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ORIGINAL ARTICLE

Risk factors for anastomotic leakage and favorable antimicrobial treatment as empirical therapy for intra-abdominal infection in patients undergoing colorectal surgery

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Abstract
Purpose Anastomotic leakage is the most concerning complication that can occur after colorectal surgery. The aim of this study was to determine the incidence of and risk factors for clinical anastomotic leakage following colorectal resection. In addition, we evaluated the efficacy of empirical antimicrobial therapy with respect to the clinical outcomes.
Methods Between January 2002 and December 2010, we prospectively collected surveillance data for patients, who were undergoing colorectal resection at Mie University Hospital.
Results A total of 918 patients undergoing elective colorectal surgery were included in our surveillance program, 633 of whom were eligible for the study. Clinical anastomotic leakage was identified in 40 (6.3 %) patients. The use of preoperative irradiation and an NNIS risk index ≧2 were found to be independent predictors of clinical anastomotic leakage after colorectal surgery. Empirical antibiotic treatment strayed from the 2010 IDSA/SIS guidelines, the length of hospital stay was prolonged and the rate of re-intervention was increased.
Conclusions Anastomotic leakage remains a major complication of colorectal surgery. Surgeons should be aware of such high-risk patients. In patients with anastomotic leakage after surgery, the empirical use of antimicrobial regimens with broad-spectrum activity against both aerobic and anaerobic organisms to treat postoperative intra-abdominal infections following colorectal surgery in accordance with the 2010 IDSA/SIS guidelines is associated with better outcomes.

Keywords Colorectal surgery · Anastomotic leakage · Intra-abdominal infection · Antibiotic

Introduction

Surgical site infections (SSIs) are the most frequent nosocomial infections among patients undergoing surgery, accounting for 38 % of all such infections [1, 2]. SSIs prolong the patient's hospital stay, increase medical costs and occasionally lead to mortality [1, 3, 4]. The most widely used definition for SSIs was provided by the Centers for Disease Control in 1992 and updated in 2003. This definition broadly categorizes SSIs into incisional and organ/space infections [5, 6]. Organ/space SSIs are severe conditions that are most often caused by anastomotic leakage following gastrointestinal surgery. Anastomotic leakage is the most concerning complication of colorectal surgery.

The occurrence of clinical anastomotic leakage following colorectal surgery results in poor functional outcomes and a reduced quality of life. In addition, the development of clinical anastomotic leakage in patients undergoing colorectal cancer surgery increases the risk of local recurrence and worsens the prognosis [7–12].

In the management of postoperative intra-abdominal infections, the selection of the empirical antimicrobial regimen is important. Indeed, postoperative peritonitis is a representative example of a nosocomial infection occurring

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in patients, who are already receiving antibiotics prophylactically. We previously reported the current use of prophylactic antimicrobials in patients undergoing colorectal surgery in Japan [13]. The identified pathogens are often outside the spectrum of activity of the initial empirical agents usually administered. In 2010, guidelines regarding proper antimicrobial regimens for intra-abdominal infections were published by the Surgical Infection Society (SIS) and the Infectious Disease Society of America (IDSA) [14]. To treat health care-associated infections, such as postoperative intra-abdominal infections, multidrug regimens that include agents with expanded spectra of activity against Gram-negative aerobic and facultative bacilli are often needed.

Obtaining a better understanding of the characteristics of patients who are at a higher risk for anastomotic leakage following colorectal surgery is important for surgeons, and among patients with anastomotic leakage after surgery, the empiric use of antimicrobial regimens is associated with better outcomes.

We conducted a prospective surveillance study of clinical anastomotic leakage following the resection for colorectal disease at a single university hospital. The aim of this study was to determine the incidence of and risk factors for clinical anastomotic leakage following colorectal resection. In addition, we evaluated the efficacy of empirical antimicrobial therapy with respect to the clinical outcomes.

Methods

From January 2002 to December 2010, all patients undergoing colorectal resection at the Departments of Gastrointestinal and Pediatric Surgery and Innovative Surgery at Mie University Graduate School of Medicine were enrolled in our SSI surveillance program. The patients were assessed daily for SSI incidence until discharge, with a postoperative follow-up of 30 days. SSI was defined according to the CDC guidelines [1, 5, 6]. We prospectively collected surveillance data, including patient name, age, gender, height, weight, diagnosis, history of diabetes, preoperative steroid use, preoperative bowel preparation use, neoadjuvant therapy, the American Society of Anesthesiologists (ASA) physical status score as determined by an anesthesiologist [15, 16], procedures, date of operation, duration of operation, surgical wound classification and duration of postoperative hospital stay. The outcome variables included the development of and data regarding SSIs.

All patients generally underwent the same protocols for perioperative care. Intravenous antimicrobial prophylaxis was given to all patients. One gram of cefmetazole or flomoxef was administered following the induction of anesthesia, and the patients received an additional dose if the operation was prolonged beyond 3 h. In addition, cefmetazole or flomoxef were administered again twice daily for one or two consecutive days after surgery. In the operative theater, the patient's hair was removed using electric clippers following the induction of general anesthesia. The surgical site was wiped with 10 % povidone iodine solution before the operation. The surgical field was draped with a disposable towel. All anastomoses were stapled, except for the anal anastomosis. Absorbable synthetic sutures were used to close the fascia and peritoneum. The skin was closed using stainless steel staples. Following the closure of the surgical wound, the site was gently wiped with normal saline and covered with a dressing. Mechanical bowel preparation was routinely performed, except in cases of inflammatory bowel disease, bowel obstruction or emergent surgery. Chemical bowel preparation was performed in cases of elective rectal surgery using kanamycin and erythromycin. Attempts were made to standardize all aspects of perioperative care.

There are many different risk factors for anastomotic leakage, according to the previous reports [20–27]. The patient-related factors analyzed in this study were age, gender, body mass index (BMI), the ASA score and the use of steroids. The surgery-related factors analyzed in this study were the operative time, the amount of blood loss, wound class, the National Nosocomial Infectious Surveillance (NNIS) risk index [1], the use of mechanical bowel preparation or chemical bowel preparation, elective vs. urgent surgery, laparoscopic vs. open procedures, ostomy formation and the need for multiple organ resection. The disease-related factors analyzed in this study included malignancy vs. inflammatory bowel disease, neoadjuvant therapy and chemo- or radiotherapy.

Definition of clinical anastomotic leakage

Clinical anastomotic leakage was defined as clinical symptoms, such as fever or septicemia, in combination with intra-abdominal or pelvic abscess formation, discharge of pus per the rectum, rectovaginal fistula formation or peritonitis within 30 days postoperatively, leading to a clinical and/or radiological examination of the patient or surgery that confirmed the presence of leakage.

Management of clinical anastomotic leakage

Patient care, including operative drainage, image-guided percutaneous drainage and antibiotic selection, was administered under the direction of the attending physicians.

Statistical analysis

Statistical analysis was performed using the JMP software program (SAS Institute Inc.). The univariate relationship between each independent variable and clinical anastomotic leakage was evaluated using the Mann–Whitney *U* test for continuous variables and Pearson's Chi square test for categorical variables. Independent variables with a $p < 0.1$ in the univariate analysis were entered into the multivariate logistic regression model using a Wald's statistic backward stepwise selection or statistic backward stepwise selection. Statistical significance was established at $p < 0.05$.

Results

A total of 918 patients undergoing colorectal surgery were included in our 9-year surveillance program. Of these, 285 patients were excluded from the analysis because they underwent resection without anastomosis, i.e., they underwent either Hartman's procedure or abdominoperineal resection. A total of 633 patients, including 266 who underwent colon surgery and 367 who underwent rectal surgery were eligible for the study. The patient characteristics and surgery-related and disease-related variables are presented in Table 1. The mean patient age was 57.8 years (range 11–94 years), and 370 (58.5 %) of the patients were males. With respect to the disease classification, there were 189 patients with colon cancer, 179 patients with rectal cancer, 148 patients with ulcerative colitis, 35 patients with Crohn's disease and 82 patients with other diseases.

SSIs were identified in 102 patients (15.4 %). Clinical anastomotic leakage was identified in 40 (6.3 %) patients (colonic anastomosis 6.0 %, rectal anastomosis 6.5 %). The average onset of anastomotic leakage was 7.7 days (2–19 days) after surgery (Fig. 1). The average postoperative hospital stay was 22.7 days (range 4–189 days) among all patients surveyed in the study, 19.8 days in the non-SSI group, 27.8 days in the incisional SSI group and 56.8 days in the leakage group.

Univariate analysis

An NNIS risk index ≧2, the use of preoperative radiation, the operative time and the amount of blood loss were found to be significantly associated with the development of clinical anastomotic leakage (Table 2).

Multivariate analysis

After the univariate analysis, variables with a $p < 0.1$ were selected for a multivariate analysis using a stepwise logistic regression model. Table 3 summarizes the results of the multivariate analysis. An NNIS risk index ≧2, and the use of preoperative radiation were found to be independently predictive of the development of clinical anastomotic leakage.

Table 1 Patient characteristics and surgery-related variables

Characteristics	
Age (years)	57.8 (11–94)
Gender	
Male/Female	370/263
Disease	
Colon cancer	189
Rectal cancer	179
Ulcerative colitis	148
Crohn's disease	35
Others	82
Anastomosis	
Colonic anastomosis	266
Rectal anastomosis	367
Wound class	
Clean-contaminated	578
Contaminated—dirty/infected	55
ASA physical status score	
1.2	584
≧3	49
Duration of operation (min)	232.4 (57–617)
NNIS risk index	
0.1	562
2.3	71
Blood loss (mL)	334.8 (3–3,474)

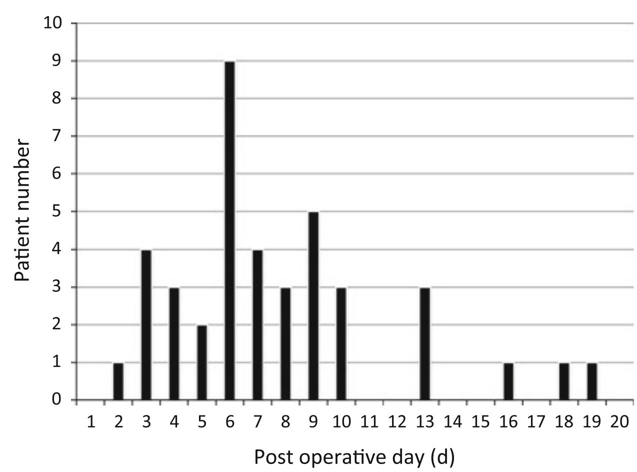

Fig. 1 Numbers of patients who were diagnosed on each postoperative day

Management of patients with clinical anastomotic leakage

Clinical anastomotic leakage was identified in 40 (6.3 %) patients. Six of these 40 patients (15 %) received urgent operative management and parenteral antibiotics, 27 (67.5 %) received image-guided percutaneous drainage and parenteral antibiotics, six (15 %) received parenteral antibiotics and one

Table 2 Univariate analysis of the characteristics of the patients with and without anastomotic leakage ($N = 633$)

Variables	Leak(+) $N = 40$	Leak(−) $N = 593$	p value
Age	58.0	57.8	0.9562
Gender (M/F)			0.3010
Male	27	343	
Female	13	250	
Body mass index >25	8	82	0.4610
Preoperative diagnosis			0.9867
Malignancy	26	342	
Inflammatory bowel disease	13	170	
Preoperative chemotherapy			0.1438
Yes	9	77	
No	31	516	
Preoperative radiation			0.0299
Yes	8	50	
No	32	543	
Mechanical bowel preparation			0.6486
Yes	26	406	
No	14	187	
Chemical bowel preparation			0.2345
Yes	15	170	
No	25	423	
Preoperative steroid			0.4451
Yes	9	105	
No	31	488	
Wound class >2	7	49	0.0884
ASA >2	5	44	0.3906
Duration of operation time	275.5	229.5	0.0024
NNIS ≧2	11	60	0.0018
State of procedure			0.8054
Elective	39	574	
Urgent	1	19	
Surgical technique			0.4993
Laparoscopic surgery	5	107	
Open surgery	35	486	
Ostomy formation			0.1104
Yes	22	242	
No	18	351	
Blood loss	529.4	332.3	0.0022
Multiple organ resection	6	83	>0.9999

was treated with bowel rest only. Thirty-nine patients treated with antimicrobial therapy received a single antimicrobial agent. Nineteen of the 39 (48.7 %) patients treated with parenteral antibiotics initially received antibiotic regimens recommended by the SIS/IDSA guidelines (surgery: two patients, image-guided percutaneous drainage: 12 patients, antibiotics: five patients). Table 4 shows a comparison of the outcome variables among the patients, who received treatment in accordance with versus not in accordance with the antibiotic regimens recommended by the SIS/IDSA guidelines. The initial antibiotic treatment was in not accordance with the 2010 SIS/IDSA guidelines in 20 (51.3 %) patients with an increased length of stay following the occurrence of anastomotic leakage and reintervention.

Table 3 Multivariate analysis

	Variables	Odds ratio	95 % CI	p value
Leak	Wound class >2	1.7	0.45–6.59	0.4210
	NNIS ≧2	3.8	1.12–10.97	0.0336
	Duration of operation time	6.4	0.84–45.65	0.0721
	Preoperative radiation	2.6	1.06–6.00	0.0383
	Blood loss	2.9	0.19–32.26	0.4124

Table 4 Comparison of outcome variables among patients who received antibiotic treatment in accordance with the guidelines and those who did not

Variable	In accordance group $N = 19$	Not in accordance group $N = 20$
Length of stay after occur anastomotic leakage	35.7 ± 5.9	59.0 ± 9.5
No. of subsequent reinterventions	0	2

Table 5 Frequency of culture of organisms from peritoneal fluid in the patients with postoperative leakage

Microorganism	Total no. of isolates
Gram-negative bacteria	10
Escherichia coli	2
Enterobacter cloacae	3
Pseudomonas species	4
Klebsiella species	1
Gram-positive bacteria	23
Enterococcus faecalis	17
Enterococcus faecium	2
Methicillin-resistant staphylococci	4
Anaerobes	8
Bacteroides species	8
Fungi	5
Candida albicans	5

Microbiological results

Twenty-eight of the 40 patients had cultures positive for bacterial species obtained during drainage or reoperation.

A total of 46 strains were isolated from peritoneal fluid (Table 5). More than one isolate was found in 16 patients. Among these microorganisms, 21.7 % were Gram negative and 50 % were Gram positive. Anaerobes were isolated from eight patients with polymicrobial infections.

Discussion

This study demonstrated that, over a complete follow-up of 30 days, among patients, who underwent colorectal surgery with anastomosis, the anastomotic leakage rate was 6.3 %, and the use of preoperative radiotherapy and an NNIS risk index ≧2 were found to be independently predictive of clinical anastomotic leakage after colorectal surgery.

Our leakage rate of 6.3 % is comparable with the findings of previous reports [8, 17–19]. There are many different independent risk factors for anastomotic leakage, including urgent surgery [20], a history of smoking [21], an elevated BMI [22], the use of mechanical bowel preparation [23] or prophylactic drainage [24], the ASA score [25], a prolonged operative time [25] and the use of corticosteroids [26] or neoadjuvant radiotherapy [27]. This study was conducted at a single university hospital; therefore, the surgical skill and protocols were standardized within the patient population. In addition, our data were prospectively collected by our infection control staff. This enabled us to minimize interhospital and interobserver variations regarding the accuracy and consistency of the diagnosis of anastomotic leakage. Therefore, we can say with confidence that our data are a true reflection of both the actual incidence of clinical anastomotic leakage and the risk factors in this patient population.

In this study, preoperative radiotherapy was implicated to be a risk factor for the development of anastomotic leakage. However, clinicians should not omit the use of neoadjuvant therapy in the treatment of rectal cancer due to improved rates of local control, overall survival and sphincter preservation. Proximal diversion is reported to control anastomotic leakage. Proximal diversion has been shown to mitigate the incidence of serious complications associated with anastomotic leakage, such as systemic sepsis, multiorgan failure and death, although this method does not reduce the incidence of anastomotic leakage itself [28]. The NNIS risk index is determined according to the ASA score, the wound classification and the operative time. In this study, the cutoff point for the duration of surgery was determined based on the 75th percentile of the NNIS operative time. Clinicians may shorten the operative time to some extent; however, the ASA score and wound classification cannot be changed. Therefore, it is important to identify and treat leakage cases early.

Antimicrobial therapy is an important element in the management of intra-abdominal infections, and there are convincing data showing that a lack of or inadequate empirical antibiotic therapy results in both increased failure rates and increased mortality [29, 30]. Health care-associated infections are commonly caused by more resistant flora, including the non-fermenting Gram-negative *P. aeruginosa* and *Acinetobacter* species, extended spectrum β-lactamase (ESBL)-producing *Klebsiella* and *E. coli*, *Enterobacter* species, *Proteus* species, MRSA, Enterococci and *Candida* species [31]. For these infections, multidrug regimens that include agents with expanded spectra of activity against Gram-negative aerobic and facultative bacilli are recommended according to the SIS/IDSA guidelines [14]. In addition, medication regimens used to treat intra-abdominal infections usually include agents with known efficacy against anaerobes, and the *Bacteroides fragilis* group contains anaerobic pathogens that are frequently isolated from patients with intra-abdominal infections. These agents include meropenem, imipenem–cilastatin, doripenem, piperacillin–tazobactam and ceftazidime or cefepime in combination with metronidazole. In our hospital, the rate of ESBL-producing *E. coli* is 7.1 % and that of ESBL-producing *K. pneumoniae* is 8.4 %, while the rates of multidrug-resistant *P. aeruginosa* and *A. baumannii* are under 1 % [32]. Therefore, the administration of ceftazidime or cefepime in combination with metronidazole is recommended if the parenteral administration of metronidazole is possible. In this study, no patients received multidrug regimens for empirical therapy. In the “in accordance” group, 15 patients received carbapenem and four patients received tazobactam/piperacillin. In the “not in accordance” group, nine patients received a third-generation cephalosporin, four patients received a fourth-generation cephalosporin and seven patients received quinolones (ciprofloxacin or pazufloxacin). The empiric antibiotic treatment was not in accordance with the 2010 SIS/IDSA guidelines in 20 (51.3 %) patients with an increased length of stay following the occurrence of anastomotic leakage and reintervention. These antibiotics lack activity against anaerobes. In this study, anaerobes were identified in only eight patients (“in accordance” group: four, “not in accordance” group: four), because all patients were already receiving intravenous antimicrobial prophylaxis, such as cefmetazole or flomoxef. In addition, obtaining anaerobic cultures is generally cumbersome. In fact, antibiotics without activity against anaerobes (e.g., cefozopran, cefpirome, cefepime, ciprofloxacin) have been reported to be effective against intra-abdominal infections [33–36]. However, the intestinal colonic flora contains 10^{12} bacteria/g of feces that are predominantly anaerobic. In general, intra-abdominal infections are biphasic, with aerobes, such as Enterobacteriaceae, as predominant pathogens in the peritonitis stage and anaerobes, such as the *Bacteroides fragilis* group, as predominant pathogens in the abscess stage [37]. In addition, β-lactamases are detected in 98 % of infections caused by the *B. fragilis* group [38]. Therefore, the coverage for anaerobic bacilli should be provided in patients with anastomotic leakage after colorectal surgery.

In this study, the "not in accordance" group exhibited an increased length of stay and rate of reintervention, despite the fact that the clinical and biological parameters were similar between the patients, who did and those who did not receive antibiotics in accordance with the SIS/IDSA guidelines, and the empirical antibiotics were changed to target therapy if the pathogens were identified to be outside the spectrum of activity, (e.g. Candida or Enterococci were grown on intra-abdominal cultures).

In conclusion, the occurrence of anastomotic leakage remains a major complication of colorectal surgery. In our department, the overall leakage rate is 6.3 %. The use of preoperative radiotherapy and an NNIS risk index $\geqq 2$ were found to be independently predictive of the development of clinical anastomotic leakage after colorectal surgery. Surgeons should be aware of such high-risk patients. In patients with anastomotic leakage after surgery, the empiric use of antimicrobial regimens with broad-spectrum activity against both aerobic and anaerobic organisms to treat postoperative intra-abdominal infections following colorectal surgery is associated with better outcomes.

Conflict of interest Minako Kobayashi and the other co-authors have no conflicts of interest to declare.

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