Comparison between oral antibiotics and probiotics as bowel preparation for elective colon cancer surgery to prevent infection: Prospective randomized trial

Sotaro Sadahiro, MD,[a] Toshiyuki Suzuki, MD,[a] Akira Tanaka, MD,[a] Kazutake Okada, MD,[a] Hiroko Kamata, MD,[a] Toru Ozaki, BS,[b] *and* **Yasuhiro Koga, MD,[c]** *Isehara and Kobe, Japan*

Background. *We have already reported that, for patients undergoing elective colon cancer operations, perioperative infection can be prevented by a single intravenous dose of an antibiotic given immediately beforehand if mechanical bowel preparation and the administration of oral antibiotics are implemented. Synbiotics has been reported to reduce the rate of infection in patients after pancreatic cancer operations. The effectiveness of oral antibiotics and probiotics in preventing postoperative infection in elective colon cancer procedures was examined in a randomized controlled trial.*

Methods. *Three hundred ten patients with colon cancer randomly were assigned to one of three groups. All patients underwent mechanical bowel preparation and received a single intravenous dose of flomoxef immediately before operation. Probiotics were administered in Group A; oral antibiotics were administered in Group B; and neither probiotics nor oral antibiotics were administered in Group C. Stool samples were collected 9 and 2 days before and 7 and 14 days after the procedure. Clostridium difficile toxin and the number of bacteria in the intestine were determined.*

Results. *The rates of incisional surgical-site infection were 18.0%, 6.1%, and 17.9% in Groups A, B, and C, and the rates of leakage were 12.0%, 1.0%, and 7.4% in Groups A, B, and C, respectively, indicating that both rates were lesser in Group B than in Groups A and C (*$P = .014$ *and* $P = .004$*, respectively). The detection rates of C. difficile toxin were not changed among the three groups.*

Conclusion. *We recommend oral antibiotics, rather than probiotics, as bowel preparation for elective colon cancer procedures to prevent surgical-site infections. (Surgery 2014;155:493-503.)*

From the Department of Surgery,[a] Tokai University, Isehara; Biofermin Kobe Research Institute,[b] Biofermin Pharmaceutical Co, Ltd, Kobe; and Department of Infectious Disease,[c] Tokai University, Isehara, Japan

Colorectal surgery has been reported to involve postoperative surgical-site infection (SSIs) in 30−40% of cases who do not receive prophylactic antibiotics.[1] According to recent reports, the rates of SSI after colon cancer operation ranges from 5.8% to 23.2%.[2-8]

Postoperative infection causes prolongation of hospitalization, an increase in medical costs, a decrease in patient satisfaction, and various other problems.[9-11] To prevent postoperative infection and ensure the appropriate use of antibiotics, the Centers for Disease Control and Prevention and other groups have issued clinical guidelines regarding postoperative infection.[12,13]

Pre- and perioperative measures intended to prevent infection in elective colon surgery include: (1) mechanical bowel preparation before surgery; (2) chemical preparation with oral antibiotics; and (3) intravenous antibiotic prophylaxis immediately before surgery.

The outcomes of these procedures, however, vary among studies with respect to their effectiveness in preventing postoperative infection, and no consensus has been reached on the need for these measures.

To establish optimal bowel preparation in this situation, it was necessary to conduct a randomized controlled trial (RCT) in which three factors—mechanical bowel preparation, preoperative oral

T. Ozaki is an employee of Biofermin Pharmaceutical Co, Ltd.

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Reprint requests: Sotaro Sadahiro, MD, Department of Surgery, Tokai University, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan. E-mail: Sadahiro@is.icc.u-tokai.ac.jp.

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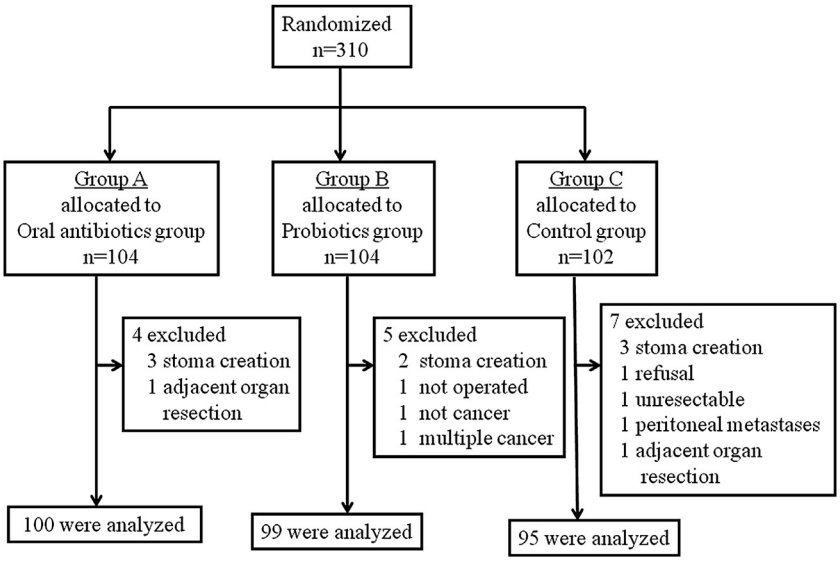

Fig 1. Trial flow chart.

antibiotic administration, and intravenous antibiotic administration immediately before surgery—were strictly controlled.

In an RCT in which we used flomoxef, a second-generation cephem antibiotic, when mechanical bowel preparation and chemical preparation with oral antibiotics are performed, a single intravenous dose of an antibiotic given immediately before operation is sufficient to prevent perioperative infection without the need for subsequent doses.[14] Flomoxef, an oxacephem antibiotic, is highly stable against β-lactamase produced by various types of bacteria compared with older-generation cephem antibiotics.[15]

In bowel preparation, the use of oral antibiotics was reported to decrease the incidence of SSI[4,16] but increasingly more surgeons have avoided the use of oral antibiotics in recent years.[17,18]

A recent report stated that the administration of oral antibiotic increases the risk of infection by *Clostridium difficile* (CD),[19] whereas other reports have stated that there is no such association.[16,20] The association between oral antibiotic prophylaxis and CD infection has not been established. An additional report indicated that CD infection occurs irrespective of the duration of antibiotic use.[21] An RCT has shown that, in hospitalized patients treated with antibiotics, *Lactobacillus*, a probiotic, is effective against CD toxin and CD-associated diarrhea.[22] It was reported that synbiotics, which are a combination of probiotics and prebiotics that are nondigestable food constituents, reduced the rate of infection in patients undergoing pancreatic cancer operations,[23] but there is no such report for patients with colon cancer.

Because the possibility cannot be ruled out that our regimen may increase the risk of CD infection despite the use of oral antibiotics for as little as 1 day, we compared the clinical usefulness of oral antibiotics with that of probiotics and control treatment in an RCT with strict control of two conditions, ie, performing the same mechanical bowel preparation and perioperative intravenous antibiotic prophylaxis in all treatment groups.

MATERIALS AND METHODS

Patients and methods. This study enrolled patients scheduled to undergo elective colon cancer operations between May 2008 and October 2011 in whom curative resection of tumor(s) was considered feasible. The eligibility criteria were as follows: 20−80 years of age; preoperative performance status of 0 or 1; and no serious coexisting medical conditions. Patients with a history of intestinal resection, patients with a stoma, patients with intestinal stenosis or obstruction that would preclude routine preoperative mechanical bowel preparation, and patients with stage IV disease on preoperative diagnosis were excluded from this study. Enrollment and randomization were performed when the operation date was fixed, and 310 patients were enrolled (Fig 1).

Enrollment and randomization. Patients randomly were assigned to one of three groups: (1) probiotics, *Bifidobacteria*-treated group (Group A); (2) oral antibiotics-treated group (Group B); and (3) control group (to which neither probiotics

Table I. Treatment in each group

Group	*Treatment*	*Time, days*
Group A		
Probiotics	BFT, 3 tablets/time, 3 times/day (oral)	−8 to −2 5–15
Group B		
Oral antibiotics	Kanamycin 0.5 g + Metronidazole 0.5 g (oral)	−1 (1, 2, 11 pm)
Group C		
Control		
Each group		
Mechanical preparation	Sodium bicosulfate 10 mL	−2
	Polyethylene glycol 2000 mL	−1
Intravenous antibiotics	Flomoxef 1 g (infusion, 1 h)	Perioperative

BFT, Bifidobacteria tablet.

nor oral antibiotics were administered) (Group C), whereas all patients underwent standard mechanical bowel preparation with an oral intestinal lavage solution (Niflec; Ajinomoto Pharma, Tokyo, Japan) and received 1 g flomoxef by intravenous drip infusion immediately before operation as common procedures. The cancer sites were categorized into three regions: right-sided colon (cecum and ascending colon), transverse colon, and left-sided colon (descending colon, sigmoid colon, and rectosigmoid junction). Randomization was performed by one of the authors (H.K.) according to the minimization method with tumor site as a stratification factor.

Patients who underwent concurrent resection of adjacent organs or stoma creation during the operation, patients who were found to have peritoneal metastases, and patients in whom the primary lesion could not be resected were considered ineligible and excluded from analyses (Fig 1).

This study was approved by the Ethics Committee of Tokai University, and all patients provided written informed consent. The trial registration number is University Hospital Medical Information Network (UMIN) Clinical Trials Registry 000003435.

Mechanical bowel preparation. All patients underwent mechanical bowel preparation. Patients orally ingested 10 mL of sodium picosulfate (Laxoberon, Teijin Ltd, Osaka, Japan) 2 days before surgery and 2,000 mL of polyethylene glycol–electrolyte sodium (Niflec, Ajinomoto Pharma, Tokyo, Japan) in the morning of the day before the operation (Table I).

Intravenous antibiotic prophylaxis. All patients received a single preoperative 1-g dose of flomoxef (Shionogi & Co, Ltd, Osaka, Japan), a second-generation cephem antibiotic. Intravenous drip infusion of flomoxef was initiated 1 hour before making an incision. When the operation time exceeded 3 hours, another 1 g dose of flomoxef was administered (Table I).

Chemical preparation and administration of probiotics. *Group A.* Patients took three *Bifidobacteria* tablets (Biofermin Pharmaceutical Co, Ltd, Kobe, Japan) orally after each meal three times daily for 7 days before the operation and from postoperative day 5 for 10 days. *Bifidobacteria* is a tablet formulation containing at least 10 billion viable *Bifidobacterium bifidum* per nine tablets, as well as maltooligosaccharide powder, dextrin, precipitated calcium carbonate, magnesium stearate, and corn starch as inactive ingredients.

Group B. Patients ingested 0.5 g kanamycin sulfate and 0.5 g of metronidazole orally at 1:00 pm, 2:00 pm, and 11:00 pm the day before the procedure as a chemical bowel preparation.

Group C. Neither probiotics nor oral antibiotics were administered.

Operative procedures. In all patients undergoing an open procedure, an abdominal midline incision was made. Disinfection of the surgical site was performed with povidone−iodine−alcohol immediately before incision. Intraperitoneal irrigation was performed with 3,000 mL of physiological saline immediately before the completion of the operation and a closed drainage tube was inserted. The peritoneum and aponeurosis were closed with an interrupted suture technique using polydioxanone sutures (PDS II, USP suture size 0; Ethicon, Inc, Bridgewater, NJ), an absorbable monofilament suture.

After we irrigated the surgical wound with 300 mL of physiological saline, the skin was closed with an interrupted suture technique with nylon sutures (USP suture size 3-0) or with a subcuticular suture technique using polydioxanone sutures (USP suture size 4-0). In laparoscopic colectomy,

intraperitoneal irrigation was performed with 300 mL of physiological saline immediately before the completion of surgery, and no drainage tube was used, in principle. After irrigating the surgical wound with 300 mL of physiological saline, the skin was closed with a subcuticular suture technique with polydioxanone sutures (USP suture size 4-0).

All operations were performed by four or five members, consisting of two or three staff surgeons (S.S., T.S., A.T., or K.O.) and one or two members of the surgery team. Intraoperative monitoring was performed by anesthesiologists, who were blinded to the study information. During the surgery, no blood sugar control was performed unless the patient had diabetes mellitus. A Bair Hugger Temperature Management Unit (Arizant, Eden Prairie, MN) was used for intraoperative warming of the patient.

Postoperative infection. In this study, "postoperative infection" was defined as infection that occurred within 30 days after surgery. Surgical site infection (SSI) was classified as incisional SSI or organ/space SSI: the former was defined as infection with a discharge or the presence of gross pus or purulent exudates in the surgical wound and the latter as infection in the organs/tissues in the area in which surgery was performed.

Pus and purulent exudates were subjected to culture. Remote infection was assessed by postoperative plain chest x-ray, and cultures of sputum, urine, blood, and the catheter used. The mean hospital stay for colon cancer patients was 14 ± 4 days (in-hospital data). Wound infection was assessed in the hospital ward during hospitalization. A diagnosis of SSI was made by one of the staff surgeons and members of the surgery team during hospital stay. After the patient was discharged, the operative wound was assessed at an outpatient visit about 4 weeks after surgery by one of the staff surgeons. The staff surgeons and members of the surgical team were blinded to the information on patient allocation in this study. Specifically, oral antibiotics and probiotics were administered by nurses, and the staff members involved in SSI assessment were blinded to the treatment information.

Collection of stool samples for fecal examination. Stool samples were collected during the 2−3 weeks before surgery (Day −9), 2 or 3 days before surgery (Day −2), and postoperative days (Day 7 and 14). The samples were quickly frozen at −20°C after collection and kept frozen at −80°C from the following day until assay.

Analysis of fecal flora. Fecal flora in individual samples was analyzed by real-time polymerase-chain reaction (PCR) assay. DNA primers used in real-time PCR assay were generated by the method of Matsuki et al.[24] *Bifidobacterium*, *Bacteroides fragilis* group, *Enterococcus spp.*, and *Escherichia/Shigella* group were quantified by the TaqMan assay and *C. difficile* by the SYBR Green assay. For PCR, the 7000 Sequence Detection System (Applied Biosystems, Foster City, CA) was used. The number of bacteria in each bacterial group was determined in comparison with the standard plate count. The number of bacteria for the four bacterial groups other than *C. difficile* was determined in almost all patients, whereas *C. difficile* was quantified only for patients in whom *C. difficile* was detected at least once on any of the measurement days.

Detection of CD toxin. *C. difficile*−derived toxin A and toxin B in feces were detected by an enzyme immunoassay using the RIDASCREEN *Clostridium difficile* Toxin A/B (R-Biopharm AG, Darmstadt, Germany).

Evaluation method. The primary end point of this study was the incidence of incisional SSI and organ/space SSI. Secondary endpoints were the incidences of remote infection, leakage, and CD toxin. Patients with leakage who were found to have abscess formation were included in those with organ/space SSI. In addition, the change in the number of bacteria in feces from before to after the operation was analyzed for each of the five bacterial groups to evaluate the changes in intestinal flora.

Statistical analysis. All statistical tests were performed two-sided at a significance level of .05. The patient baseline characteristics were examined for homogeneity among the 3 groups (Groups A, B, and C). To confirm their homogeneity, one-way analysis of variance was performed for continuous variables, including age, American Society of Anesthesiologists (ASA) score, height, weight, body surface area, operation time, blood loss, hemoglobin, and albumin. The Fisher exact test was performed for sex and the presence or absence of laparoscopic surgery, blood transfusion, and CD toxin. The χ^2 test was performed with the tumor site as a nominal-scale variable. The Kruskal-Wallis test was performed with ordinal categorical variables of the ASA score and the change in the number of bacteria in feces. Between-group comparisons were performed by the Fisher exact test with respect to the presence or absence of incisional SSI, organ/space SSI, suture failure (leakage), and remote infection as clinical outcome measures.

The number needed to treat was estimated on the basis of data from the preceding clinical study.

Table II. Patient characteristics

	Group A	*Group B*	*Group C*	P *value*
No. of patients	100	99	95	
Sex, male/female	49/51	56/43	51/44	.99
Age, mean ± SD, yr	67 ± 9	67 ± 11	66 ± 12	.74
BSA, mean ± SD, m^2	1.57 ± 0.18	1.62 ± 0.17	1.60 ± 0.18	.11
Tumor site				
Right colon	33	33	33	.99
Transverse colon	13	14	11	
Left colon	54	52	51	
Preoperative condition				
ASA score				
1/2/3	52/33/15	52/33/14	49/37/9	.75
Albumin, g/dL	4.1 ± 0.4	4.0 ± 0.4	4.0 ± 0.5	.14
Hemoglobin, g/dL	12.9 ± 1.9	12.9 ± 2.0	12.6 ± 2.4	.55
Surgery				
Laparoscopic/open	28/72	27/72	25/70	.99
Duration, mean ± SD, min	131 ± 34	147 ± 29	133 ± 39	.89
Blood loss, mean ± SD, mL	141 ± 154	147 ± 140	155 ± 211	.77
Blood transfusion	5	2	6	.31

ASA, American Society of Anesthesiologists; *BSA*, body surface area.

Assuming an SSI rate of 9% each in the oral antibiotics group and the probiotics group and an SSI rate of 30% in the control group, we calculated the number needed to treat that would have 90% power to detect differences between the oral antibiotics group and the control group and between the probiotics group and the control group by the Fisher exact test at an overall level of significance of 0.05 (two-sided). We then calculated the number needed to treat per group at a two-sided significance level of 0.0253 for each comparison, adjusting for multiplicity associated with multiple tests by the Dunn-Sidak method. The number needed to treat was thus calculated to be 92 per group. To allow for possible dropouts, a sample size of 300 patients (100 patients per group) was established for this study.

RESULTS

Three hundred ten patients scheduled to undergo elective colon cancer surgery were enrolled. We excluded 16 patients (including eight patients undergoing creation of a stoma and two patients undergoing concurrent resection of adjacent organs) from the analyses (Fig 1). Enrollment was stopped when the number of eligible patients assigned to Group A had reached 100. The numbers of patients analyzed in Groups B and C were 99 and 95, respectively.

Patient characteristics are summarized in Table II. No significant differences were found among the groups with respect to age, sex, body surface area, tumor site, proportion of laparoscopic surgery, preoperative ASA score, hemoglobin level, or albumin level, nor were they found with respect to operation time, blood loss or the presence or absence of transfusion. The rates of concomitant diabetes were 13% (13 of 100) in Group A, 7% (7 of 99) in Group B, and 6% (6 of 95) in Group C, indicating no substantial differences ($P = .19$). No patients had inflammatory bowel disease. Eighteen patients (6.1%) had a history of hospitalization within 30 days before the surgery: eight had 2- or 3-day hospitalization for endoscopic polypectomy of any site outside the intestine before colectomy; seven had two- or three-day hospitalization for cardiac catheterization as a preoperative examination; one each was hospitalized for diabetes control, for detailed examination of loss of consciousness, and for pneumonia. All patients were followed up for four weeks after the surgery.

The rates of postoperative infection, including incisional SSI, organ/space SSI, and remote infection, were 24.0% (24 of 100) in Group A, 11.1% (11 of 99) in Group B, and 25.3% (24 of 95) in Group C (Table III). The rates of incisional SSI as the primary end point were 18.0% (18 of 100), 6.1% (6 of 99), and 17.9% (17 of 95) in Group A, B, and C, respectively, and the lowest rate was noted in Group B with a significant difference among the 3 groups ($P = .014$). Between-group comparisons of Group A versus Group C and Group B versus Group C revealed a difference between Groups B and C ($P = .028$), indicating that the rate of incisional SSI was lesser in Group B than in Group C. In contrast, no difference was found between Groups A and C ($P = 1.00$). No

Table III. Postoperative infectious diseases and other complications

	Group A (n = *100*)	*Group B* (n = *99*)	*Group C* (n = *95*)	P *value*
Incisional SSI	18 (18.0%)	6 (6.1%)	17 (17.9%)	.014
	Adj-*P* = 1.00	Adj-*P* = .028	–	
Organ/space SSI	4 (4.0%)	4 (4.0%)	5 (5.3%)	.88
	Adj-*P* = .93	Adj-*P* = .93	–	
Remote infection	2 (2.0%)	1 (1.0%)	2 (2.1%)	.88
	Adj-*P* = 1.00	Adj-*P* = .85	–	
Total	24 (24.0%)	11 (11.1%)	24 (25.3%)	
Leakage	12 (12.0%)	1 (1.0%)	7 (7.4%)	.004
	Adj-*P* = .56	Adj-*P* = .06	–	
Leakage (abscess free)	11 (11.0%)	1 (1.0%)	5 (5.0%)	.008

Adj-P, Adjusted *P* value by Dunn-Sidak method of Fisher's exact test compared to Group C; *P*, Fisher exact test; *SSI*, surgical-site infection.

differences were found among the three groups with respect to organ/space SSI or remote infection (Table III).

The open operation group and the laparoscopic operation group had incisional SSI rates of 12.6% (27 of 214) and 17.5% (14 of 80), respectively ($P = .37$). The rates of organ/space infection, remote infection, and leakage also did not differ significantly between the two surgical techniques.

The leakage rates were 12.0% (12 of 100), 1.0% (1 of 99), and 7.4% (7 of 95) in Groups A, B, and C, respectively, and the lowest rate was noted in Group B with a difference among the three groups ($P = .004$); however, between-group comparison of Group B versus Group C revealed no significant difference ($P = .06$).

Of patients with leakage, consisting of 12 in Group A, 1 in Group B, and 7 in Group C, 1 in Group A, and 2 in Group C were included in those with organ/space SSI because of a documented abscess on diagnostic imaging. The remaining 11 patients in Group A, 1 in Group B, and 1 in Group C were found to have purulent drainage containing digestive fluids but required no particular antibiotic treatment (Table III).

The isolation and identification of pathogens causing SSI were performed in 15 of 18 patients in Group A, 6 of 6 patients in Group B, and 11 of 17 patients in Group C (Table IV). SSI-causing pathogens identified in Group A included *Enterococcus* spp., *Escherichia coli*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as *Bacteroides fragilis* group as anaerobic bacteria. In Group B, *P. aeruginosa* was detected in five of six patients, and other pathogens identified were only *Enterococcus faecalis*, *Staphylococcus aureus*, and *Corynebacterium* spp. Pathogens identified in Group C included *Enterococcus* spp., *Serratia marcescens*, methicillin-resistant *S. aureus*, and *P. aeruginosa*, as well as *B. fragilis* group as anaerobic bacteria. Most bacteria detected in the 3 groups were not covered by the antibacterial spectrum of flomoxef.

The detection rates of CD toxin before the operation were 2.0% (2 of 100), 5.1% (5 of 99), and 2.1% (2 of 95) in Groups A, B, and C, respectively (Table V), and the corresponding rates after surgery were 7.0% (7 of 100), 9.1% (9 of 99), and 10.5% (10 of 95) in Groups A, B, and C, respectively. Although the detection rates on postoperative day 14 were higher than those before surgery in all groups, no significant differences were found among the three groups in the detection rate either before or after surgery. In addition, none of the patients in Group A, B, or C developed CD-associated diarrhea (data not shown).

Regarding fecal flora, no changes were found in any of the five bacterial groups during the preoperative period (from Days −9 to −2) in three groups. On postoperative day 7, the number of bacteria in four bacterial groups other than *Enterococcus* spp. was found to have significantly decreased in Group B treated with oral antibiotics (Fig 2). In addition, the proliferation of *C. difficile* in the intestine after surgery tended to be inhibited in Group A.

DISCUSSION

Colorectal cancer surgery still involves a high rate of SSI, even if it is managed with mechanical bowel preparation, oral antibiotic prophylaxis, and intravenous antibiotic prophylaxis given immediately before the procedure.[25] Perioperative bowel preparation consists of three procedures: mechanical bowel preparation, preoperative oral antibiotic administration, and perioperative intravenous antibiotic administration as systemic therapy.

Table IV. Culture isolates from incisional SSI

Group	*Patient no.*	*Organisms**
A	1	*Enterococcus faecalis* 1+, *Clostridium perfringens* (trace)
A	2	*Escherichia coli* 1+, *Bacteroides fragilis* group 2+, *Enterococcus* sp 1+
A	3	*Staphylococcus epidermidis* 1+, *Bacteroides fragilis* group 2+
A	4	*Citrobacter freundii* 2+, *Enterococcus faecalis* 2+, alpha hemolytic *streptococcus* 1+, *Bacteroides fragilis* group 2+
A	5	*Pseudomonas aeruginosa* 1+
A	6	*Staphylococcus epidermidis* MRS 1+, *Bacteroides* sp. 1+, *peptostreptococcus* sp 1+
A	7	*E. coli* 2+, *Bacteroides fragilis* group 2+
A	8	*Enterococcus* sp (trace), *Bacteroides fragilis* group 1+, *corynebacterium* sp 1+
A	9	*Pseudomonas aeruginosa* (trace), *Enterococcus avium* 1+, *Bacteroides fragilis* group 1+, Anaerobic Gram-positive rod 1+
A	10	*Streptococcus pneumonia* (trace), *Bacteroides fragilis* group 1+
A	11	*Pseudomonas aeruginosa* 1+
A	12	*Bacteroides fragilis* group 1+, *peptostreptococcus* 1+
A	13	Gram-positive rod 1+, *Bacteroides fragilis* group 1+, *Staphylococcus epidermidis* (trace)
A	14	alpha hemolytic *streptococcus* 1+, *Bacteroides fragilis* group 1+
A	15	*E. coli* 1+, alpha hemolytic *streptococcus* 1+, *Bacteroides fragilis* group 2+, *Staphylococcus epidermidis* (trace)
B	1	*Enterococcus faecalis* 1+
B	2	*Pseudomonas aeruginosa* 2+, *Staphylococcus aureus* 2+
B	3	*Pseudomonas aeruginosa* 1+
B	4	*Pseudomonas aeruginosa* 1+
B	5	*Pseudomonas aeruginosa* 1+
B	6	*Pseudomonas aeruginosa* 2+, *corynebacterium* sp 2+
C	1	*Bacteroides fragilis* group 1+
C	2	*Bacteroides fragilis* group 1+
C	3	*Enterococcus cloacae* 2+, *corynebacterium* sp (trace)
C	4	*Eubacterium lentum* 2+, *Bacteroides fragilis* group 1+, *Clostridium subterminale* 1+
C	5	*Serratia marcescens* 1+, *Staphylococcus aureus* MRSA 3+
C	6	*Enterococcus* sp (trace), *Bacteroides fragilis* group 1+, anaerobic Gram-positive rod 2+
C	7	*Enterococcus faecalis* 1+, *Bacteroides fragilis* group 1+
C	8	*Pseudomonas aeruginosa* (trace), anaerobic Gram-positive rod (trace)
C	9	*Pseudomonas aeruginosa* (trace), *Bacteroides fragilis* group 1+
C	10	*Pseudomonas aeruginosa* 2+
C	11	*Pseudomonas aeruginosa* 1+, *Staphylococcus warneri* 1+

*Growth level on the dish: 1+, low; 2+, intermediate; 3+, high.
SSI, Surgical-site infection.

Table V. Detection rate of *C. difficile* toxin

	Group A (n = *100)*	*Group B* (n = *99)*	*Group C* (n = *95)*	P *value*
Preoperative	2 (2.0%)	5 (5.1%)	2 (2.1%)	.48
Postoperative day 14	7 (7.0%)	9 (9.1%)	10 (10.5%)	.69

P, Fisher exact probability test.

Polyethylene glycol (PEG) and sodium phosphate are used primarily for mechanical bowel preparation,[26] but bowel preparation with PEG and bowel preparation with sodium phosphate may result in different rates of SSI.[27,28] Several RCTs demonstrated that mechanical bowel preparation could be omitted in patients who are not treated with oral antibiotics.[29-34] There is also a report that mechanical bowel preparation is harmful rather than beneficial.[35] In contrast, under the condition that patients underwent mechanical bowel preparation and received an intravenous dose of antibiotic immediately before surgery, oral antibiotic administration significantly reduced the rate of SSI in one study and yielded no significant difference from the control in another studies.[16,36]

Results from a questionnaire survey of surgeons demonstrated that in bowel preparation for elective colorectal surgery, the rate of the use of oral antibiotics was 92% in 1990.[17] Subsequently, the rate was reported to be 75%,[37] followed by a lower value of 33% in a recent report.[18] As a cause of the less frequent use of oral antibiotics, Zomora et al[37] indicated that 49% of surgeons who participated in their survey doubted the effectiveness of oral antibiotics.

CD as a nosocomial infection can be a serious problem. Even very limited exposure to antibiotics, such as a single-dose of operative antibiotic prophylaxis, may increase a patient's risk of CDI[21,38]; however, other reports revealed that there was no association[16,19,20] in elective colorectal surgery. Whether there is an association is unknown.

In the present study, we compared the clinical usefulness of probiotics with that of oral antibiotics under the condition that all patients underwent mechanical bowel preparation with PEG and received an intravenous dose of flomoxef, a second-generation cephem antibiotic, immediately before operation. We used kanamycin and metronidazole as oral antibiotics, both of which have activity against both aerobes and anaerobes.

In Group B, treated with oral antibiotics, the rate of incisional SSI was lesser than in Groups A and C, and the leakage rate was also low. The incisional SSI rate of 6.1% and the leakage rate of 1.0% observed in Group B were equivalent to the incisional SSI rate of 8% and the leakage rate of 1% observed in an RCT using PEG and oral antibiotics (kanamycin sulfate + metronidazole), in which different lengths of intravenous antibiotic prophylaxis were compared, as we previously reported.[14]

A decreased rate of leakage by adding oral antibiotics to mechanical bowel preparation was reported from an RCT of 116 patients in 1977,[39] but not from recent large-scale studies; as shown in Fig 2, oral antibiotic treatment decreased the number of intestinal bacteria, and in Group B, this may have reduced stimulation by exposure to pathogens such as anaerobes at the incision site, resulting in less frequent inflammation and leakage than in Groups A and C; however, the mechanism of this effect remains to be elucidated.

In Group B treated with oral antibiotics, the numbers of *B. fragilis* and *E. coli* in feces decreased, and it was presumed that, as a consequence, the rate of incisional SSI in Group B was lesser than in the other groups. *Enterococcus*, resistant to oral antibiotics and intravenous flomoxef, also proliferated in Group B after surgery, as seen in Group A or C, and might become a pathogen causing SSI through bacterial translocation. However, *C. difficile* also proliferated in Group B after surgery because it was resistant to antibiotics as the result of its spore formation capability in the intestine[40]; however, the absolute number of bacteria (per gram of feces) was lower than that of *Enterococcus* by approximately three orders of magnitude. It was therefore presumed that, because of its low bacterial count, *C. difficile* did not become a pathogen causing SSI. Because *Pseudomonas* was resistant to oral antibiotics and flomoxef, it was isolated as a causative agent of SSI at a similar frequency in all groups. Because the number of *Pseudomonas* in the intestine is low (no more than 10^2/g of feces) as reported by Sugawara et al,[41] it is considered very likely that *Pseudomonas* infection was caused by exogenous bacteria that entered the body during surgery, rather than by the translocation of endogenous bacteria. In patients with colon cancer who were undergoing an elective procedure, the incidence of SSI was inhibited by the administration of antibiotics orally under the conditions that they received PEG as mechanical bowel preparation and intravenous flomoxef, a second-generation cephem antibiotic, immediately before the procedure.

Outbreaks of infection caused by toxin-producing strains are a serious problem in the United States and Europe. Nakamura et al[42] reported that *C. difficile* is carried by 15% of healthy young adults and approximately 7.0% of healthy elderly adults. In Japan, for the risk of CD infection associated with oral antibiotics, it is difficult to collect a sufficient number of patients for evaluation because of the low incidence rate; therefore, we determined the number of *C. difficile* in the intestine and CD toxin for evaluation. In our study, *C. difficile* was detected by PCR assay in 20% (19/96), 14% (13/96), and 22% (20/93) of patients in Groups A, B, and C, respectively. CD toxin was detected at a similar frequency in each group, and there was no particular tendency toward an increased detection rate of CD toxin in the group treated with oral antibiotics. CD-associated diarrhea was not observed in any group; however, the number of *C. difficile* tended to increase after operation in all groups, although the absolute number was quite low. These results suggested that a single-day prescription of oral antibiotics may be effective in preventing SSI without increasing the risk of CD infection. Further research is warranted to determine whether a similar preventive effect can be expected from oral antibiotic prophylaxis alone, if mechanical bowel preparation is omitted.

In this study, the preventive effect of oral administration of probiotics on postoperative infection could

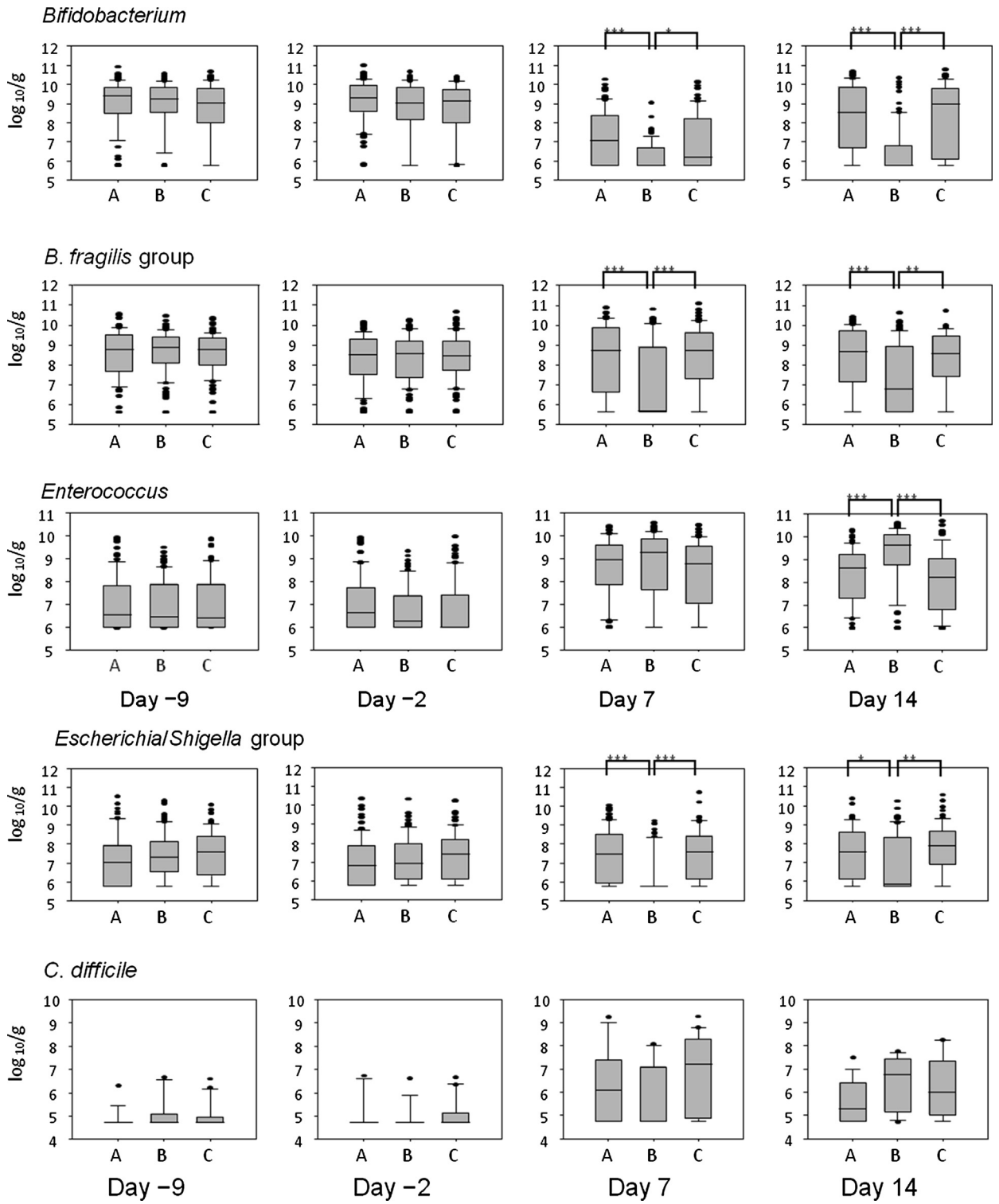

Fig 2. Changes of fecal flora before and after operation. (*A*) Probiotics treatment group ($n = 96$). (*B*) Oral antibiotics treatment group ($n = 96$). (*C*) Control group ($n = 93$). In the case of *C. difficile*, the number of samples in Groups A, B, and C is 19, 13, and 20, respectively. Day −9, preoperative day 9; Day −2, preoperative day 2; Day 7, postoperative day 7; Day 14, postoperative day 14. Data are presented as box-and-whisker plots. Statistical evaluation of the results was performed using Kruskal Wallis test, $*P < .05$; $**P < .01$; $***P < .001$. The detection limit of the real-time polymerase chain reaction analysis of fecal *Bifidobacterium*, *B. fragilis* group, *Enterococcus*, *Escherichia/Shigella* group, and *C. difficile* was 5.77, 5.63, 5.99, 5.76, and 4.74 (Log 10 number of organisms per g of feces), respectively.

not be confirmed, contrary to a report in pancreatic cancer patients from Rayes et al.[23] We deduce that this difference in the preventive effect may be explained by the difference in bacteriological cleanliness between the pancreas and the large intestine.

A patient group in the study that we previously reported[14] and Group B of the present study underwent bowel preparation with a combination of mechanical bowel preparation by PEG, oral antibiotics, and a preoperative single intravenous dose of a second-generation cephem antibiotic. These groups had incisional SSI rates of 8.4% and 6.1%, respectively. The leakage rates were 0.6% and 1.0%, respectively. Because these results were reproduced in the present study, we recommend the combination of mechanical bowel preparation with polyethylene glycol, preoperative oral antibiotic administration, and a preoperative single intravenous dose of a second-generation cephem antibiotic as the standard method of bowel preparation for elective colon cancer surgery.

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