

Randomized, Multicenter Trial of Antibiotic Prophylaxis in Elective Colorectal Surgery

Single Dose vs 3 Doses of a Second-Generation Cephalosporin Without Metronidazole and Oral Antibiotics

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Hypothesis: Use of prophylactic antibiotics in elective colorectal surgery is essential. Although single-dose prophylactic antibiotics are recommended, the efficacy of single-dose cephalosporin without metronidazole and oral antibiotics is not fully proven. We conducted a multicenter, randomized trial of a single dose vs 3 doses of the second-generation cephalosporin cefmetazole.

Design: A prospective, randomized, multicenter trial in patients undergoing elective colorectal surgery.

Setting: Seven major hospitals in Japan that offer cancer treatment.

Patients: Patients with colorectal cancer treated from May 6, 2004, to April 25, 2005.

Interventions: Patients were randomized to 1 of 2 groups: a single-dose group given a single dose of cefmetazole just before skin incision and a 3-dose group given 2 additional doses of cefmetazole every 8 hours after the first dose just before skin incision.

Main Outcome Measures: Incidences of incisional surgical site infection (SSI), organ or space SSI, and all other infectious complications within 30 days after surgery.

Results: A total of 384 patients were enrolled. Seven patients were excluded because of additional surgery or the inability to tolerate mechanical preparation. The incidence of incisional SSI was higher in the single-dose group (27/190 or 14.2%) than in the 3-dose group (8/187 or 4.3%) ($P = .009$). Incidences of organ or space SSI and other postoperative infectious diseases did not differ significantly between the 2 groups. In multivariate analysis, antibiotic dose was the only significant factor related to the incidence of incisional SSI.

Conclusion: Three-dose cefmetazole administration is significantly more effective for prevention of incisional SSI than single-dose antibiotic administration.

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PROPHYLACTIC ANTIBIOTICS have become a standard treatment for patients undergoing colorectal surgery,^{1,2} but controversy still persists concerning the administration route for antibiotics (oral, intravenous, or both) and the number of administrations.³ A recent meta-analysis¹ and a literature review⁴ have suggested that oral administration of antibiotics is of no added value

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when appropriate parenteral antibiotics are administered. Moreover, preoperative oral antibiotics increase the incidence of *Clostridium difficile* colitis⁵ and gastrointesti-

nal symptoms, including nausea, vomiting, and abdominal pain.⁶ A single dose of antibiotics has been shown to be as effective as multiple doses in many trials that have compared a single-dose regimen with a multiple-dose regimen.¹ Although the 1999 Hospital Infection Control Practices Advisory Committee guidelines for prevention of surgical site infection (SSI)² recommend cefoxitin or some other second-generation cephalosporin in the distal intestinal tract, the efficacy of a single-dose regimen of cephalosporin without metronidazole and oral antibiotics is not clear, because combination regimens, such as cephalosporin and metronidazole or cephalosporin and oral antibiotics, have been used in most studies of antibiotics dose.¹ In fact, in trials without metroni-

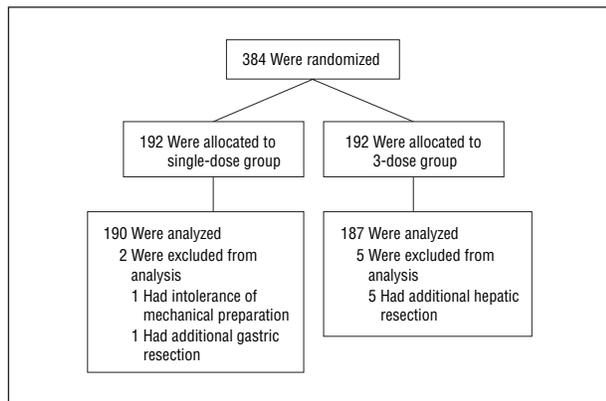


Figure. Flowchart of the trial.

dazole, the number of enrolled patients was small and the difference in the incidence of incisional SSI between a single-dose and a multiple-dose regimen was unclear.⁷ Moreover, a single-dose regimen of cephalosporin without metronidazole was associated with a slightly higher incidence of incisional SSI than a regimen of metronidazole alone.⁷⁻⁹ Therefore, we conducted a multicenter, randomized trial of single-dose vs 3 doses of the second-generation cephalosporin cefmetazole without metronidazole and oral antibiotics.

METHODS

This randomized multicenter trial was conducted at 7 major hospitals in Japan that offered cancer treatment from May 6, 2004, to April 25, 2005. The protocol was approved by the institutional review board at each hospital, and written informed consent was obtained from all of the patients who participated.

Patients aged 20 through 80 years scheduled to undergo elective colorectal surgery were eligible for enrollment in the study. Exclusion criteria included emergency operations, obstruction of the small bowel, stomal surgery or bypass surgery, preoperative infectious diseases, penicillin or cephalosporin allergy, antibiotic administration before hospitalization, inflammatory bowel diseases, angina or myocardial infarction, mild or severe renal dysfunction, mild or severe diabetes mellitus, and steroid administration before surgery.

Patients underwent mechanical bowel preparation with 2 L of polyethylene glycol–electrolyte solution (Niflec, Ajinomoto Pharma, Tokyo, Japan) 1 day before surgery. On the basis of a block-randomized, computer-generated list balancing tumor site, the patients were randomized by a study secretary into 1 of 2 groups: a single-dose group given a single intravenous dose of 1 g of cefmetazole just before skin incision and a 3-dose group given an intravenous dose of 1 g of cefmetazole just before skin incision and 2 postoperative 1-g doses at 8 and 16 hours after the first administration. Although additional doses during surgery and every 3 or 4 hours were recommended in the 1999 guidelines for prevention of SSI,² no additional dose was given, even for operations that lasted more than 3 hours. The surgeon was notified of the allocation after the randomization. To ensure that the trial results were applicable generally, specific instructions on surgical techniques and on postoperative management were not included in the protocol.

The primary end point was incidence of incisional SSI. Secondary end points were incidences of organ or space SSI and

Table 1. Patient Characteristics^a

Characteristic	Single-Dose Group (n = 190)	3-Dose Group (n = 187)	P Value
Age, mean ± SD, y	59.4 ± 11.1	62.1 ± 9.8	.01
Sex			.07
Male	126	107	
Female	64	80	
Tumor site			.91
Colon	122	119	
Rectum	68	68	
Type of surgery			.50
Conventional	129	133	
Colectomy	73	77	
Anterior resection	56	53	
Abdominoperineal resection	0	3	
Laparoscopic	61	54	
Colectomy	49	42	
Anterior resection	12	12	
Operative time, mean ± SD, min	178.8 ± 69.4	170.0 ± 77.5	.25
Blood loss, mean ± SD, mL	164.3 ± 272.6	162.7 ± 397.9	.96

^aData are presented as number of patients unless otherwise indicated.

other infectious diseases, including urinary tract infection, pneumonia, septicemia, infective diarrhea, and intravenous line sepsis. Other postoperative complications and postoperative hospital stay were also examined. Demographic data, including sex, age, operative procedure, operative time, and operative blood loss, were collected for all patients. Incisional SSI, organ or space SSI, and other infectious diseases were checked for daily by an attending surgeon until hospital discharge and checked for again at the first postoperative hospital visit.

This trial was designed as a noninferiority test to detect a 5% difference in the incidence of incisional SSI between the 2 groups, with a confidence interval of 95% and a power of 90%, assuming that the incidence of incisional SSI in the 3-dose group would be 5%. Therefore, a sample size of 238 was required in both arms. After 1 year of enrollment, interim analysis was performed. Because a significant difference in the incidence of incisional SSI was seen between the groups, enrollment was stopped. The χ^2 test or Fisher exact test, which was used when the variables were lower than 5, was used to analyze categorized variables. The *t* test was used to analyze continuous variables. In multivariate analysis, logistic regression analysis was used. Significance was defined as $P < .05$.

RESULTS

PATIENT CHARACTERISTICS

A total of 384 patients were enrolled in this study (Figure). Seven patients were excluded because of additional surgery (gastric and hepatic resection) or the inability to tolerate mechanical preparation. Therefore, 377 patients were examined. All of the enrolled patients had colon or rectal cancer. The numbers of patients in the single-dose and 3-dose groups were 190 and 187, respectively. Patient characteristics are given in Table 1. Although patient age was significantly higher in the 3-dose

Table 2. Incisional SSI, Organ or Space SSI, and Other Postoperative Infectious Diseases

Complication	No. (%) of Patients		P Value
	Single-Dose Group (n = 190)	3-Dose Group (n = 187)	
Incisional SSI	27 (14.2)	8 (4.3)	.009
Organ or space SSI	5 (2.6)	9 (4.8)	.26
Other	12 (6.3)	9 (4.8)	.52
Total	40 (21.1)	24 (12.8)	.03

Abbreviation: SSI, surgical site infection.

group than in the single-dose group, other patient characteristics, including sex, tumor site (colon or rectum), type of surgery (conventional or laparoscopic), operative time, and operative blood loss, were identical.

SSI AND OTHER POSTOPERATIVE INFECTIOUS DISEASES AND COMPLICATIONS

The incidence of incisional SSI was significantly higher in the single-dose group (27/190 or 14.2%) than in the 3-dose group (8/187 or 4.3%) ($P = .009$; **Table 2**). The total incidence of incisional and organ or space SSI and other postoperative infectious diseases in the single-dose group (40/190 or 21.1%) was also significantly higher than in the 3-dose group (24/187 or 12.8%) ($P = .03$). Among these postoperative infectious diseases, the incidences of organ or space SSI and other infectious diseases were similar between the groups, and only the incidence of incisional SSI differed significantly. The incidence of other postoperative complications, mainly small-bowel obstruction, was 9.5% (18/190) in the single-dose group and 9.6% (18/187) in the 3-dose group. The mean \pm SD postoperative hospital stay was 12.5 ± 7.4 days in the single-dose group and 12.2 ± 5.6 days in the 3-dose group. Postoperative complications and hospital stay were identical between the groups, with no statistically significant differences ($P = .96$ and $.66$, respectively). However, the mean \pm SD postoperative stay of the patients with incisional SSI ($n = 35$) was significantly longer than that of patients without incisional SSI ($n = 342$) (14.6 ± 9.3 and 12.1 ± 6.2 days, respectively; $P = .03$).

INCISIONAL SSI IN SUBSETS

Because only the incidence of incisional SSI differed significantly between the groups, this variable was examined in subset analysis. In every subset except for laparoscopic surgery, the incidence of incisional SSI was significantly higher in the single-dose group than in the 3-dose group (**Table 3**). Although the difference in the incidence of incisional SSI was not significant in the laparoscopic surgery subset, a large difference was found between the groups: 9.8% in the single-dose group and 1.9% in the 3-dose group. A multivariate analysis that examined age, sex, tumor site, operative time, operative blood loss, and type of surgery showed that antibiotic dose was the only significant factor associated with incisional SSI ($P = .002$).

Table 3. Incisional Surgical Site Infections in Patient Subsets

Characteristic	No. (%) of Patients		P Value
	Single-Dose Group (n = 190)	3-Dose Group (n = 187)	
Age, y			
≤ 60	14/95 (14.7)	4/80 (5.0)	.045
> 60	13/95 (13.7)	4/107 (3.7)	.02
Sex			
Male	18/126 (14.3)	6/107 (5.6)	.03
Female	9/64 (14.1)	2/80 (2.5)	.01
Tumor site			
Colon	15/122 (12.3)	6/119 (5.0)	.046
Rectum	12/68 (17.6)	2/68 (2.9)	.009
Type of surgery			
Conventional	21/129 (16.3)	7/133 (5.3)	.04
Laparoscopic	6/61 (9.8)	1/54 (1.9)	.12
Operative time			
≤ 3 h	14/104 (13.5)	6/123 (4.9)	.02
> 3 h	13/86 (15.1)	2/64 (3.1)	.02
Operative blood loss			
≤ 200 mL	19/152 (12.5)	7/152 (4.6)	.01
> 200 mL	8/38 (21.1)	1/35 (2.9)	.03

COMMENT

Many studies^{1,2,10} have shown that prophylactic antibiotics are essential for patients undergoing elective colorectal surgery. If prophylactic antibiotics are not used in colorectal surgery patients, the reported incidence of incisional SSI is 30% to 50%.¹¹⁻¹⁶ After the efficacy of oral antibiotics was initially proven,¹¹ oral, intravenous, or oral plus intravenous antibiotics were adopted, and the incidence of incisional SSI improved to approximately 5% to 20%. A meta-analysis¹ confirmed that the use of prophylactic antibiotics is effective for prevention of incisional SSI after colorectal surgery. In this analysis, there were no significant differences between single-dose and multiple-dose regimens, and oral antibiotics gave no added value when appropriate parenteral antibiotics were administered. However, in many single-dose vs multiple-dose trials, metronidazole was used, and the incidence of incisional SSI for the single-dose regimen was the same as that for the multiple-dose regimen.^{7,17-19} In trials without metronidazole, the number of trials was limited, and the difference between the incidence of SSI for the single-dose regimen and that for the multiple-dose regimen was unclear.^{7,20,21} Moreover, a single-dose regimen of cephalosporin without metronidazole was associated with a higher incidence of incisional SSI than a metronidazole regimen.⁷⁻⁹ The incidence of incisional SSI for a single-dose regimen of cephalosporin without metronidazole was 10% to 15% and that for a single-dose regimen of cephalosporin with metronidazole was 5% to 10%. Therefore, single-dose cephalosporin without metronidazole has not been proved to be an ideal prophylaxis for patients undergoing colorectal surgery. These findings prompted us to perform the present trial.

Our study clearly showed that 3-dose administration of the second-generation cephalosporin cefmetazole was sig-

nificantly more effective for prevention of incisional SSI than single-dose administration. This phenomenon was observed in every subset, including age (≤ 60 years or > 60 years), sex (male or female), tumor site (colon or rectum), type of surgery (conventional or laparoscopic), operative time (≤ 3 hours or > 3 hours), and operative blood loss (≤ 200 mL or > 200 mL). Therefore, our finding was not considered to be the result of chance. Because the incidence of incisional SSI in the 3-dose group was 4.3%, which was compatible with the incidence for the single-dose regimen of cephalosporin with metronidazole,^{4,7,17-19} 3-dose administration of cephalosporin without metronidazole should be considered as one of the options for prevention for SSI in patients undergoing colorectal surgery.

This trial was not a double-blind study. Although double-blinding is ideal, placebo is expensive and was not used in this study. Because of this, every surgeon in charge was easily aware of the allocation and therefore could not be a blinded observer. One solution is to prepare a blinded observer to document the occurrence of infectious diseases. Because the blinded observer needs to be a physician or a nurse who is unaware of the nature of the trial, which was difficult in the present multicenter trial setting, an attending surgeon was asked to examine patients for infectious diseases in this trial.

The disadvantage of oral antibiotics is their adverse effects. Preoperative oral antibiotics increase the incidences of gastrointestinal symptoms, including nausea, vomiting, and abdominal pain,⁶ and of *C difficile* colitis.⁵ The latter is a well-known complication of colorectal surgery and is thought to be caused by mechanical cathartic agents and oral antibiotics, which diminish the variety of intraluminal bacteria and predispose the colon to *C difficile* colonization. A previous study⁵ found that the incidences of *C difficile* colitis in colorectal surgery patients who received oral antibiotics and in those who did not were 7.4% and 2.6%, respectively, the difference in incidence being significant ($P = .03$). In our study, *C difficile* colitis occurred in only 2 patients in the 3-dose group (1.1%) and in none of the patients in the single-dose group. A randomized comparative study²² of 137 patients undergoing elective colorectal surgery for carcinoma and receiving oral, systemic, and intraluminal antibiotics found no significant differences in the incidence of incisional SSI among the 3 groups, and the oral antibiotic regimen induced a greater change in the intestinal flora and was associated with more frequent postoperative diarrhea. Recently, the role of mechanical bowel preparation in lowering the incidence of postoperative infectious complications has been questioned by several randomized trials.²³ These data also indicated that use of oral antibiotics may not offer additional advantages over parenteral antibiotics. In fact, a recent survey of members of the American Society of Colon and Rectal Surgeons indicated that more than 50% of the respondents were skeptical about the usefulness of oral antibiotics.³

To be effective against SSI, the level of antibiotics in the tissue around the surgical site should be sufficient at the time of bacterial contamination.^{2,24} Cephalosporin exhibits a time-dependent antibacterial action, and the therapeutic effect is maintained when the level of the antibiotic exceeds the minimum inhibitory concentration for

the target pathogen. A pharmacokinetic study²⁵ of cefmetazole showed that additional doses were unnecessary for surgery that lasted less than 3 hours from the time of initial administration, because the tissue concentration at wound closure exceeded the minimum inhibitory concentration against *Staphylococcus aureus* and *Escherichia coli*. Therefore, we analyzed the relationship between incisional SSI and operation time. In our study, the incidence of incisional SSI in the 3-dose group was lower even in patients whose surgery lasted 3 hours or less than that in the single-dose group. This result indicated that postoperative administration of cephalosporin was important even for short operations.

Because the length of surgery is reported to be an important factor in SSI,²⁶⁻²⁸ an additional dose of antibiotics is recommended during operations that exceed the time during which the therapeutic level of antibiotics is lower than the minimum inhibitory concentration.² Logically, maintaining the therapeutic level of antibiotics during surgery is important for prevention of SSI.² In this study, the incidence of incisional SSI did not change in patients whose operations lasted more than 3 hours, even in the single-dose group. Therefore, the efficacy of an additional dose of antibiotics in patients undergoing colorectal surgery that lasted more than 3 hours should be examined in a randomized study.

Because the incision in laparoscopic surgery is shorter than that in conventional open surgery, the former is considered to have a lower incidence of incisional SSI.²⁹ In our study, the incidences of incisional SSI in patients undergoing laparoscopic surgery were 9.8% and 1.9% and those in patients undergoing open surgery were 16.3% and 5.3% in the single-dose group and 3-dose group, respectively. The incidence of incisional SSI associated with laparoscopic surgery was thus lower than that in conventional surgery, although the difference was not statistically significant.

Other patient characteristics, including age, sex, and operative blood loss, did not affect the incidence of incisional SSI. Among these factors, blood loss is considered to be related to SSI, because blood loss reduces the concentration of antibiotics. In fact, the incidence of incisional SSI in patients who lost more than 200 mL of blood was 21.1% in the single-dose group, which was higher than that in patients who lost 200 mL of blood or less. However, no such difference was seen in the 3-dose group, and the finding was not statistically significant.

Incisional SSI is generally associated with a prolonged hospital stay. Although the period of hospitalization did not differ between the single-dose and 3-dose groups, that for patients with incisional SSI was significantly longer than for patients without. Therefore, prevention of incisional SSI is important for reducing the period of hospitalization and thus cost. Our results indicate that a single dose of prophylactic antibiotics does not always save costs.

In conclusion, if oral antibiotics and metronidazole are not used for prophylaxis in patients undergoing colorectal surgery, administration of the 3-dose second-generation cephalosporin cefmetazole is significantly more effective for prevention of incisional SSI than single-dose antibiotic administration regardless of patient age,

sex, tumor site, type of surgery, operative time, or operative blood loss.

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