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The effect of mupirocin dressings on postoperative surgical site infections in elective colorectal surgery: A prospective, randomized controlled trial

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ABSTRACT

Background: Surgical site infections (SSIs) are the most common nosocomial infection among surgical patients. We hypothesized that mupirocin ointment would decrease SSI rates compared to standard surgical dressings in patients undergoing colorectal surgery.
Methods: A prospective randomized controlled trial was performed, including patients undergoing elective open and minimally invasive colorectal surgery. Patients were randomized 1:1 to receive standard gauze dressings or mupirocin ointment (2%) dressings. The primary outcome was incisional SSI at 30 days postoperative.
Results: A total of 192 patients were enrolled; 150 underwent randomization: 75 to the mupirocin arm, and 75 to the standard gauze dressing arm. Three SSIs occurred; one (1%) in the mupirocin group, and two (3%) in the standard gauze group ($P = 0.560$). There was no significant difference between standard gauze dressings and mupirocin dressings.
Conclusion: Mupirocin (2%) ointment failed to show a benefit compared to standard dressings for postoperative SSI.

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Introduction

Surgical site infections (SSIs) are the most common nosocomial infection among surgical patients and are the third most common nosocomial infection among all hospitalized patients.[1] Although all patients undergoing surgical procedures are at risk for developing SSIs, colorectal surgery has consistently had high rates of surgical site infections, ranging from 3 to 45%.[2,3] This can be contributed to multiple factors including complex surgery, longer operative times, blood transfusions, potential for fecal contamination, emergency surgery, and often times a cancer diagnosis with neoadjuvant radiation therapy. Additionally, much of colorectal surgery is time-sensitive and often times patients' comorbidities are not able to be modified prior to surgical intervention.[2,3] Numerous studies have shown the adverse effects of SSIs, including increased length of hospital stay, morbidity, mortality, readmissions and costs.[2–4] In a recent study analyzing various surgical procedures, including colorectal operations, surgical site infection was found to be the number one cause of unplanned readmission.[4]

Various methods have been performed to decrease the colorectal SSI rate. Care bundles including preoperative antibiotics, mechanical and chemical bowel prep, normothermia and chlorhexidine skin prep are some of the variables that have been found to reduce the incidence of SSI.[2,5,6] Most of these care pathways focus on preoperative and intraoperative risk reduction; however, there has not been standardized postoperative strategies to reduce SSI rates.

A few notable randomized controlled trials investigating postoperative dressings and their effect on SSI's include a trial comparing negative pressure wound therapy to standard gauze dressings.[7] This study failed to show a benefit in terms of reducing the rate of surgical site infections. Another study using silver impregnated dressings to surgical incisions did show a decrease in the occurrence of SSIs when compared to standard gauze dressings.[8]

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Mupirocin is an antibiotic ointment with activity against gram positive and gram-negative bacteria. It has often been used to treat skin infections and intranasally to treat methicillin resistant *Staphylococcus Aureus* (MRSA) colonization. It is readily available, cost effective, with low risk of antibiotic resistance.[9] Most recently, a European prospective, randomized controlled trial compared colorectal SSI rates in open surgery between mupirocin, silver, and standard gauze surgical dressings. The results of this study show that mupirocin has the greatest effect on reducing SSI rate when compared to standard gauze and silver dressings.[10] Further studies from this European group using mupirocin as part of a surgical SSI prevention bundle have been performed for laparoscopic colorectal oncologic surgery, with similar results of reducing incisional and organ-space SSI rate.[11] These studies have not been performed in the United States and have only been studied on either open or laparoscopic colorectal oncologic surgery.

The aim of this study is to evaluate an expanded use of mupirocin dressings compared to standard surgical dressings and their respective SSI rates at a United States community hospital in patients undergoing elective open and minimally invasive (laparoscopic and robotic) colorectal surgery.

Materials and methods

A prospective randomized controlled trial was initiated at our institution after receiving Institutional Review Board approval. The electronic medical records were reviewed for each enrolled patient undergoing elective colorectal surgery from November 2015 through July 2018. Inclusion criteria included patients 18 years or older, any elective colorectal surgery, open and minimally invasive cases, partial or total colectomies, abdominoperineal resection and low anterior resection. Patient with known allergies to mupirocin were excluded, as well as any operation where the incision was left open or partially open.

The sample size was initially calculated based on historical SSI rates of 20% at our institution in colorectal surgery patients.[12] It was calculated that 71 patients were required in each arm of the study to detect a 15% difference in SSI rates with 80% statistical power.

Patients were randomized 1:1 to receive either standard gauze island dressings for 2 days or mupirocin ointment (2%) and an island dressing for 5 days (±2 days) on the extrication site. The duration of each dressing was consistent with a previous European study with goals to reproduce their favorable results.[10] Randomization assignments were performed by computer generated randomization.

Surgical procedure

Patients underwent mechanical and chemical bowel prep with polyethylene glycol and neomycin and metronidazole, respectively. Weight-based dosing of standardized preoperative antibiotics (ceftriaxone and metronidazole) were administered intravenously within 30 min of the procedure and re-dosed appropriately. Preoperative surgical scrub was performed with 2% chlorhexidine unless the patient had an allergy to this, in which case povidone-iodine (Betadine) was used. Enrolled patients underwent colon resection as per usual surgical technique. An abdominal wound protector was utilized, as well as a special closing tray including a change of gloves prior to closure. The abdominal fascia was closed with slowly absorbable monofilament. After fascial closure, the circulating nurse opened an envelope that revealed the patient's randomization assignment. Skin was then closed with staples or suture per surgeon preference. The skin was cleansed with sterile saline. After drying, a thick layer of mupirocin was applied to the incision for the experimental group and covered with an island dressing. In minimally invasive cases, only the incision from which extrication of bowel was performed was covered with the mupirocin dressing. A simple island dressing was placed in the control group. The mupirocin dressing remained in place until postoperative day 5, whereas the island dressing was removed per protocol on postoperative day 2. All patients were treated per our institution's Enhanced Recovery After Surgery (ERAS) pathway as previously described.[13] Residents and all surgeons in the department were involved in every aspect of the patients' care.

Dressings were removed at any point if a SSI was suspected. Several patients in each group were excluded due to fecal contamination of dressings by nearby ostomies or excess drainage from the incision. For patients who were randomized to the mupirocin group and were discharged before postoperative day 5, a follow-up phone call was made to verify that the patient had removed their wound dressing on the appropriate date.

Surgical site infection occurrence was determined by the American College of Surgeons National Surgical Quality Improvement Program® (ACS NSQIP) criteria within 30 days postoperative. Assessment of the surgical site was performed during the hospital stay and postoperative visits by the surgical team. Patients in both groups had removed their wound dressings prior to the first postoperative follow-up appointment in which the incisions were examined for signs of infection. These follow-up appointments were also commonly scheduled with a nurse practitioner who was not involved in the patient's surgery. Review of patients' medical records was completed independently by the study coordinator and by our institution's validated NSQIP clinical reviewer to identify any documented postoperative superficial, deep, or organ space SSI per Centers for Disease Control and Prevention definitions.[14] Organ-space SSI was diagnosed by a radiologist blinded to the treatment groups.

Variables

The independent variable investigated was the use of mupirocin. Multiple dependent variables included age, gender, body mass index (BMI), comorbidities (including diabetes, chronic kidney disease, tobacco use, and hypertension), operation time, and blood transfusions.

Additional variables included approach of surgery (open or minimally invasive), wound class, and American Society of Anesthesiologists (ASA) classification.

Statistics

Statistical analysis included χ^2 tests and Wilcoxon rank sum tests. Data were analyzed based on intention-to-treat. A P value < 0.05 was considered significant. The study was approved by the Institutional Review Board at our medical center and all included patients signed an informed consent form to be included in the study.

Results

A total of 192 patients were enrolled; 150 underwent randomization: 75 to the mupirocin arm and 75 to the standard gauze arm. Exclusions involved not proceeding to surgery or deviation from the study protocol (Fig. 1). Patient demographics were similar for those in the mupirocin vs. standard gauze dressing for age and sex (Table 1). Four patients in each group underwent neoadjuvant chemotherapy, while 7 and 9 patients in the mupirocin and standard dressing group, respectively, underwent adjuvant treatment. Indications for surgery and operative approaches were similar between the two groups (Table 2). The mean length of stay was

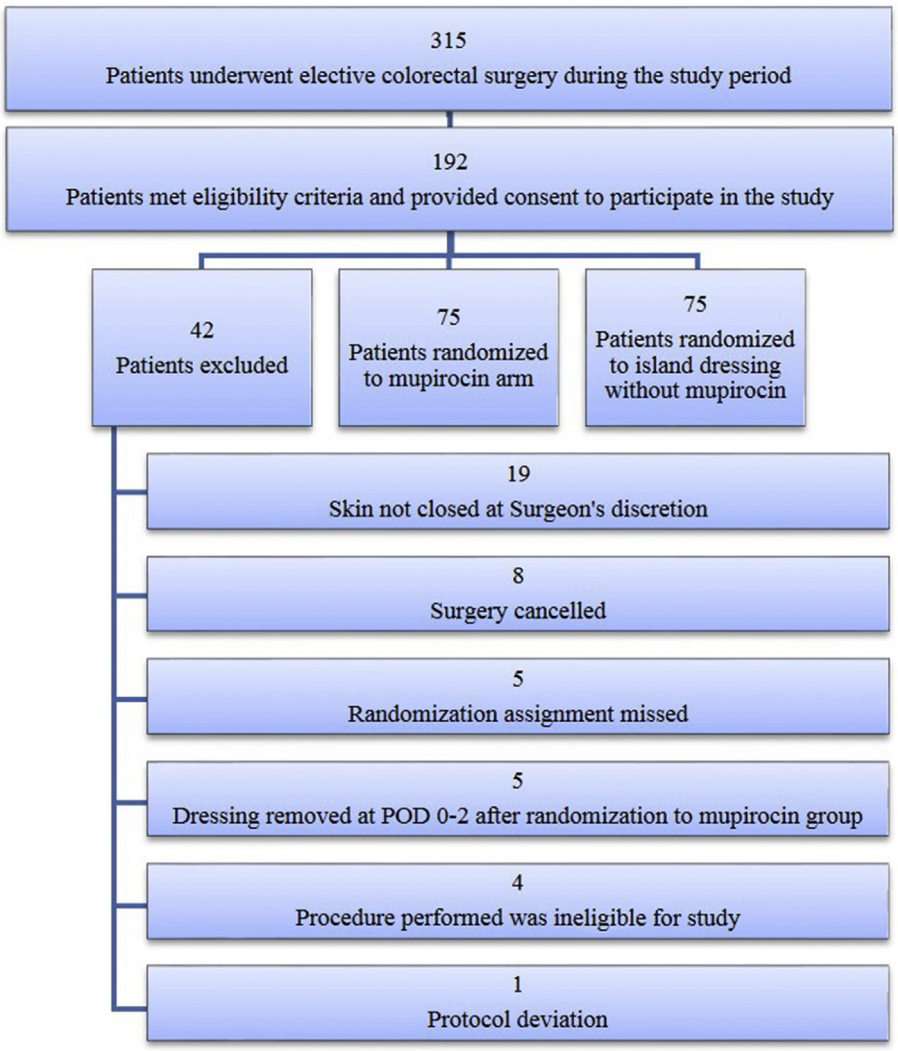

Fig. 1. Study enrollment.

5.0 ± 5.6 days in the mupirocin group and 4.7 ± 2.9 days in the standard dressing group ($P = 0.511$). Patients in the mupirocin group were more likely to have hypertension and a higher BMI. There were no significant adverse outcomes directly attributed to mupirocin.

Three SSIs occurred; one (1%) in the mupirocin group (1

Table 1
Demographic and preoperative characteristics of patients by study group.

Variable	Mupirocin group n = 75	No mupirocin group n = 75	*P* value
Mean age, years	66.2 ± 13.2	62.2 ± 15.4	0.077
Mean BMI, kg/m^2	31.3 ± 6.0	29.5 ± 6.3	0.043
Sex, n (%)			0.414
Female	36 (48)	41 (55)	
Male	39 (52)	34 (45)	
Tobacco use, n (%)			0.811
Current	10 (13)	8 (11)	
History	29 (37)	34 (45)	
Never	36 (48)	33 (44)	
Co-morbidities, n (%)			
Type 2 diabetes	15 (20)	10 (13)	0.276
Chronic kidney disease	11 (15)	7 (9)	0.318
Hypertension	46 (61)	30 (40)	0.009
Peripheral vascular disease	2 (3)	1 (1)	0.566
Chronic obstructive pulmonary disease	5 (7)	6 (8)	0.758
Dyslipidemia	38 (51)	31 (41)	0.254
Coronary artery disease	12 (16)	5 (7)	0.073
Immunocompromised	2 (3)	1 (1)	0.159

BMI = body mass index.

Table 2
Perioperative characteristics of patients by study group.

Variable	Mupirocin group n = 75	No mupirocin group n = 75	*P* value
Indication for surgery, n (%)			0.386
Cancer	25 (33)	28 (37)	
Unresectable polyp/mass/adenoma	26 (35)	14 (19)	
Diverticulitis	20 (27)	22 (29)	
Fistula	2 (3)	2 (3)	
Inflammatory bowel disease	1 (1)	5 (7)	
Other	1 (1)	4 (5)	
Median operative time, minutes (IQR)	210 (157–288)	209 (169–296)	0.574
Approach, n (%)			0.497
Laparoscopic/robotic	62 (83)	65 (87)	
Open	13 (17)	10 (13)	
Wound class, n (%)[a]			0.681
Clean	1 (1)	0	
Clean-contaminated	64 (85)	63 (84)	
Contaminated	7 (9)	7 (9)	
Dirty/Infected	2 (3)	5 (7)	
ASA Class, n (%)			0.028
1	2 (3)	3 (4)	
2	29 (39)	42 (56)	
3	43 (57)	29 (39)	
4	1 (1)	1 (1)	

IQR = interquartile range; ASA = American Society of Anesthesiologists.
[a] Wound class was not documented for one patient in the mupirocin group.

superficial SSI after laparoscopic surgery), and two (3%) in the standard gauze group (2 organ space infections, both intra-abdominal abscesses after laparoscopic surgery, one of which was secondary to an anastomotic leak) ($P = 0.560$). The SSIs in the standard gauze group were due to *Candida albicans*, whereas the SSI in the mupirocin group was secondary to *Staphylococcus epidermidis* (Table 3). One additional patient who was randomized to the mupirocin group underwent an abdominoperineal resection and was noted to have an organ space infection in the perineal wound, but no infection at the extrication site to which the mupirocin was applied; therefore, he was not included in the SSI rate. Additional complications included venous thromboembolism (1% vs. 3%; $P = 0.999$), *Clostridium difficile* infection (1% vs. 1%; $P = 0.999$), and urinary tract infection (0 vs. 3%; $P = 0.477$) in the mupirocin versus standard dressing group, respectively. Bleeding requiring transfusion occurred in two patients in the mupirocin group, and no patients in the standard dressing group ($P = 0.477$). Unplanned reoperations occurred in 2 patients in the standard dressing group for an anastomotic leak and bowel perforation. One patient in the mupirocin group underwent an ostomy revision on POD 5.

This study was originally powered to resolve a 15% absolute reduction in SSI rates, based on a historical SSI rate after colorectal surgery of approximately 20%, corresponding to an odds ratio of approximately 0.20 for mupirocin versus control patients. This yielded a sample of 71 patients per group required for 80% statistical power, with alpha set to 0.05. Concurrent to this study, several hospital-wide and departmental quality improvement initiatives aimed at decreasing SSIs were implemented, resulting in a marked reduction in overall SSI rates to approximately 7%. This global reduction in SSI rates significantly reduced the power of this study to resolve potential effects of mupirocin application. At this current SSI rate (7%), this prospective study would now require an additional 4000 patients to reach 80% statistical power to detect a 2% relative effectiveness of mupirocin dressings versus standard dressings.

Discussion

Colorectal surgery has consistently had high rates of surgical site infections, which can subsequently lead to increased length of hospital stay, morbidity, mortality, readmissions, and increased cost of up to $20,000 per occurrence.[2–4] Several perioperative care bundles have been published in order to prevent SSIs in colorectal surgery. These methods include preoperative strategies of skin cleansing with chlorhexidine, and mechanical and chemical bowel prep. Intraoperative factors of normothermia, tight glycemic control, antibiotic administration and appropriate re-dosing, chloroprep scrub, as well as closure techniques including a separate closure tray and change of gloves all contribute to successful reduction of SSI.[6,15,16] Our institution has adopted several of these techniques, which have been implemented through our ERAS protocol.[13]

Prior to these modifications, colorectal SSI rates at our institution had been a high outlier in ACS NSQIP reports as compared to the national average for several years. Additional efforts have been initiated to reduce these rates, including a change in the type of antibiotic used based on collaborative research identifying the most common organisms cultured from colorectal SSIs at our institution. Our preoperative antibiotic regimen changed from a single agent, cefoxitin, to ceftriaxone and metronidazole. In addition, a new protocol to maintain normothermia and improved glycemic control

Table 3
Timing and wound culture results for cases with surgical site infections.

Patient number	Group	Procedure	SSI diagnosis date	SSI type	Wound culture results
14	Standard Dressing	Laparoscopic right colon resection	POD 3	Organ space	*Candida albicans*
41	Standard Dressing	Laparoscopic right hemicolectomy	POD 7	Organ space	*Candida albicans*
36	Mupirocin Dressing	LAR, nephrectomy, loop ileostomy	POD 12	Superficial	*Staphylococcus epidermidis*

LAR = low anterior resection.

intraoperatively was initiated to help reduce the occurrence of SSI.

Mupirocin is an antibiotic ointment that has broad antibacterial activity. It was initially isolated from *Pseudomonas fluorescens* and is bacteriostatic in low concentrations and bacteriocidal in high concentrations. It is most notable for its activity against MRSA; however, it also has activity against other gram-positive cocci, gram negative rods and Candida. It has a unique mechanism of action by selectively binding to bacterial isoleucyl-tRNA synthetase, inhibiting the incorporation of isoleucine into bacterial proteins. This unique mechanism of action reduces the likelihood of antibiotic cross-resistance.[17,18] Many colorectal SSIs are due to gram-negative bacteria such as *Escherichia coli, Enterobacteriaceae* and anaerobes such as *Bacteroides fragilis.* However, approximately 25% of SSIs are due to gram-positive organisms such as *Streptococcus* and *Enterococcus*. Despite the fact that 25% of patients in the U.S are colonized with *Staphylococcus aureus*, MRSA is not a common cause of SSI in colorectal surgery. Often, these SSIs can occur in patients who are not known carriers.[10,19,20] Studies have been performed showing that intranasal mupirocin may have a role in reduction of SSI in cardiac and orthopedic surgery.[21,22] However, investigation on the effects of topical mupirocin in general surgery are not as robust. European studies have shown that mupirocin dressings decrease the incidence of SSI in open colorectal cancer surgery when compared to gauze dressings or in laparoscopic surgery when added to a standardized care bundle.[10,11]

In comparison to previous studies, our randomized study examined a broader patient population undergoing colorectal surgery for a variety of diagnoses, with approximately 85% being performed in a minimally invasive manner. Whereas our study did not show a significant difference in SSI rates with mupirocin dressings, another prospective randomized study in open colorectal oncologic surgery has shown a benefit in comparison to standard gauze dressings.[10] Therefore, mupirocin may have a greater role in decreasing SSI rates in open colorectal surgery. Our surgical technique differed in terms of pre and postoperative skin prep as well as with use of mechanical and chemical bowel prep. The patients in this study were cared for by residents and all department staff. We were ultimately unable to show a statistically significant decrease in SSIs with use of mupirocin topical ointment.

Our study was prospective and randomized, thus any changes in perioperative surgical protocol that occurred during our study period including type of antibiotic, stricter glucose and temperature control had no effect on our data. Our institutional colorectal SSI rates did decrease dramatically from the start of our study, likely due a combination of these changes. Furthermore, our study used a nationally validated database (ACS NSQIP) which captured all of our colorectal cases for review. The surgeon and all operating room staff were blinded to the type of dressing that was utilized until the completion of the procedure, preventing bias during the case.

Limitations to our study include a heterogenous group of procedures for various disease processes resulting in an inability to control for all risk factors for SSIs. In addition, our study had a small sample size, which in combination with a reduced SSI rate, resulted in underpowering of the study. It is possible that some patients may have presented to an outside hospital for an SSI, however, 30-day follow-up was captured through NSQIP. At our institution's current SSI rate (7%), it would not be feasible to obtain data for enough patients to power our study; therefore, we report the results of the original design of the study. Although postoperative protocols are standardized and encouraged, there may be deviation in protocol per surgeon preference. Our intent was to reproduce the published report of mupirocin efficacy in reduction of SSIs. In those protocols, standard dressings were applied for two days and mupirocin for five days. Further research studies may consider application of dressings for an equal amount of days or performing multi-institutional studies to increase the enrollment and subsequent power of the study.

Conclusion

In a prospective randomized trial, although underpowered, mupirocin (2%) ointment failed to show a benefit in decreasing postoperative SSIs when compared to standard gauze dressings. This study included multiple surgeons and a variety of disease processes and surgical techniques in order to accurately reflect clinical practice with a validated outcome instrument (ACS NSQIP) and standardized ERAS perioperative pathway.

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Conflicts of interest

There are no conflicts of interest to disclose.

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