Optimal duration of prophylactic antibiotic administration for elective colon cancer surgery: A randomized, clinical trial

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Background. *Procedures for perioperative infection prophylaxis in elective colon cancer surgery consist of preoperative mechanical preparation, chemical preparation with oral antibiotic administration, perioperative intravenous antibiotic administration, and others. However, the optimal combination of these procedures and drugs and their durations of administration have not yet been established. A randomized study was conducted to determine the optimal duration of perioperative antibiotic administration with use of mechanical and chemical preparation.*

Methods. *A total of 370 patients who were to undergo elective colon cancer surgery were randomized into 2 groups. After mechanical and chemical preparations, a single, 1-g dose of flomoxef was administered immediately before surgery to patients in group A. Flomoxef 1 g was administered twice daily for a total of 4 days from the day of surgery to postoperative day 3 to patients in group B.*

Results. *Comparison was performed between 179 patients in group A and 181 patients in group B with analyzable data. The incidences of incisional surgical site infections (SSIs), organ/space SSIs, and remote infections (RIs) were 15 patients (8.4%), 1 patient (0.6%), and 8 patients (4.5%), respectively, in group A, and 13 patients (7.2%), 2 patients (1.1%), and 6 patients (3.3%), respectively, in group B. There were no differences in the incidence of incisional SSIs, organ/space SSIs, or RIs between groups A and B.*

Conclusion. *It was shown that a single dose of intravenous antibiotic immediately before surgery is sufficient as perioperative infection prophylaxis in elective colon cancer surgery when mechanical and chemical preparation is performed. (Surgery 2011;149:171-8.)*

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Postoperative infection causes various problems, such as prolongation of hospital stay, increase in medical costs, and decrease in patient satisfaction.[1-3] Guidelines for the prevention of postoperative infection and proper antibiotic use have therefore been proposed by the Centers for Disease Control and Prevention (CDC) and other organizations.[4,5]

In digestive tract surgery, the benefits of prophylactic antibiotic administration for prevention of surgical site infection (SSI) have been established.[6-8] Based on the US guidelines, single-dose administration of an antibiotic within 1 hour before surgery and the duration of administration within 24 hours after the end of surgery had been recommended, even in clean-contaminated surgery.[4,5] The Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy published guidelines in 2005, in which the duration of prophylactic antibiotic administration should be 4 days or less in clean-contaminated surgery.

A questionnaire survey conducted in 1994 showed that the duration of antibiotic administration after colon cancer surgery was within 3 days in only 25.2% of cases and ≥5 days in 59.1% of cases.[9] The survey in 2003 showed that administration within 3 days postoperatively accounted for 63.3% of cases.[10] A questionnaire survey conducted by the Japan Society for Surgical Infection in 2008 revealed a tendency toward decrease in the duration of administration, with administration within 3 days postoperatively accounting for 96% of cases. However, there is still a large

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difference from the recommendations of the US guideline.[11]

Surgery of the large bowel is associated with a high incidence of SSI compared with other parts of the digestive tract. It has been reported that 30–40% of patients experience postoperative SSIs when prophylactic antibiotic is not administered.[12] The reported causal microorganisms are anaerobes and *Escherichia coli*, which account for 56% and 46%, respectively, of such infections.[13] There are 10^{6-8} aerobes and 10^{10-11} anaerobes (mainly *Bacteroides*) in 1 g of feces. Therefore, the important factor in selecting a prophylactic antibiotic is antimicrobial activity against anaerobes.[14] The CDC guidelines recommend use of antibiotics that are also effective against anaerobes, as a single agent or in combination to prevent postoperative infection in colorectal surgery.[4]

Flomoxef is an oxacephem antibiotic with higher stability than conventional cephem antibiotics against β-lactamase, which is produced by various bacteria. Flomoxef, which shows bactericidal activity, is classified as a second-generation cephem based on its antibacterial spectrum against Gram-positive and -negative organisms. Flomoxef exhibits potent antimicrobial activity against anaerobes such as *Bacteroides fragilis*.[15] Currently, flomoxef is widely used to prevent postoperative infection after clean-contaminated surgery in Japan.

The Diagnosis-Related Group system was introduced in the United States in 1983 and in Japan in 2003 to reduce medical costs.[16] In particular, there has been much interest in the optimal duration of perioperative prophylactic antibiotic administration for prevention of postoperative infection; however, this duration has yet to be established.

Three measures are used for prophylaxis of perioperative infection in elective colorectal surgery: (1) preoperative mechanical bowel preparation; (2) preoperative chemical preparation with oral antibiotic administration; and (3) perioperative intravenous antibiotic administration. We conducted a randomized study to establish the optimal duration of perioperative antibiotic administration of flomoxef in patients undergoing elective colon cancer surgery, by determining the incidence of SSIs with use of mechanical preparation and chemical preparation together with oral antibiotic administration.

PATIENTS AND METHODS

Of 547 patients who underwent elective laparotomy for colon cancer from August 2002 to October 2007, 370 patients were enrolled in this study after excluding patients with stoma, those who could not undergo the normal mechanical preparation owing to stenosis or obstruction, and those with a preoperative diagnosis of stage IV and American Society of Anesthesiologists (ASA) score of $\geq$3 (Fig). This study was approved by the institutional review board, and written informed consents were obtained from all patients.

Registration and randomization. The patients were randomized into 2 groups using a random number table 1 week before operation. Group A received a single dose, whereas group B received 3 additional days of treatment. For randomization, the minimization method was used with gender as an adjustment factor. All patients underwent the same bowel preparations and operative procedures.

Preoperative preparations and operative procedures. All patients underwent mechanical and chemical preparation of the bowel. For mechanical preparation, 10 mL of sodium picosulfate (Laxoberon) was orally administered 2 days before surgery, and 2,000 mL of Niflec (2 L of polyethylene glycol-electrolyte sodium; Ajinomoto Pharma, Tokyo, Japan) was orally administered in the morning of the day before surgery. As chemical preparation, 0.5 g of kanamycin sulfate, and 0.5 g of metronidazole were orally administered at 1, 2, and 11 PM on the day before the operation.

All patients underwent laparotomy through median incision. Immediately before the completion of surgery, intra-abdominal irrigation was performed using 3,000 mL of physiologic saline, and a closed drain was placed. The peritoneum and aponeuroses were closed with interrupted absorbable monofilament sutures, polydioxanone (PDSII, USP suture size 0). After cleansing the wound with 300 mL of physiologic saline, the skin was closed with interrupted, nonabsorbable, monofilament sutures, nylon (USP suture size, 3-0).

Prophylactic antibiotics. For the single-dose group (group A), a single dose of flomoxef 1 g was administered before surgery. For the 3-day group (group B), flomoxef 1 g was administered twice daily for a total of 4 days from the day of surgery to postoperative day 3. In both groups, flomoxef was given by intravenous drip infusion from 1 hour before the incision was made. When the operative time exceeded 3 hours, flomoxef 1 g was additionally administered.

Postoperative infection. Postoperative infection was defined as the infection occurring within 30 days after surgery. SSIs were diagnosed by $\geq$2 physicians. Incisional SSI was defined as macroscopic abscess or purulent discharge observed on

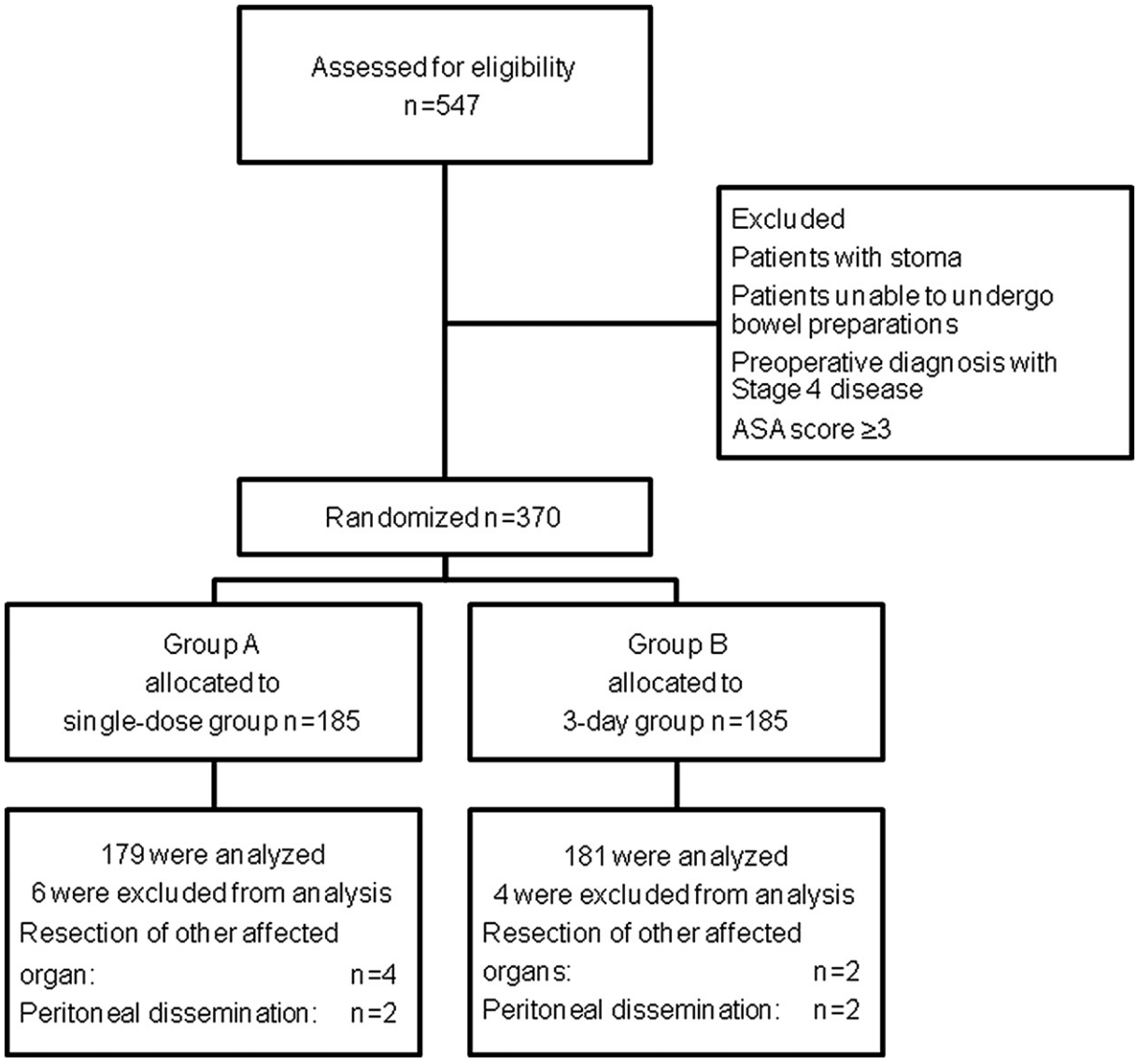

Figure. Trial profile.

the operative wound. Organ/space SSI was defined as infection in the organ subjected to surgery. Culture tests were performed using abscess or purulent discharge. Remote infection (RI) was evaluated by chest plain films, sputum, urine, blood, or catheter culture after surgery. The mean hospital stay of patients with colon cancer is 15 ± 4 days (facility data). Wound infection was assessed in the hospital ward during hospitalization. After discharge, wound condition was evaluated at a hospital visit 4 weeks postoperatively. Infected wounds were qualitatively cultured for aerobes and anaerobes using standard laboratory techniques.

Outcome measures. The primary end point was the incidence of incisional SSIs and organ/space SSIs. The secondary end point was the incidence of RIs.

Statistical analysis. Comparisons between groups were performed using the Student *t* test for continuous variables, the Chi-square test for binary or nominal categorical variables, and the Mann-Whitney *U* test for ordinal categorical variables, with findings of $P < .05$ considered significant. A handicap test was performed to demonstrate noninferiority, with a significance level of .025.

The results of the national survey conducted by the Japanese Society of Chemotherapy showed that the incidence of postoperative SSIs in patients who received a preoperative oral antibiotic was 11.4% in lower intestinal surgery.[17] Based on this result, assuming a 12% wound infection rate, a 10%

Table I. Patient characteristics

Characteristic	*Single-dose group 185*	*3-day group 185*	P *value*
Age, mean ± SD (y)	65 ± 11	66 ± 9	.40*
Gender			
Male	101	101	>.99†
Female	84	84	
Tumor location			
Right side	66	50	.17‡
Transverse	33	42	
Left side	86	93	
T category			
Tis, T1	21	29	.29†
T2–T4	164	156	
TNM classification			
I	35	48	.13‡
II	81	85	
III	67	50	
IV	2	2	
Diabetes mellitus			
Yes	17	14	.71†
No	168	171	
ASA score			
1	163	168	.50†
2	22	17	
Preoperative Hb (g/dL)	12.1 ± 2.2	12.1 ± 2.0	.89*
Preoperative Alb (g/dL)	4.1 ± 0.5	4.1 ± 0.5	.83*
Operative time, mean ± SD (min)	140 ± 39	145 ± 40	.25*
Blood loss, mean ± SD (mL)	199 ± 147	178 ± 149	.17*
Blood transfusion			
Yes	7	8	>.99†
No	178	177	
Additional dose	29	34	.49

*Student *t* test.
†Chi-square test.
‡Mann-Whitney *U* test.
ASA, American Society of Anesthesiologists; *Hb*, hemoglobin; *Alb*, albumin.

Table II. Postoperative infectious disease and other postoperative complications, no. (%) of patients

	Single-dose group (n = *179*)	*3-day group* (n = *181*)	P *value* (*Δ = 0.10*)
Incisional SSI	15 (8.4)	13 (7.2)	.0008
Organ/space SSI	1 (0.6)	2 (1.1)	<.001
Remote infection	8* (4.5)	6† (3.3)	<.0001
SBO	5 (2.8)	8 (4.4)	<.0001
C. difficile colitis	0 (0)	0 (0)	<.0001
Other	2‡ (1.1)	2§ (1.1)	<.0001

*Catheter infection in 6 patients, internal jugular vein phlebitis in 1 patient, pneumonia in 1 patient.
†Catheter infection in 4 patients, pneumonia in 1 patient, urinary tract infection in 1 patient.
‡Venous thrombosis of the leg in 1 patient, duodenal stenosis in 1 patient.
§Postoperative hemorrhage in 1 patient, duodenal stenosis in 1 patient.
Δ, Noninferiority margin; *SSI*, surgical site infection.

noninferiority margin, and a 10% dropout rate, the sample size required to demonstrate noninferiority of group A to B by ≥10% was calculated to be 183 patients. This study was designed to have 0.80 power and a 1-sided significance level of 0.025.

RESULTS

A total of 370 patients were enrolled in the study, with 185 patients in each group. Patient clinical characteristics are shown in Table I. No difference was observed between the groups in age, gender, tumor sites, preoperative hemoglobin or albumin levels, presence or absence of diabetes mellitus, ASA score, distribution of histologic stage, operative time, amount of bleeding, presence or absence of transfusion, or additional dose of flomoxef.

Peritoneal metastasis was detected in 2 patients each in groups A and B. Four patients in group A and 2 patients in group B underwent resection of other affected organs. These 10 patients were excluded from analysis as ineligible, and comparisons were performed between 179 patients in group A and 181 patients in group B (Fig 1).

On analysis of the primary end point, the incidence of incisional SSIs was 15 patients (8.4%) in group A and 13 patients (7.2%) in group B (Table II). In addition, organ/space SSI was found in 1 patient (0.6%) in group A and 2 patients (1.1%) in group B. These 3 organ/space SSIs were caused by anastomotic leakage. Given the noninferiority margin of 10%, group A was considered noninferior to group B regarding incisional SSI and organ/space SSI. It thus seemed that the incidence of infection in the single-dose group was not ≥10% higher than that in the 3-day dose group. On analysis of the secondary end point, the incidence of RI was 8 patients (4.5%) in group A and 6 patients (3.3%) in group B, showing that group A was noninferior to group B for incisional and organ/space SSIs.

Other postoperative complications included small bowel obstruction in 5 patients, venous thrombosis of the lower extremities in 1 patient, and duodenal stenosis in 1 patient in group A, and small bowel obstruction in 8 patients, postoperative hemorrhage in 1 patient, and duodenal stenosis in 1 patient in group B, with no significant

difference between the groups (Table II). In addition, no colitis caused by *Clostridium difficile* was observed in either group.

The causal micro-organisms of SSIs were isolated and identified for 11 of 15 patients in group A and 12 of 13 patients in group B (Table III). Microorganisms isolated in group A were *Staphylococcus epidermidis, S aureus,* methicillin-resistant *S aureus* (MRSA), *Enterococcus* spp., *Enterococcus faecalis, Enterobacter cloacae, Pseudomonas aeruginosa*, and *B. fragilis* group organisms as anaerobes, whereas those in group B were *S. epidermidis, S. aureus, Enterococcus* spp., *E. faecalis, E. cloacae*, and *P. aeruginosa*. Three organ/space SSIs were identified by examination of drained intestinal fluid.

Eleven of 15 patients in group A and all 13 patients in group B with SSIs did not develop fever, and were improved by removal of some sutures and abscess drainage. In group A, 2 patients developed fever and were treated with antibiotics as well as abscess drainage. In group B, no patient received an additional antibiotic. Each organ/space SSI patient developed fever and required reoperation.

Catheter infection, 1 of the RI, was found in 6 patients in group A and 4 patients in group B. The causal microorganism in 4 patients in group A and 3 patients in group B was *S. epidermidis*. The RIs were detected on the third day or later in group A and on postoperative day 5 or later in group B (Table IV). All patients with catheter infection developed fever. In 5 patients in group A and 3 patients in group B, the fever resolved after catheter removal and antibiotic administration. In 1 remaining patient each in groups A and B, pyrexia resolved after catheter removal only.

Table III. Culture isolates from incisional SSI

Patient no.	*Administration*	*Organisms**
2	Single	*Staphylococcus epidermidis* (trace)
3	Single	*Pseudomonas aeruginosa* 2+, *Enterococcus* spp.(trace)
4	Single	*Staphylococcus aureus* 1+
5	Single	*Enterococcus* spp. 1+, *Staphylococcus epidermidis* (trace)
6	Single	MRSA 2+
7	Single	MRSA 3+, *Enterococcus faecalis* 2+
8	Single	*Pseudomonas aeruginosa* 1+
10	Single	*Enterococcus faecalis* 1+, *Staphylococcus epidermidis* 1+, *Bacteroides fragilis* group 1+
11	Single	*Enterobacter cloacae* trace, MRSA 3+, *Enterococcus faecalis* 2+
12	Single	*Pseudomonas aeruginosa* 2+
14	Single	*Pseudomonas aeruginosa* 3+
16	3-day	*Pseudomonas aeruginosa* 3+
18	3-day	*Staphylococcus aureus 2+*
19	3-day	*Pseudomonas aeruginosa* 1+
20	3-day	*Enterococcus* spp. 1+
21	3-day	*Pseudomonas aeruginosa* 1+, *Enterococcus* spp. 1+
22	3-day	*Enterococcus faecalis* 1+
23	3-day	*Pseudomonas aeruginosa* 1+, *Enterobacter cloacae* 1+, *Enterococcus faecalis* 1+
24	3-day	*Pseudomonas aeruginosa* 1+
25	3-day	*Staphylococcus epidermidis* 2+
26	3-day	*Enterococcus faecalis* (trace)
27	3-day	*Pseudomonas aeruginosa* 3+
28	3-day	*Pseudomonas aeruginosa* 1+

*Growth level on the dish: (trace); 1+, low; 2+, intermediate; 3+, high.

DISCUSSION

The following 3 perioperative measures have been discussed as infection prophylaxis in elective surgery of large intestine, unlike other digestive tract operations: (1) preoperative mechanical preparation; (2) preoperative chemical preparation; and (3) intravenous antibiotic administration from immediately preoperatively.

There are reports indicating lack of difference in the incidence of SSIs whether or not mechanical preparation was performed.[18-21] However, Platell et al[22] combined the results of 2 trials (Jung et al[20] and Contant et al[21]) and reported that the incidence of anastomotic leakage and intraperitoneal abscess was 4.8% with mechanical preparation and 7.2% without it, indicating a significant decrease after mechanical preparation.[22] Recently, Slim et al[23] reported a lack of difference in the incidence of SSIs, abdominal abscess, or anastomotic leakage whether or not mechanical preparation was performed, in a meta-analysis of the results of 14 randomized studies (4,859 patients).

The US guidelines recommend preoperative antibiotic administration, including a combination of oral nonabsorbable neomycin and erythromycin with antimicrobial activity against anaerobes or a combination of oral neomycin and metronidazole with antimicrobial activity against anaerobes. Because neomycin has not been approved in Japan, we used kanamycin instead. In the United States, the frequency of use of oral antibiotics was 70% in 2000; however, this percentage has subsequently tended to decrease.[24] In Japan, a recent survey showed that preoperative oral antibiotic administration was used in 17.8% of cases and percentage of use of mechanical preparation alone without oral antibiotic is 80.7%.[10]

Table IV. Culture isolates from remote infections

Patient no.	*Administration*	*Remote infection**	*Organisms†*
1	Single	Pneumonia	*Pseudomonas aeruginosa* 2+
2	Single	Catheter infection	MRSA 1+
3	Single	Catheter infection	*Staphylococcus epidermidis* 1+
4	Single	Jugular vein phlebitis‡	MRSA 2+
5	Single	Catheter infection	*Staphylococcus epidermidis* (trace)
6	Single	Catheter infection	*Staphylococcus epidermidis* 1+
7	Single	Catheter infection	*Staphylococcus epidermidis* 1+
8	Single	Catheter infection	*Candida tropicalis* 1+
9	3-day	Catheter infection	*Staphylococcus epidermidis* 1+
10	3-day	Pneumonia	*Pseudomonas aeruginosa* 2+, *Haemophilus parainfluenzae* 3+
11	3-day	Catheter infection	*Staphylococcus epidermidis* 1+
12	3-day	Catheter infection	*Enterococcus faecalis* 3+
13	3-day	Urinary tract infection	*Enterococcus faecalis* 10^7, *Enterobacter cloacae* 10^5, *Klebsiella oxytoca* 10^5, *Staphylococcus haemolyticus* 10^5
14	3-day	Catheter infection	*Staphylococcus epidermidis* 1+

*The organisms were isolated and identified using sputum from patient 1, urine from patient 13, and catheters of all other patients.
†Growth level on the dish: (trace); 1+, low; 2+, intermediate; 3+, high.
‡Patient 4 was diagnosed with phlebitis, because MRSA was isolated from the inserted catheter (IVH) and from abscess of the IVH insertion site; however, MRSA was not isolated from blood, and the patient suffered from obstruction thought to have been induced by thrombus and prolonged fever.
Values obtained from urine are shown as viable cell count/mL.
MRSA, Methicillin-resistant *Staphylococcus aureus.*

Two meta-analyses revealed no significant difference in the incidence of SSIs in major operations between a single dose of intravenous antibiotic administration and multiple doses.[25,26] However, there are also reports that short-term prophylactic antibiotic administration has not been complied with.[27] Based on the report of 2005 by Bratzler et al,[24] the duration of prophylactic antibiotic administration for major surgery in the U.S. was not more than 12 hours in 14.5% of cases and was not more than a day remained in 40.7% of cases.

The presence or absence of the preoperative mechanical preparation and chemical preparation with oral antibiotic administration and the methods were various among trials that have been conducted to examine infection prophylaxis measures in colorectal surgery. The optimal duration of intravenous antibiotic administration has not yet been determined. The results of meta-analyses of 147 trials indicated that an antibiotic effective against both aerobes and anaerobes should be given in large intestinal surgery.[28]

Therefore, we sought to determine the optimal duration of antibiotic administration using flomoxef in patients who undergo elective colon cancer surgery, with provision of mechanical preparation and oral antibiotic administration on the day before surgery in accordance with the CDC guidelines. To ensure homogeneity among patients, patients with a preoperative diagnosis of stage IV disease were excluded. In addition, patients with an intraoperative diagnosis of stage IV disease and those who underwent resection of other affected organs were excluded from the analysis. ASA classification, wound classification, and operative times have been reported as risk factors for SSI.[29] Other reported factors include age ≥65 years,[30] diabetes mellitus, inadequate nutrition, anemia, transfusion, and the number of coexisting disorders.[4,31,32] In the present study, there was no difference in any of these factors between the 2 groups (Table I).

With a noninferiority margin of 10%, there were no differences in the incidence of SSIs, organ/space SSIs, or RIs between group A, given a single dose of prophylactic antibiotic administration immediately preoperatively (single-dose group) and group B, given doses of prophylactic antibiotic administration for 4 days, including the day of operation (3-day group).

Recently, Fujita et al[33] conducted a randomized study using cefmetazole to determine the duration of administration required to prevent postoperative infection in colon and rectal cancer surgeries. Cefmetazole has strong antimicrobial activity

against anaerobes and is classified as a second-generation cephem, like flomoxef. The incidence of SSIs after 3 doses of cefmetazole (just before skin incision and 8 and 16 hours later) was significantly lower than that with a single dose (just before skin incision), and the authors concluded that use of 3 doses is beneficial. However, an oral antibiotic was not administered on the day before surgery in their study; this was a major difference from our protocol.

Aerobes believed to be skin derived were isolated from a total of 7 patients in group A, including 3 patients with *S. epidermides*, 1 patient with *S. aureus*, and 3 patients with MRSA. In group B, *S. epidermidis* and *S. aureus* were isolated from 1 patient each. Aerobes believed to be enteric bacteria derived were isolated from a total of 10 patients in group A, including 4 patients with *P. aeruginosa*, 2 patients with *Enterococcus* spp., 3 patients with *E. faecalis*, and 1 patient with *E. cloacae*. In group B, aerobes were isolated from a total of 13 patients, including 7 patients with *P. aeruginosa*, 2 patients with *Enterococcus* spp., 3 patients with *E. faecalis*, and 1 patient with *E. cloacae*. Anaerobes account for most of the enterobacterial flora. However, anaerobes were detected in only 1 patient in group A and were not detected in group B. These results indicate that intravenous infusion of flomoxef together with mechanical preparation and metronidazole administration are effective in removing anaerobes. *S. epidermides*, *Enterococcus* spp., and *P. aeruginosa* were relatively frequently isolated in both groups A and B. This seemed to be because of insufficient prophylaxis; flomoxef is not indicated for these types of bacteria and, regarding *P. aeruginosa*, kanamycin, compared with other newer aminoglycoside antibiotics, given preoperatively is easily affected by various inactivated enzymes that bacteria produce.[34]

Recently, there has been an unfavorable opinion for preoperative oral antibiotic administration, since enterobacterial flora is disturbed, and isolation frequency of *C. difficile* increases even by a single dose preoperatively.[35] In the present study, no patient suffered from *C. difficile*-induced colitis.

In conclusion, it is sufficient as perioperative infection prophylaxis to provide a single dose of prophylactic intravenous antibiotic immediately preoperatively, and an additional dose every 3 hours when the operative time exceeds 3 hours in elective colon cancer surgery, when providing mechanical preparation with polyethylene glycol (PEG) and preoperative oral antibiotic administration for 1 day. These findings support the CDC guidelines for perioperative antibiotic administration. Further investigation is needed to determine whether oral antibiotic administration on the day before surgery is required, when providing a single dose of antibiotic. In addition, a separate investigation is needed to determine the required frequency and duration of prophylactic antibiotic administration in patients with stoma, those who cannot undergo the normal preoperative mechanical preparation owing to stenosis or obstruction, and those with rectal cancer.

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