Title: A Randomized Controlled Trial of Prevena™ Incisional Negative Pressure Wound Therapy to Reduce Surgical Site Infection in Re-operative Colorectal Surgery.

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Introduction

Surgical site infections (SSIs) are a common problem and a significant cause of morbidity in surgical patients. They present a substantial burden to the health care system in the United States and contribute more than 1.6 billion dollars in excess cost and 1 million in extra hospital days in affected patients[1]. SSIs are associated with a multitude of complications including an increased risk of incisional hernia and prolonged hospital stay[2]. Despite optimum surgical care there remains an inability to significantly reduce SSI rates following colorectal surgery and this field represents a critical priority for study[3]. When one examines the control arms of recent high quality randomized controlled trials, the SSI rate following colorectal surgery ranges from 22.0-26.1%[4-6], emphasizing the prevalence of this complication.

Many strategies have been attempted to reduce SSI rates. The Centers for Medicare and Medicaid Services introduced the Surgical Care Improvement Project infection project with the aim of reducing SSI incidence and morbidity. These measures include prophylactic intravenous antibiotics administered within 1 hour of skin incision, appropriate prophylactic antibiotic selection, discontinuation of prophylactic antibiotics within 24 hours after surgery, appropriate hair removal, and maintenance of perioperative normothermia[7]. Despite the enforcement of these measures through quality reporting and pay-for-performance measures, significant controversy exists as to their overall effectiveness[8], especially in the high-risk colorectal surgical population[9]. Laparoscopic surgery has been shown to improve SSI rates in the colorectal population[10]; however, not all patients are appropriate candidates for this approach and the inability of promising interventions such as wound edge protection[6] and gentamicin sponges[4] to improve SSI rates following colorectal surgery mandate the investigation of novel techniques.

Initiated in the orthopaedic literature, a new technique of wound dressing has been described to reduce SSI[11]. Incisional negative pressure wound therapy (NPWT) using devices such as the Prevena™ involves applying a wound vacuum sponge over a standard wound closure (including fascial closure and skin closure with staples). The incisional NPWT dressing is then left in place for 5 to 7 days before removal. A recent retrospective study by Bonds *et al*. described the ability of incisional NPWT to reduce SSI rates in open colorectal surgery from 29.3-12.5%[12].

The aim of the current study is to assess the clinical effectiveness of incisional NPWT to reduce SSI rates in open, re-operative colorectal surgery. The primary endpoint of this study is the occurrence of superficial SSI within 30 days after surgery and the secondary endpoints include, length of hospital stay and cost effectiveness.

Methods

Study design and patients

This investigator-initiated trial will be a prospective, unicentre, randomized controlled trial. It is planned to be conducted from July 2015 to June 2018 at the Department of Colorectal Surgery at the Cleveland Clinic, Ohio. However, it is likely given the high volume practice of department, that

it will be completed sooner. Patients aged over 18 years undergoing re-operative colorectal surgery defined as the excision or revision of a prior anastomosis, intestinal resection with an incisional hernia repair or enterocutaneous fistula repair in both elective and emergency settings are eligible for enrolment. Patients undergoing completion proctectomy and ileal pouch anal anastomosis with a mucous fistula from their rectal stump will also be included. Laparoscopic or laparoscopic assisted procedures, patients who had undergone a laparotomy within the preceding three months and an active SSI at the time of surgery will be excluded. Institutional review board approval will be sought before trial commencement, written informed consent will be obtained from all patients before enrolment and the trial will be registered with clinicaltrials.gov. The number and reason of patients excluded and lost to follow-up will be prospectively recorded.

Randomization

Enrolled patients will be randomly assigned through a concealed centralized secure web based system in a 1:1 ratio to either the control arm (standard post-operative care) or the intervention arm (the application of the Prevena™ NPWT system (Acelity, San Antonio, TX)). Randomization will be performed when the patient attends the last preoperative visit using the REDCap™ (Research Electronic Data Capture) secure online system. In our department this visit occurs on the day prior to surgery, facilitating ease of enrolment.

The departmental SSI prevention bundle will be used in all cases including preoperative mechanical bowel preparation with the addition of oral antibiotics, a preoperative patient shower with Hibiclens (Mölnlycke Health Care, Norcross, GA), intravenous antibiotics administered 1 hour before skin incision, antiseptic preparation of the abdomen, the routine use of a wound protector, surgical glove changes following contamination and before wound closure and separate instruments used for wound closure. The non-NPWT dressing will be left in place for 48 hours before changing.

Surgeons in the Colo-rectal surgery department trained in the application of the Prevena™ NPWT system will enroll and operate on patients included in this trial. All wounds will be irrigated with sterile saline before closure and the attending staff surgeon will perform all closures themselves. The fascia will be closed with interrupted or running # 1 Maxon™ (Covidien), followed by skin closure with staples. Control patients with standard wound dressings will have gauze and tape dressings applied while those in the NPWT group will have the Prevena™ system applied; both before the maturation of the ostomy to avoid contamination of the wound with enteric content. The Prevena™ system will remain in place for 7 $\pm$ 1 days. However, if concern exists for the patients wound, it will be removed, the wound assessed and this will be recorded as a break from trial protocol. The Prevena™ will however be reapplied if the wound is not infected.

Efficacy outcomes

The primary endpoint will be the occurrence of superficial surgical site infection within 30 days after the operation. Diagnosis will be based on criteria developed by the Centers for Disease Control (CDC)[13]. All wound assessors will be experienced in the appraisal of postoperative wounds and will be provided with standardized criteria and instruction regarding assessment.

Secondary endpoints will include length of hospital stay, cost effectiveness, and the clinical efficacy of the device in relation to the degree of contamination, patient comorbidity, and operative demographics. This information will be recorded contemporaneously on standardized clinical

report forms. Data for this study will then be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the Cleveland Clinic.

Procedures

Preoperative evaluation will include the prospective assessment and recording of demographic data related to the patient and their co-morbidities. Operative details, including any deviation from allocation, will be recorded immediately after the operation (Appendix 1). The post-operative wound will be assessed daily by the attending staff surgeon. A trained reviewer independent from the surgical team performing the interventionwill formally assess the wound on post-operative day seven. If the patient is discharged prior to post-operative day 7, an early outpatient assessment will be scheduled for day 7 $\pm$ 1 day as is the standard practice of our department. A second formal wound review will be performed at 30 (+/-7) days, which will involve the patient returning to hospital for a physical review of the wound. At this same visit, patients will also complete a supervised, self-reported post-discharge questionnaire (PDQ) with the study investigator to identify any occurrence of SSI during the intervening period between the two clinical assessments. The questionnaire is based on the validated Health Protection Agency surgical site infection surveillance system[6], which is based on the original CDC definitions (Appendix 2) and has been used in prior high quality randomized trials of SSIs[6]. To our knowledge, this will represent the first time this questionnaire is used in a trial of Prevena™. On day 7 $\pm$ 1 day and 30 $\pm$ 7 days a photograph will be taken of the wound to be evaluated by a blinded assessor of wound healing at a later date and scored on a modified 10-point Likert scale (1 = very poorly healed; 10 = fully healed).

Cost Analysis

The objective of the economic evaluation is to explore the relative cost-effectiveness of Prevena™ NPWT compared to standard care. Cost and resource use data will be collected prospectively for both arms of the trial. Trial co-coordinators will identify hospital utilization items and primary care utilization items will be determined by patient interview at the post-operative 30-day clinic visit. Unit costs will be valued in $ (2015 value). The cost of the intervention (Prevena™ NPWT) will be obtained from the manufacturer. Inpatient care resource items will be sourced from the Cleveland Clinic Reference Costs data. Total resource costs will be obtained by summation of the individual resource costs for each category of resource item accessed by trial patients. Individual resource costs will be obtained by multiplying the resource use by the corresponding unit costs.

Statistical analysis

We hypothesize that the use of Prevena™ incisional NPWT in adults reduces SSI rates in open, re-operative colorectal surgery. For re-operative colorectal surgery, the Department of Colorectal Surgery at the Cleveland Clinic, Ohio has observed a 19.4% overall SSI rate (unpublished internal audit). Assuming a 2.34 fold reduction in SSI rates based on a prior retrospective study in the setting of Colorectal Surgery[12] (19.4% to 8.3%), 298 patients (149 per control and intervention arm) are required to achieve a power of 80% and a two-sided type I error rate of 0.05 (StudySize v3.0, CreoStat HB, Gothenburg, Sweden). As there is only one primary endpoint (SSI development), adjustments for multiplicity are not required.

Results will be analyzed according to the intention to treat principal. For the primary endpoint,

missing data will be handled by the principal of complete-case analysis, thus, participants with missing data will be excluded from the analysis. Descriptive statistical comparisons between the two study groups will be performed with the use of chi-square tests or Fisher's exact test, as appropriate, for categorical end points and analysis-of-variance techniques or Wilcoxon rank-sum tests, as appropriate, for continuous end points. The log-rank tests will be used to compare the time to first surgical-site infection between the two study groups. Kaplan–Meier survival estimates of the time to first surgical-site infection will also calculated. Analyses will be performed with SPSS version 20.0 (IBM Corp, Armonk, NY, USA). $P<0.05$ will be considered statistically significant. A formal, interim analysis is planned to take place when a total of one hundred patients have been accrued for both arms all together.

References

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<u>Appendix 1</u>: Perioperative clinical variables recorded.

Pre-operative Factors
Age
Sex
Body mass index (Kg/M^2)
Charleson co-morbidity index
Diabetic
Current smoker
Chronic kidney disease
Medications: -Steroids -Immunosuppressants
Preoperative serum albumin
Pathology -Malignancy -Inflammatory bowel disease -Other benign
ASA grade (1-4)
Urgency of operation: -Elective -Urgent -Emergent
Procedure performed
Intra-operative
Skin preparation used: -Chlorhexidine -Aqueous povidone-iodine -Alcoholic povidone-iodine
Duration of Surgery (minutes)
Prophylactic antibiotics given: -Before induction -During procedure
Degree of contamination: 1. Clean 2. Clean-contaminated 3. Contaminated 4. Dirty
Operation site: -Large bowel -Small bowel -Both
Ostomy: -Ileostomy -Colostomy
Mesh used for a hernia? If so, type?

Blood loss (mL)
Wound length (cm)
Number of staples used to close the wound
Type of Prevena used (peel & place Vs customizable)
Post-operative
Overall post-operative complications (Clavien-Dindo Grade[14])
Removal of VAC early? If so, for what reason?
VAC leakage
Peri-operative transfusion
Surgical site infection: 1-Superficial 2-Deep 3-Organ space -If so, occurred on which day?
Procedures undertaken for SSI: -Opening of wound -Opening the wound and packing -Exploration of the wound under general anesthesia -Application of a vacuum dressing -Oral antibiotics -Intravenous antibiotics
Wound healing Likert Score (1-10) from wound photographs taken on post-operative day 0, 7 and 30

Appendix 2: Patient post-discharge questionnaire (PDQ)

Please complete the following questionnaire:

Please fill in the date you completed this questionnaire ____/____/____
Have you had any problems with the healing of your wound? ❒YES ❒NO

If you have answered NO you do not need to continue with the rest of the form. Thank you for taking the time to do this. If you have answered YES, please read the following carefully and complete the rest of the form.

Since you were discharged from hospital after your operation, have you noticed any of the following symptoms?

Was there any discharge or leakage of fluid from any part of the wound? ❒Yes ❒No
If yes, was it either;
❒Clear or blood stained
❒ Yellow/green (pus)
❒Other-please specify

Please tick any of the following additional symptoms that applied to your wound:
❒ Pain or soreness in addition to the discomfort experienced following the operation.
❒Redness or inflammation spreading from the edges of the wound.
❒The area around the wound felt warmer/hotter than the surrounding skin.
❒The area around the wound became swollen
❒ The edges of any part of the wound separated or gaped open.

Did any health care worker take a sample from your wound to send to the laboratory?
❒Yes ❒No

If you saw a health care worker because of these symptoms, please indicate who you saw from the list below-
❒Primary care physician
❒Home care nurse
❒Doctor or nurse at the hospital
❒Other – please specify
❒ Did not see one about my wound

Please tell us the date you noticed these symptoms. If you cannot remember the exact date, please give an approximate date
_____/____/_____

Have you been prescribed antibiotics for an infection in the wound?
❒Yes ❒No
If yes, who prescribed them? _____

Have you been re-admitted to hospital with an infection of the surgical wound?
To the hospital at which the operation was carried out? ❒ Yes ❒ No
To another hospital? ❒ Yes ❒ No
If yes, which one? _____
Other comments_____

To be complete by the trial investigator
Patient reported SSI meets definition ❒ Yes ❒ No If yes enter criteria for SSI: ❒Criterion 1: Discharge pus + antibiotics prescribed Clinical signs* + dehiscence ❒Criterion 2: Clinical signs* + antibiotics prescribed ❒Criterion 3: Clinical signs* + antibiotics prescribed