiring procedural intervention was significantly higher in Groups 1 & 2 (16.54% & 21.43%) than Group 3 (2.68%; $p<0.001$). No difference was seen in LOS or incidence of readmission between groups. Table 3 summarizes primary and secondary outcomes. Multivariate analysis demonstrated that COPD (OR 3.70; 95% CI 2.4-6.93), contaminated wound (OR 2.96; 95% CI 1.97-8.17), and dirty wounds (OR 3.84; 95% CI 2.93-13.37) were all significant predictors of SSI. Use of dual antibiotic irrigation significantly reduced the risk of SSI (OR 0.33; 95% CI 0.14-0.58).

Subgroup analysis of patients undergoing RM repair +/- TAR with permanent synthetic mesh in CDC class 1,2 or 3 wounds only demonstrated similar benefits and serve as the basis for this trial. In this subgroup comparing only dual antibiotic irrigation (n=224) to saline alone (n=111), antibiotic irrigation reduced the rate of SSI in clean (10 vs 3.33%), clean-contaminated (16.67 vs 4%), and contaminated (40 vs 7.41%) cases.

		No Irrigation	Gentamycin	Gentamycin/Clindamycin	*P*-value
Primary outcomes					
SSI		43 (16.54)	40 (15.21)	16 (5.35)	<0.001*
	Superficial	28 (10.77)	19 (7.22)	12 (4.01)	0.102
	Deep	9 (3.46)	16 (6.08)	2 (0.67)	0.056
	Organ space	6 (2.31)	5 (1.9)	2 (0.67)	1
SSO		73 (28.08)	93 (35.36)	59 (19.73)	<0.001*
Secondary outcomes					
LOS, Median (interquartile range)		3 (0, 6)	4 (3, 7)	4 (3, 6)	<0.001*
Readmission		22 (8.46)	25 (9.51)	22 (7.36)	0.506
Reoperation		43 (16.54)	57 (21.67)	8 (2.68)	<0.001*

* Statistically significant finding.

	Odds Ratio	95% Confidence Interval
Intercept	0.1602	(0.0062, 1.7214)
Patient factors		
Age	0.9848	(0.9646, 1.0057)
Female	0.9453	(0.5741, 1.5642)
BMI	1.0154	(0.9841, 1.0477)
Active smoker	1.0345	(0.5927, 1.776)
DM	1.3418	(0.7617, 2.3324)
Hypertension	1.4189	(0.8179, 2.4763)
COPD	3.6999*	(2.1556, 6.3768)
ASA 1	Reference	
ASA 2	0.4398	(0.0707, 8.5997)
ASA 3	0.5871	(0.0925, 11.5701)
ASA 4	2.3261	(0.2543, 53.5323)
Wound classification		
Clean	Reference	
Clean-contaminated	1.3257	(0.6892, 2.5037)
Contaminated	2.9577*	(1.3886, 6.2113)
Dirty	3.842*	(1.4876, 9.6897)
Technique		
Retromuscular	Reference	
Onlay	1.781	(0.5802, 4.8802)
PP	0.4499*	(0.1986, 0.9564)
RM + TAR	1.2652	(0.7219, 2.2072)
Mesh type		
PS	Reference	
BC PS	1.5185	(0.4988, 4.0667)
AS	2.0647	(0.8929, 4.6683)
Biologic	1.7752	(0.6299, 4.8243)
Intervention		
No irrigation	Reference	
Gentamicin alone	1.0515	(0.6059, 1.833)
G + C	0.3298*	(0.1558, 0.6734)

* Statistically significant finding.

Important limitations of our initial data include selection bias, variation in mesh choice and surgical technique, and its retrospective nature. To address these limitations and evaluate the true impact of dual antibiotic irrigation at the time of mesh placement during open RM OVHR, we propose a registry based, RCT.

Purpose:
Evaluate the impact of dual antibiotic irrigation at the time of mesh implantation during open VHR.

Hypothesis:
Use of dual antibiotic irrigation at the time of synthetic mesh placement during open retromuscular ventral hernia repair reduces the incidence of surgical site infection.

Study Design:
The study design would be a registry-based RCT through the AHSQC to evaluate the effect of dual antibiotic irrigation at the time of mesh placement during open RM +/-TAR OVHR. Registry-based trials gather information from a pre-existing database to increase the effectiveness of carrying out RCT's (10). A power analysis was performed to determine the needed sample size. For this purpose, dirty (CDC wound class 4) patients were excluded (n=51 patients), as SSI rate in this group was significantly higher

across groups, and the presence of active infection more likely impacts the operative intervention, technique, and mesh choice. We included only patients receiving permanent synthetic mesh in a retromuscular fashion, with or without TAR. This left 224 patients in the antibiotic irrigation group compared to 111 in the saline only irrigation with a difference in SSI of 16.22 vs 4.46%. To detect this reduction in SSI with 80% power, a total of 210 patients are needed (105 in each arm). To account for 20% patient withdrawal or failure to complete 90 day follow-up, we plan to enroll a total of 250 patients (125 in each arm).

Inclusion Criteria:

Age >18 y/o.
Elective, open ventral hernia repair in a retromuscular fashion, with or without TAR.
Clean, clean-contaminated, or contaminated wounds.

Exclusion Criteria:

Age <18 y/o.
Pregnancy.
Emergency hernia repair.
Laparoscopic, robotic, or hybrid approach.
Dirty wounds.
Use of biologic or absorbable synthetic mesh.
Onlay, intraperitoneal or preperitoneal mesh placement.

In order to achieve enrollment targets and increase the generalizability of the results, data collection will be via the AHSQC, a multicenter, national, hernia-specific registry. The AHSQC includes independently audited data, surgeon entered, at each site. Data is gathered prospectively during routine care for the purpose of quality improvement, and the registry also has the capability to host embedded clinical trials. All patient demographics, operative details and outcomes data will be collected prospectively from participating surgeons and entered into the AHSQC. Randomization will be performed using the Research Electronic Data Capture (Redcap) randomization module. To avoid potential variance of wound classification between groups, a stratified contaminated cases in each group. The irrigation used will be the only clinical data point collected outside of that already documented in the AHSQC. There will be a total of 8 sites participating in this study, including Greenville Health System, Washington University, Cleveland Clinic, Pennsylvania State University, Oregon Health and Science University, Ohio State University, New Hanover Regional Medical Center, and University of Pennsylvania.

Surgical Technique:

All patients included will undergo an open RM VHR +/-TAR. Preoperative intravenous antibiotics should be administered according to local protocol. A midline or other appropriate laparotomy incision will be made. Any indicated adhesiolysis will be performed, along with any concurrent procedures. Retromuscular dissection will then proceed in standard fashion, separating the posterior rectus sheath away from the rectus abdominis muscle laterally to the linea semilunaris. If indicated, additional transversus abdominis myofascial release may be performed on one or both sides. Additional subcutaneous dissection and/or external oblique myofascial release may be used if deemed necessary by the operating surgeon. All patients will receive a mid-weight, large-pore, monofilament polypropylene mesh. Acceptable meshes include Prolene soft (Ethicon / Johnson & Johnson), Bard Soft (Bard-Davol, Inc), Parietene (Medtronic), or Vitamesh (Aran Biomedical). Mesh fixation is at the discretion of the operating surgeon. After mesh is placed, randomization will occur (see below). Drain placement is at the discretion of the operating surgeon. Anterior fascia will then be closed over the mesh to complete the repair. Skin closure is at the discretion of the surgeon.

Randomization:
Randomization will occur at the time of mesh placement intraoperatively. Redcap will be used to create tables to randomly assign patients to either saline irrigation alone (Group 1 – control) or dual antibiotic irrigation (Group 2 – study).

Irrigation Protocol:
Group 1 (control): Normal saline is to be placed into the dissected retromuscular space AFTER placement and fixation of mesh. This should fill the cavity completely to the level of the skin. Irrigant is to be left to stand for a total of three minutes and then evacuated. Additional irrigation with saline PRIOR to the randomization is permitted at the surgeons' discretion for hemostasis with no requirement for duration. Additional saline irrigation of the subcutaneous space after fascia closure should be performed prior to skin closure.

Group 2 (study): Antibiotic solution is prepared consisting of 240 mg gentamicin and 600 mg clindamycin in 500 ml saline to ensure proper concentration. This solution should be placed into the dissected retromuscular space AFTER placement and fixation of mesh. This should fill the cavity completely to the level of the skin. Irrigant is to be left to stand for a total of three minutes and then evacuated. Additional irrigation with saline PRIOR to the randomization is permitted at the surgeons' discretion for hemostasis with no requirement for duration. Additional antibiotic irrigation of the subcutaneous space after fascia closure should be performed prior to skin closure. This second irrigation is not timed.

Both of the groups listed above are accepted standard of care practices used by surgeons.

Follow-up:
All patients are required to follow-up 30 days (+/- 15 days) from the time of surgery to determine incidence of surgical site infection. Additional follow-up will occur at 90 days (+/- 30 days) in office or over the phone, with determination of surgical site infection. Additional office visits are at the discretion of the surgeon.

Primary Endpoint:
Incidence of surgical site infection (SSI) at 30 days.

Secondary Endpoint:
Incidence of SSI requiring reoperation or other procedural intervention at 30 days.
Incidence of SSI at 90 days.
Incidence of SSI requiring procedural intervention (SSIPI) at 90 days.
Incidence of SSO at 30 and 90 days.
Incidence of SSO requiring procedural intervention (SSOPI) at 30 and 90 days).
Incidence of readmission.

Data Collection:
AHSQC data collection.
Redcap database will house the study ID number, date of birth, dates of procedures, AHSQC ID number, inclusion/exclusion criteria and randomization module. We will be collecting protected health information (PHI) at each site, which is logged into the AHSQC registry (which all sites already use for patients regardless of study). That data is only available at the local site (i.e. we can see our patients only, not patients at other sites). All data analysis will be done at the AHSQC and no-one will have access to any patient level data. The Redcap data will link to the AHSQC ID, but will not have any other identifying information. All data for this study will be kept confidential.

Potential Risks:
As with any surgical procedure, there are some associated risks that will be described in a separate treatment consent form.

It is possible to have allergic type reactions to the antibiotics used for irrigation. Allergic reactions may range from minor itching or rash to major reactions, even leading to death in rare cases. However, this is not the same as receiving the antibiotics by mouth or through injection in a vein. Most participants with an allergy to the antibiotic taken by mouth or injection will not have a reaction when the antibiotic is placed in the irrigation.

The study records are considered confidential, but absolute confidentiality cannot be guaranteed. This study may result in presentations and publications, but steps will be taken to make sure participants are not identified by name.

Potential Benefits:
It is not possible to know if there will be any potential benefit beyond what is expected for treatment utilizing the standard of care. Study participation will help us better understand if rinsing the abdominal wall and mesh with antibiotic irrigation is any better than irrigating with saline alone in lowering the risk of infection after surgery.

Participant Withdrawal:
Participants may refuse to participate or choose to withdrawal from the study at any time without fear of being penalized or losing benefits. Participants may be withdrawn from the study at any time if it is in the study Physician's judgment that withdrawal is in the participant's best interest, if the participant's medical condition changes or if the participant no longer follows the study instructions.

Informed Consent:
The study doctor will assess each patient for eligibility per the protocol. If eligible, the study doctor will discuss the study and will review the consent form with the patient and their family (as applicable). The study doctor will consent the patient before any study procedures are completed. All communication will take place in a private setting. The patient will be given ample time to read the consent and have all questions answered prior to providing signature. The consent will be signed and dated by all parties and a copy will be provided to the patient at the time of consent. A copy of the consent will also be placed in the patient's medical chart.

Alternatives:
The alternative to participating in this study is simply not to participate. Patients will not be penalized or lose any benefits if they decline participation in this study. This decision will not affect the patient's relationship with his/her doctor or hospital.

Privacy and Confidentiality:
All data for this study will be kept confidential. The AHSQC is a secure quality improvement database with the purpose to better hernia care delivery. Likewise, redcap is a password protected, secure network, and only approved members of the study team will have access to the study in redcap.

Costs:
This study is not expected to yield any additional costs to participants. Participants will not be compensated to participate in this study.

Analysis / Data Safety Monitoring:
A Data Safety Monitoring Board (DSMB) will be established, consisting of a biostatistician and two surgeons who are not participants in the trial. Interim analysis will occur at the midpoint of patient accrual (125 patients). No events are anticipated that would trigger immediate cessation of the trial. If interim analysis demonstrates significantly greater differences in infection than anticipated, the recommendations of the DSMB will be followed.

Data analysis will consist of standard statistical methods. Chi square and Fischer's exact test will be used for comparison of patient and operative characteristics. Analysis of variance will be used to determine differences in continuous variables. Multivariate logistic regression will be used to test the impact of clinically-relevant factors (comorbidities, hernia characteristics, wound class, irrigation).

Potential for Future Study:
While our experience and initial analysis demonstrates a significant impact of a dual antibiotic irrigation, other antibiotic choices or methods of use may have a similar or even greater impact. Many centers commonly use a pulse lavage of 3L saline containing cefazolin, bacitracin, and gentamicin. Variation in dwell time of the antibiotic irrigation could produce different results. The application of antibiotic irrigation to other mesh types may also have a significantly different result.

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