

Clinical Research

The Effect of Preoperative Oral Antibiotics in the Prevention of Surgical Site Infection after Laparoscopic Colorectal Cancer Surgery: A Propensity Score Matching Study

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Abstract

Objectives: Recent findings suggest that the combination of mechanical bowel preparation (MBP) and preoperative oral antibiotics (OA) decreases the risk of surgical site infection (SSI) in colorectal surgery; however, this remains controversial. The present study examined the efficacy of OA plus MBP in laparoscopic colorectal cancer (CRC) surgery using propensity score matching (PSM).

Methods: A total of 1080 patients with CRC underwent MBP followed by laparoscopic surgery between 2007 and 2019. OA was administered to all patients with CRC who underwent colectomy from 2018. PSM was performed to compare the effects of OA plus MBP (OA) versus MBP only (non-OA) on the rate of superficial SSI.

Results: Overall, 128 patients received OA. Significant differences were observed in age, the American Society of Anesthesiologists performance status (ASA-PS), liver disease, and preoperative serum albumin (Alb) between the OA and non-OA groups. The enrolled patients were matched using PSM into two groups based on the following factors: sex, age, body mass index, ASA-PS, diabetes mellitus, liver disease, Alb, and tumor location, which resulted in the disappearance of significant differences. A univariate analysis showed that blood loss of 100 g or more, non-OA, and preoperative chemotherapy or radiation correlated with SSI ($p = 0.021, 0.010, 0.038$). A multivariate analysis of these three variables identified blood loss of 100 g or more and non-OA as independent risk factors for SSI (hazard ratio (HR): 3.238, $p = 0.031$; HR: 2.547, $p = 0.033$).

Conclusions: The present study revealed that OA plus MBP markedly reduced SSI rate. OA with MBP needs to be adopted in laparoscopic CRC surgery.

Keywords

oral antibiotics, surgical site infection, colorectal cancer, laparoscopic surgery, propensity score matching

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Introduction

Surgical wounds in colorectal cancer (CRC) surgery have been categorized as clean-contaminated wounds (Class II)

based on the surgical wound calcification grade defined by the Centers for Disease Control and Prevention (CDC)[1]. Surgical site infection (SSI) rate is higher in clear-contaminated surgery, such as CRC surgery, than in other

clean surgeries[2,3]. The high rate of SSI in CRC surgery has a negative impact on short-term outcomes, lengthens hospital stays, increases medical costs, and worsens esthetic outcomes[4,5]. A relationship was recently reported between postoperative infectious complications and long-term outcomes in CRC, with SSI or anastomotic leakage decreasing the overall and relapse-free survival in patients with CRC[6-8]. These outcomes were suggested and proven in basic and clinical research. Furthermore, systematic or focal inflammation was shown to induce tumor proliferation, invasion, or metastasis[9,10]. In clinical research, high values for perioperative serum inflammation markers were found to be associated with survival in patients with CRC[11,12]. Therefore, the prevention of SSI may contribute not only to better short-term outcomes after surgery but also to long-term oncological outcomes in CRC, and various strategies have been adopted to reduce SSI rate.

The clinical importance of intravenous antibiotics in the perioperative setting to prevent SSI has already been confirmed[13-15]. Mechanical bowel preparation (MBP) has mainly been employed; however, it is not preferred in Europe because MBP alone does not affect SSI rate[16], and enhanced recovery after surgery (ERAS) protocols also avoid it[17]. Controversy remains regarding oral antibiotics (OA) in the preoperative setting. Although the use of OA has been recommended by the CDC, they are not administered in Japan because preoperative OA may increase the risk of methicillin-resistant *Staphylococcus aureus* infection. However, recent studies reported that short-term OA did not promote an outbreak of resistant bacteria[18], and the combination of MBP and preoperative OA decreased the rate of SSI[19,20]. Based on these findings, preoperative OA plus MBP has been recommended for use in Japan since 2019[21].

These recommendations were based on a mixture of data obtained from open, laparoscopic, elective, and nonelective surgery. Since the rate of laparoscopic surgery in CRC surgery has markedly increased in the past decade, the risk of postoperative complications also needs to be evaluated in a cohort including only laparoscopic surgery.

Meanwhile, the diversity of patient background also exists in laparoscopic surgery. The length of surgical incision in laparoscopic surgery of the right side colon is generally longer than that in the left side colon, which may be associated with SSI rate. Moreover, multimodal therapies containing preoperative chemotherapies or chemoradiotherapies have been widely performed for patients with CRC in recent years. Preoperative therapies may affect the rate of SSI. Therefore, we considered that the effect of OA in the prevention of SSI should be analyzed in laparoscopic colectomy under the homogenization of the diversity using propensity score matching (PSM) to exactly evaluate the significance of OA. Many retrospective and prospective studies

have examined the clinical value of OA; however, few cohort studies using PSM have been conducted to date[22,23]. The present study investigated the clinical value of OA in laparoscopic CRC surgery using PSM.

Patients and Methods

All methods were conducted in accordance with relevant guidelines[24].

Study design and patients

This was a retrospective diagnostic accuracy study that used PSM to investigate the clinical value of OA combined with MBP in laparoscopic CRC surgery. The present study included patients with CRC who underwent curative surgery between April 2007 and December 2019 at the Division of Digestive Surgery of Kyoto Prefectural University of Medicine (KPUM). The exclusion criteria were as follows: (1) patients with bowel obstruction caused by a tumor, (2) patients with colon cancer that prevented the passage of endoscope into the proximal side of the tumor, (3) patients who did not receive preoperative MBP, and (4) patients who underwent open surgery or conversion from laparoscopic to open surgery.

Ethical approval and consent to participate

The present study was approved by the Research Ethics Committee of the Kyoto Prefectural University of Medicine (No. ERB-C-1187-1). Comprehensive informed consent for the use of clinical data was obtained from all eligible patients. Moreover, informed consent was also obtained from the parents and/or legal guardians of minor patients involved in the study (age under 18 years).

MBP and preoperative OA

MBP, consisting of magnesium citrate 34 g and sodium pyrosulfate 75 mg, was performed on the day prior to surgery. A glycerin enema was also conducted on the morning of surgery. Preoperative OA were administered to all patients with CRC who underwent colectomy in KPUM from January 2018. In patients who underwent preoperative OA, kanamycin 2 g/day and metronidazole 2 g/day were perorally administered in two doses after MBP on the day prior to surgery.

Other preventative strategies for SSI

Cefmetazole sodium was intravenously administered during surgery and on postoperative days 1 and 2. All gloves were changed after operations, such as bowel anastomosis or intestinal transection. Wound lavage was performed after fascia closure using 500 ml saline. The skin and fascia were sutured using absorbable monocryl. The preventative method of SSI besides OA was performed for all eligible patients in

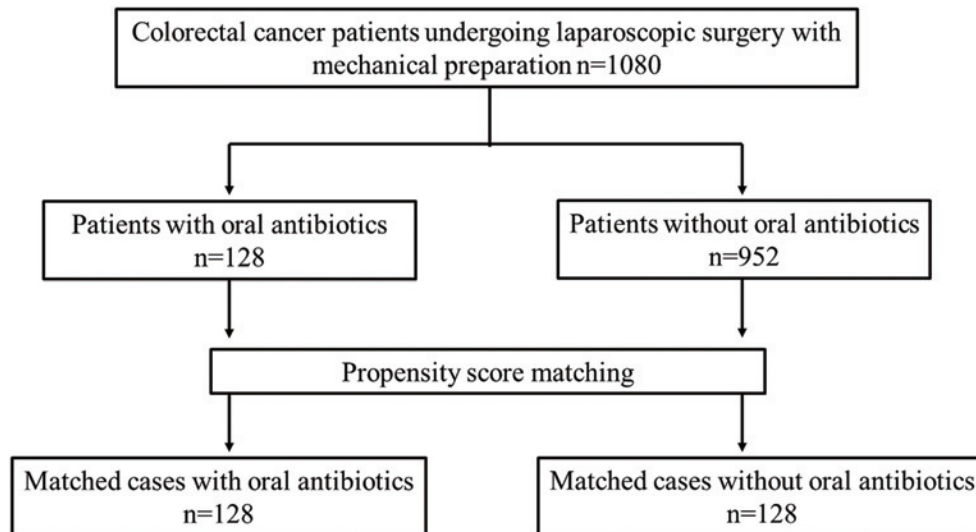


Figure 1. Flowchart showing the selection process for patient inclusion in the present study.

the same way.

Definition of SSI

SSI were diagnosed by surgeons or the colorectal cancer team of KPUM according to the CDC definition[1]. In the present study, incisional SSI rate was analyzed. The occurrence of SSI was recorded into the CRC database of KPUM until the discharge of patients. SSI data in the present study was extracted from the database.

Surgical procedures

All surgeries were performed or supervised by surgeons with sufficient experience and certificated by the Japan Society of Endoscopic Surgery and the Japanese Society of Gastrointestinal Surgery. The surgical procedure was selected based on the Japanese CRC guidelines[25]. Colectomy with radical lymph node dissection was performed on all patients with CRC.

Statistical analysis

A univariate analysis was performed using the variables of patients with CRC, grouped by OA (OA and non-OA groups). The Student's *t*-test was used for parametric continuous variables and the Mann-Whitney test for nonparametric variables. For categorical variables, the chi-squared test or Fisher's exact test was used. A multivariate analysis was performed using a logistic regression analysis to investigate the relationship between preoperative OA and SSI rate.

PSM was used to perform a 1:1 match on the following eight factors in two groups: sex, age, body mass index (BMI), the American Society of Anesthesiologists performance status (ASA-PS), diabetes mellitus, liver disease, preoperative serum albumin (Alb) levels, tumor location, and preoperative therapies. The match tolerance of PSM was set

at 0.20, and replacements were not allowed. All statistical tests were two-sided. P values of less than 0.05 were considered to be significant. All statistical analyses were performed using JMP version 10.

Results

Clinicopathological characteristics of all enrolled cases

The present study targeted 1080 patients with CRC according to inclusion and exclusion criteria, and 128 received preoperative OA. A flowchart of the present study is shown in Figure 1. Patient characteristics are summarized in Table 1. The median of age of patients was 67 years (14-93 years). The median BMI was 22.2 kg/m² (12.2-40.0). There were 126 and 17 patients with diabetes mellitus and severe liver disease, respectively. The median preoperative serum Alb value was 4.2 mg/dl (1.3-5.3 mg/dl). The tumor location was on the left side (rectum, sigmoid, and descending colon) in 723 patients and on the right side in 357 patients. Overall, 43 patients received preoperative chemotherapy or chemoradiotherapy. The median surgical time and blood loss were 219 minutes and 10 g, respectively. Incision SSI occurred in 121 patients (11.2%) and anastomotic leakage in 36 (3.3%).

Relationship between OA and clinical factors before PSM

The relationships between OA and clinical factors in all patients were examined (Table 2). No significant differences were observed in sex, BMI, diabetes mellitus, or tumor location. The OA group was significantly older than the non-OA group ($p = 0.038$). Preoperative serum Alb levels were significantly lower in the OA group than in the non-OA group ($p < 0.001$). The physical status of the OA group was sig-

Table 1. Patient Characteristics before Propensity Matching.

		n	
Total cases		1080	
Clinical characteristics			
Gender	Male	604	
	Female	476	
Age	Median	67	(14-93)
Body mass index	Median	22.2	(12.2-40)
ASA	1	657	
	2	387	
	3	35	
	4	1	
Diabetes mellitus	(+)	126	
	(-)	954	
Liver disease	(+)	17	
	(-)	1063	
Serum albumin (mg/dl)	Median	4.2	(1.3-5.3)
Location	Left	723	
	Right	357	
Oral antibiotics	(+)	128	
	(-)	952	
Preoperative therapy	(+)	43	
	(-)	1037	
Surgical findings			
Surgical time		219	(70-1009)
Blood loss	Median	10	(10-1843)
Postoperative complications			
Surgical site infection	(+)	121	
	(-)	959	
Anastomotic leakage	(+)	36	
	(-)	1044	

ASA-PS, American Society of Anesthesiologists performance status; left, left-side colon (rectum, sigmoid, and descending colon); right, right-side colon (transverse, ascending colon and cecum)

nificantly worse than that of the non-OA group ($p < 0.001$). The number of patients with severe liver disease was significantly higher in the OA group than in the non-OA group ($p = 0.002$).

PSM between OA and non-OA groups

PSM between the OA and non-OA groups was performed on the eight factors shown in Table 2. The relationship between OA and clinical factors in matched cases was shown in Table 3. No significant differences were observed in any of the factors tested between the OA and non-OA groups ($p = 0.283-1.000$).

Clinical value of preoperative OA for preventing SSI

Univariate and multivariate analyses of the relationships between SSI and clinical factors are shown in Table 4. No significant differences were observed in sex, age, BMI, ASA-PS, diabetes mellitus, liver disease, serum Alb levels, tumor location, or SSI. Blood loss, preoperative therapy, and

OA correlated with the rate of SSI ($p = 0.021, 0.010, \text{ and } 0.038$, respectively). The multivariate analysis of significant factors identified blood loss of 100 g or more and oral non-OA as independent risk factors for predicting SSI (hazard ratio (HR): 3.238, 95% confidence interval (CI): 1.119-8.712, $p = 0.031$; and HR: 2.547, 95%CI: 1.072-6.590, $p = 0.033$, respectively).

Discussion

Over the past 20 years, advances have been achieved in surgical techniques for CRC. Open colectomy was the standard surgery as a curative treatment until the 1980s and involved a long surgical incision of between 20 and 30 cm. Jacobs et al. performed the first series of laparoscopic colonic resections on 20 patients in 1991[26], and evidence for the safety and efficacy of laparoscopic colectomy was established[27-29]. The rate of laparoscopic surgery in all CRC surgeries was 72.0% in Japan in 2015. In our institute, the rate of laparoscopic surgery and conversion rate from laparoscopic to open surgery in 2018 were 91.6% and 3.3%, respectively. Since laparoscopic surgery is less invasive than open surgery, the rate of postoperative complications was predicted to be lower. Based on the background of CRC surgery, a cohort that contains only patients undergoing laparoscopic or open surgery needs to be analyzed in clinical research aimed at investigating the risk of postoperative complications in these surgeries.

Therefore, we herein examined the clinical value of OA using a cohort of patients with CRC undergoing laparoscopic surgery. The clinical value of OA was initially analyzed without PSM, and the results obtained showed that the right side colon, operative time, and BMI were independent risk factors of SSI (Supplement Table 1). The surgical procedure of laparoscopic surgery for the right side colon in our institute is as follows: (1) the right side of the colon is mobilized, (2) the artery and vein are dissected, and (3) the mobilized right side and ileum are pulled outside the abdomen. Therefore, the surgical incision for removing resected specimens needs to be sufficiently long to allow the passage of two intestinal tracts. However, the subcutaneous fat of patients with a high BMI or females under the surgical incision was thicker than that of patients with a low BMI or males, suggesting that the rate of SSI may be higher in these patients. Based on the results shown in Supplement Table 1, the homogenization of the frequency of these variables between the OA and non-OA groups needs to be performed using a statistical matching method, such as PSM, to accurately analyze the efficacy of OA.

The present study demonstrated that OA, blood loss, and preoperative therapies correlated with the rate of SSI in the univariate analysis. The multivariate analysis showed that blood loss and OA were independent risk factors for predict-

Table 2. The Association of OA with Clinical Factors before Propensity Matching.

Variables	Oral antibiotics (+)		Oral antibiotics (-)		<i>p</i>	
	n = 128	%	n = 952	%		
Gender	Male	73	57	531	55.8	0.788
	Female	55	43	421	44.2	
Age	Mean + SD	68.3 ± 12.4		65.8 ± 11.6		0.038
Body mass index		22.6 ± 3.5		22.5 ± 3.4		0.607
ASA-PS	1	53	41.4	604	63.4	<0.001
	2	68	53.1	319	33.5	
	3	7	5.5	28	2.9	
	4	0	0	1	0.1	
Diabetes mellitus	(+)	19	14.8	107	11.2	0.233
	(-)	109	85.2	845	88.8	
Liver disease	(+)	6	4.7	11	1.2	0.002
	(-)	122	95.3	941	98.8	
Albumin (mg/dl)	Mean + SD	3.98 ± 0.5		4.18 ± 0.4		<0.001
Location	Right	45	35.2	312	32.8	0.590
	Left	83	64.8	640	67.2	
Preoperative therapies	(+)	9	7	34	3.5	0.060
	(-)	119	92.9	918	96.4	

SD, standard deviation; ASA-PS, American Society of Anesthesiologists performance status; left, left-side colon (rectum, sigmoid, and descending colon); right, right-side colon (transverse, ascending colon and cecum)

Table 3. The Association of OA with Clinical Factors after Propensity Matching.

Variables	Oral antibiotics (+)		Oral antibiotics (-)		<i>p</i>	
	128	%	128	%		
Gender	Male	73	57	76	59.4	0.703
	Female	55	43	52	40.6	
Age	Mean + SD	68.3 ± 12.4		67.6 ± 11		0.683
Body mass index		22.6 ± 3.5		22.6 ± 3.6		0.976
ASA-PS	1	53	41.4	53	41.4	1.000
	2	68	53.1	68	53.1	
	3	7	5.5	7	5.5	
Diabetes mellitus	(+)	19	14.8	14	10.9	0.351
	(-)	109	85.2	114	89.1	
Liver disease		6	4.7	7	5.5	0.775
		122	95.3	121	94.5	
Albumin (mg/dl)		3.98 ± 0.5		3.98 ± 0.61		0.991
Location	Right	45	35.2	37	28.9	0.283
	Left	83	64.8	91	71.1	
Preoperative therapies	(+)	9	7	9	7	1.000
	(-)	119	92.9	119	92.9	

SD, standard deviation; ASA-PS, American Society of Anesthesiologists performance status; left, left-side colon (rectum, sigmoid, and descending colon); right, right-side colon (transverse, ascending colon and cecum)

ing SSI. Although a significant difference was not detected in BMI, SSI rate was slightly higher in patients with a high BMI than in those with a low BMI (7.7% vs 2.2%, $p < 0.102$). In future studies using a large cohort, BMI may also correlate with SSI. Furthermore, the rate of postoperative

complications did not increase after OA administration, and hospital stays were slightly shorter in the OA group than in the non-OA group (data was not shown). These results suggest that preoperative OA with MBP is safe and effective for the prevention of SSI in laparoscopic surgery for patients

Table 4. Univariate and Multivariate Analyses for Detecting Risk Factors of Surgical Site Infection.

		Univariate analysis				Multivariate analysis			
		SSI (+) n = 26		SSI (-) n = 230		p	HR	95%CI	p
Gender	Male	17	65.4	132	57.4	0.433			
	Female	9	34.6	98	42.6				
Age	≥81	1	3.8	31	13.5	0.159			
	<81	25	96.2	199	86.5				
Body mass index	≥30	2	7.7	5	2.2	0.102			
	<30	24	92.3	225	97.8				
ASA-PS	1	10	38.5	96	41.7	0.850			
	2	14	53.8	122	53				
	3	2	7.7	12	5.2				
Diabetes mellitus	(+)	4	15.4	29	12.6	0.689			
	(-)	22	84.6	201	87.4				
Liver disease	(+)	1	3.8	12	5.2	0.762			
	(-)	25	96.2	218	94.8				
Severe renal disease	(+)	1	3.8	3	1.3	0.321			
	(-)	25	96.1	227	98.7				
Severe pulmonary disease	(+)	0	0	4	1.7	0.497			
	(-)	26	100	226	98.2				
Steroid use	(+)	0	0	5	2.1	0.447			
	(-)	26	100	225	97.8				
Albumin (mg/dl)	≥3	25	96.2	215	93.5	0.593			
	<3	1	3.8	15	6.5				
Hemoglobin (g/dl)	≥10	20	76.9	150	65.2	0.231			
	<10	6	23	80	34.7				
Location	Right	9	34.6	73	31.7	0.767			
	Left	17	65.3	157	68.2				
Surgical time	≥210	16	61.5	125	54.3	0.484			
	<210	10	38.5	105	45.7				
Blood loss	≥100	8	30.8	23	10	0.021	3.238	1.119-8.712	0.031
	<100	18	69.2	207	90		Ref		
Oral antibiotics	(-)	18	69.2	110	47.8	0.038	2.547	1.072-6.590	0.033
	(+)	8	30.8	120	52.2		Ref		
Preoperative therapy	(+)	5	19.2	13	5.7	0.010	2.717	0.724-8.930	0.131
	(-)	21	80.8	217	94.3		Ref		

ASA-PS, American Society of Anesthesiologists performance status; severe renal disease, severe chronic renal disease or dialysis patients; severe pulmonary disease, respiratory failure with oxygen administration; steroid use, 5 mg or more prednisolone per day.

with CRC.

The present study has some limitations. This was a retrospective study with a small sample size, which may have limited the statistical power and generated a statistical bias. Although PSM was used to limit selection bias, some residual confounding factors may still have been unaccounted for. The longitudinal nature of the present study may have introduced a statistical bias between two groups due to changes in anesthetic or surgical techniques over the time period included; however, no major changes were noted other than the administration of OA.

Conclusion

The present PSM study using a cohort of patients who underwent laparoscopic CRC surgery only revealed that OA plus MBP prevented the occurrence of SSI, which is consistent with previous findings. OA with MBP needs to be adopted in laparoscopic surgery for colon cancer cases.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

M.K. and M.N. analyzed and interpreted the patient data

and were the major contributor in writing the manuscript. Y. K., T.A., H.S, J.K., H.I., T.K., H.F., and K.O. collected the patient data, such as clinicopathological factors. E.O. supervised all of the present study. K.K. performed a propensity score matching of the cohort. All of authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

The present study was approved by the Research Ethics Committee of the Kyoto Prefectural University of Medicine (No. ERB-C-1187-1). Comprehensive informed consent for the use of clinical data was obtained from all eligible patients. Moreover, informed consent was also obtained from the parents and/or legal guardians of minor patients involved in the study (age under 18 years).

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Supplementary Files

Supplementary Table 1. Univariate and multivariate analyses to identify risk factors for surgical site infection in a non-matched cohort.

Please find supplementary file(s);

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