Int Surg 2012;**97:**169–176

A Prospective Randomized Study to Assess the Optimal Duration of Intravenous Antimicrobial Prophylaxis in Elective Gastric Cancer Surgery

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The duration of antimicrobial prophylaxis in gastric cancer surgery is not yet established. This prospective randomized study was performed to confirm the noninferiority of single-dose versus multiple-dose antimicrobial prophylaxis in terms of the incidence of surgical-site infection in gastric cancer surgery. Three hundred twenty-five patients undergoing elective resection for gastric cancer were randomized to receive only single-dose cefazolin (1 g) during surgery (single-dose group) or an additional 5 doses every 12 hours postoperatively (multiple-dose group). The overall incidence of surgical-site infections was 9.1% in the single-dose group and 6.2% in the multiple-dose group [difference (95% confidence interval): −2.9% (−5.9%–0.0%)]. Multivariate logistic regression analysis identified blood loss, being overweight, and advanced age as significant independent risk factors for surgical-site infection. Single-dose antimicrobial prophylaxis seemed to be acceptable, and choosing multiple-dose prophylaxis may have little impact on the prevention of surgical-site infections in elective gastric cancer surgery.

Key words: Gastric cancer – Antimicrobial prophylaxis – Surgical-site infection

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Short-term antimicrobial prophylaxis is known to be useful for the prevention of wound infection in various types of surgery. For the prevention of surgical-site infection (SSI) following gastrointestinal surgery, the guidelines of the Centers for Disease Control and Prevention (CDC) recommend that intravenous antimicrobial prophylaxis be limited to within the intraoperative period or within 24 hours postoperatively.[1] In addition, most previously published studies comparing short-term prophylaxis with more prolonged regimens have focused on the outcomes in patients undergoing colorectal surgery[2–5] or cholecystectomy.[6–9]

Single-dose prophylaxis is ideal, since it would be expected to reduce the risk of antibiotic-related complications and would be cheaper than multiple-dose prophylaxis. Notably, there is not much information comparing single-dose versus multiple-dose prophylaxis in relation to the risk of SSIs following gastric cancer surgery, which usually involves complicated surgical techniques for lymph node dissection.

We performed a prospective randomized study to confirm the validity of single-dose antimicrobial prophylaxis for the prevention of SSI and examined independent risk factors influencing the development of SSIs following elective gastric cancer surgery.

Patients and Methods

This study was conducted with the approval of the ethics committee of Saitama Medical Center, Saitama Medical University. Written informed consent was obtained from each patient.

Randomization of patients

A total of 360 patients who underwent elective surgery for gastric cancer between February 2007 and November 2010 in our department were assessed in terms of eligibility for this study. The exclusion criteria were patients less than 20 years old, those with known allergy to cephalosporins, those with any infection within the prior 2 weeks, those with synchronous cancer at any sites other than the stomach, and those needing colon resection because of tumor involvement. After induction of anesthesia, 1 g of cefazolin was administered intravenously. An additional dose was administered when the duration of surgery exceeded 3 hours. After the surgery, the patients were randomly assigned to one of two groups by sealed envelopes containing randomized sheets. Patients were also stratified for the analyses based on the type of gastrectomy (total gastrectomy or proximal/distal gastrectomy). Patients in the single-dose group were assigned to intravenous cefazolin during the surgery only, while patients in the multiple-dose group were given 5 additional doses every 12 hours postoperatively.

Procedures related to prevention of surgical-site infection and follow-up

Surgical wounds in patients having conventional gastrectomy were covered with surgical towels, while those of patients having minilaparotomy, performed with or without laparoscopic assistance,[10] or standard laparoscopic assisted–gastrectomy were covered with a wound protector (Applied Medical, Rancho Santa Margarita, CA). Stapled anastomoses were routinely performed, regardless of the type of gastrectomy or reconstruction. The abdominal cavity was washed with copious amounts (2–3L) of saline before closing the wounds. All gloves were changed after washing the abdominal cavity. After the fascia was approximated by absorbable sutures, the incisional site was washed with 200 mL of saline before closing the skin, which was approximated by a skin stapler. Closed-suction drains (BLAKE silicone drains, Ethicon, Johnson & Johnson, Somerville, NJ) were placed subhepatically and/or subphrenically according to the type of gastrectomy, brought out through separate stab wounds, and connected with J-VAC suction reservoir (Ethicon). The incision site was covered with a sterile dressing, which was removed within 48 hours. Intra-abdominal drains were removed after 5 to 7 days, and the staples were removed after 7 days. The wounds were inspected daily until the patients were discharged from the hospital, and the wounds of each patient were inspected at the outpatient clinic until 30 days after the surgery. SSIs (incision site infection and organ/space infection) were diagnosed according to the definitions of the CDC.[1] Anastomotic dehiscence, included as organ/space infection, was confirmed by clinical and/or X-ray examination. Remote infection was defined as an infection occurring at a site other than the surgical site, such as pneumonia, urinary tract infection, enteritis, or bloodstream (catheter-related) infection.

Sample size

This trial was designed as a noninferiority test to detect an 8% difference in the incidence of SSIs between the 2 groups, with a confidence interval (CI) of 95% and a power of 80%; assuming that the incidence of SSIs in the multiple-dose group would

Table 1 Patient characteristics

	Single-dose group (n = 164)	Multiple-dose group (n = 161)	P value
Age	68 (33–90)	68 (39–91)	0.82
Sex			
Male:Female	118:46	117:44	0.89
BMI, kg/m^2	21.7 (15.2–31.9)	21.9 (15.4–31.6)	0.90
Serum albumin, g/dL	3.9 (2.4–5.0)	3.8 (1.7–5.1)	0.12
ASA			
I/II:III	139:25	137:24	0.93
Diabetes mellitus			
Present:Absent	38:126	36:125	0.86
Duration of surgery, min	181.5 (60–400)	185 (70–463)	0.53
Blood loss, g	250.0 (0–2910)	265.0 (5–2090)	0.94
Blood transfusion			
Performed:Not performed	10:154	21:140	0.03
Laparoscopic surgery			
Yes:No	18:146	20:141	0.68
Type of surgery			
Total gastrectomy:Proximal/distal gastrectomy	66:98	66:95	0.89
Combined resection	37	36	0.97
Gallbladder	15	13	
Spleen	23	20	
Pancreas	3	2	
Liver	2	2	
Small intestine	0	1	
Lymph node dissection			
≥D2:D1/D0	73:91	73:88	0.88
Depth of invasion			
T1:T2/T3/T4	94:70	95:68	0.78
Regional lymph node metastasis			
N0/1:N2/3	80:84	88:73	0.29
Pathologic stage			
I/II:III/IV	54:110	65:96	0.16

be 9% based on our previous data on the incidence of SSIs after gastric cancer surgery performed between April 2005 and December 2006. Therefore, a sample size of 159 was estimated to be required in both treatment arms.

Statistics

The primary objective of this study was to show that the single-dose prophylaxis was not inferior to the multiple-dose prophylaxis in terms of the overall incidence of SSIs. The single-dose prophylaxis was judged not to be inferior to the multiple-dose prophylaxis if the lower limit of the 2-sided 95% CI for the difference in the incidence of SSI was above −8%. Data shown in the tables are expressed as median and range or 95% CI. For the statistical analyses, a statistical software package (StatFlex Version 6.0, Artec, Inc, Osaka, Japan) running on a Windows personal computer was used. For comparison of nominal variables, either the χ^2 test or Fisher exact probability test was used. For comparison of continuous variables, Mann-Whitney U test was used. Univariate and multivariate logistic regression analyses were applied to identify the factors independently influencing the risk of development of SSIs. Variables with $P < 0.10$ identified by univariate analysis were entered into the multivariate analysis model with forward stepwise selection. P values of <0.05 were considered to denote statistical significance.

Results

Patient characteristics

Among the 360 patients who underwent elective gastric cancer surgery, 27 patients were excluded;

Table 2 Surgical-site infection

	Single-dose group	Multiple-dose group (n = 164)	Difference (95% CI) (n = 161)
Overall surgical incision	15 (9.1%)	10 (6.2%)	−2.9% (−5.9–0.00)
Incisional-site infection	14 (8.5%)	7 (4.3%)	−4.2% (−6.9–−1.5)
Organ/space infection	11 (6.7%)	6 (3.7%)	−3.0% (−5.5–−0.6)

one patient refused to participate in this study, and 26 patients did not fulfill the inclusion criteria. After entry into the study, cefazolin-related allergic reaction occurred during the operation in one patient, and colectomy combined with gastrectomy was required in 7 patients. These 8 patients were also, therefore, excluded from the study. Thus, a total of 325 patients were randomized to the single-dose group (n = 164) or multiple-dose group (n = 161) postoperatively and found to be eligible for this study.

The baseline characteristics of the patients in both groups are shown in Tables 1 and 2. The 2 groups did not differ significantly in relation to age, sex, body mass index (BMI), serum albumin concentrations, ASA (American Society of Anesthesiologists physical status) score, or prevalence of diabetes mellitus. The 2 groups also did not differ significantly in relation to the duration of surgery, blood loss, type of gastrectomy, frequency of laparoscopic-assisted surgery, frequency of combined resection of other organ(s), level of lymph node dissection, or pathologic staging according to the Japanese Classification of Gastric Carcinoma.[11] Blood transfusion was required more frequently in the multiple-dose group than in the single-dose group (P = 0.03) (Table 1).

SSI

The incidence of incisional-site infection was 8.5% (14 cases) in the single-dose group and 4.3% (7 cases) in the multiple-dose group. All the incisional-site infections were judged as superficial incisional-site infections. The incidence of organ/space infection was 6.7% (11 cases) in the single-dose group and 3.7% (6 cases) in the multiple-dose group. Of the 17 organ/space infections, 16 (10 in the single-dose group, and 6 in the multiple-dose group) were related to anastomotic dehiscence and/or pancreatic fistula. Nine patients in the single-dose group and 3 patients in the multiple-dose group developed both incisional-site and organ/space infection. There was no infection associated with drain placement in terms of incisional-site infections at the drain sites or organ/space infections around the tips of drains. Therefore, the overall incidence of SSIs was 9.1% (15 cases) in the single-dose group and 6.2% (10 cases) in the multiple-dose group. The difference (95% CI) in the incidence of surgical site infection between the 2 groups was −2.9% (−5.9–0.0%). Because the lower limit of the 2-sided 95% CI was above −8%, the single-dose group was considered to be noninferior to that in the multiple-dose group in terms of the incidence rate of SSIs (Table 2). Cultures were obtained from 15 SSI sites. The bacteria isolated were methicillin-sensitive *Staphylococcus aureus* (2 in the single-dose group), methicillin-resistant *Staphylococcus aureus* (1 in the single-dose group), *Pseudomonas aeruginosa* (1 in the single-dose group and 2 in the multiple-dose group), *Enterococcus faecalis* (2 in the single-dose group, 1 in the multiple-dose group), *Enterobacter cloacae* (1 in the single-dose group, 1 in the multiple-dose group), *Corynebacterium* (2 in the single-dose group, 1 in the multiple-dose group), and *Bacteroides spp.* (2 in the single-dose group) (Table 3).

Table 3 Detected bacteria in cases of surgical-site infections

	Single-dose group	Multiple-dose group
Methicillin-sensitive *Staphylococcus aureus*	2	
Methicillin-resistant *Staphylococcus aureus*	1	
Pseudomonas aeruginosa	1	2
Enterococcus faecalis	2	1
Enterobacter cloacae	1	1
Corynebacterium spp	2	1
Bacteroides spp	2	

Remote infection

Remote infection occurred in 6 cases (3.7%) in the single-dose group and 5 cases (3.1%) in the multiple-dose group. The remote infections were pneumonia (n = 3), enterocolitis (n = 1), urinary tract infection (n = 1), and bloodstream infection (n = 1) in the single-dose group; pneumonia (n = 2), enterocolitis (n = 2), and bloodstream infection (n = 1) in the multiple-dose group. There was no significant difference in the incidence of remote-site infections between the 2 groups (P = 0.78; Table 4). Cultures

Table 4 Remote-site infections

	Single-dose group (n = 164)	Multiple-dose group (n = 161)	P value
Remote infections	6 (3.7%)	5 (3.1%)	0.78
Pneumonia	3	2	
Enterocolitis	1	2	
Urinary tract infection	1	0	
Bloodstream infection	1	1	

were obtained from the remote-infection sites in 6 patients. The bacteria isolated were methicillin-resistant *Staphylococcus aureus* (1 in the single-dose group, 1 in the multiple-dose group), *Pseudomonas aeruginosa* (1 in the multiple-dose group), *Escherichia coli* (1 in the single-dose group, 1 in the multiple-dose group), and *Haemophilus influenzae* (1 in the single-dose group) (Table 5).

Risk factors for SSIs

To determine the factors influencing the risk of SSIs, 12 nominal variables including age, sex, duration of intravenous antibiotic use (single-dose versus multiple-dose), ASA score (I/II versus III), BMI [≥25 kg/m^2 (overweight) versus <25 kg/m^2 (not overweight)],[12] serum albumin concentration, pathologic stage (stage I/II versus stage III/IV), diabetes mellitus (present versus absent), duration of surgery, blood loss, blood transfusion (administered versus not administered), type of operation (total gastrectomy versus proximal/distal gastrectomy), level of lymph node dissection (D0/D1 versus D2), operative approach (open surgery versus laparoscopic-assisted), and combined resection of other organ(s) (performed versus not performed) were assessed. On univariate logistic regression analysis, 6 variables, including BMI (P = 0.03), duration of surgery (P < 0.01), blood loss (P < 0.01), type of operation (P = 0.02), age (P = 0.06), and blood transfusion (P = 0.07) were selected and entered for the multivariate analysis with forward stepwise selection. Greater blood loss [P < 0.01, odds ratio (95% CI) = 1.13 (1.05–1.23), Δ: every 100 mL increment], BMI ≥ 25.0 kg/m^2 [P = 0.03, odds ratio (95% CI) = 2.76 (1.10 ~ 6.90)], and advanced age [P = 0.046, odds ratio (95% CI) =1.65 (1.01–2.70), every 10 years increment] were identified as independent risk factors for SSI by this analysis (Table 6).

Table 5 Detected bacteria in cases of remote infections

	Single-dose group	Multiple-dose group
Methicillin-resistant *Staphylococcus aureus*	1	1
Pseudomonas aeruginosa		1
Escherichia coli	1	1
Haemophilus influenzae	1	

Discussion

This study clearly showed that single-dose antimicrobial prophylaxis was noninferior to multiple-dose antimicrobial prophylaxis in terms of the overall incidence of SSIs following gastric cancer surgery. In addition, although not a primary outcome measure, the risk of remote infection was also not increased by single-dose prophylaxis. According to the guidelines of the CDC,[1] the surgical wound in gastric surgery is categorized into class II (clean-contaminated), and the guidelines recommend that a first-generation cephalosporin or a penicillin be administered intravenously within 30 minutes of the surgical incision every 3 to 4 hours, for 24 hours or less postoperatively. However, the optimal duration of antimicrobial prophylaxis for elective gastric cancer surgery is not yet established. Intravenous antimicrobial prophylaxis is usually administered for 3 or 4 days in elective gastric cancer surgery in Japan, where the extent of lymph node dissection is wider than that in Western countries. The reasons behind the longer use of antimicrobial prophylaxis do not seem to be evidence based; many Japanese surgeons believe that the surgical stress related to gastrectomy with such lymph node dissection might deteriorate the host immune system, increasing the risk of postoperative complications, including SSIs and remote infections, which might be prevented by longer antibiotic use. A recent study on general perioperative management of gastric cancer patients at high-volume centers in Korea and Japan revealed that antimicrobial prophylaxis for elective gastrectomy was administered for over 2 days in many hospitals.[13] Many surgeons in Western countries also seem to believe the rationale that surgical drains and intravenous catheters might lead to bacterial seeding of surgical sites. Bratzler *et al*[14] reported that the

Table 6 Factors influencing the risk of development of surgical-site infections identified by univariate and multivariate logistic regression analyses

Factors	Odds ratio (95% CI)	*P* value
Univariate regression analysis		
Age (every 10 years increment)	1.57 (0.10–2.47)	0.06
Sex (male)	2.10 (0.70–6.33)	0.18
Duration of antimicrobial prophylaxis (single-dose)	1.52 (0.66–3.49)	0.32
ASA (III)	1.07 (0.35–3.30)	0.89
BMI ($\geq$25 kg/m^2)	2.62 (1.10–6.25)	0.03
Serum albumin (every 0.5g/dL decrement)	1.04 (0.72–1.50)	0.84
pStage (III/IV)	1.66 (0.73–3.78)	0.22
Diabetes mellitus (present)	1.66 (0.69–4.04)	0.26
Duration of surgery (every 30 min increment)	1.39 (1.11–1.57)	$<$0.01
Blood loss (every 100 mL increment)	1.13 (1.06–1.22)	$<$0.01
Blood transfusion (yes)	2.63 (0.91–7.60)	0.07
Type of operation (total gastrectomy)	2.82 (1.21–6.59)	0.02
Lymph node dissection ($\geq$D2)	1.14 (0.51–2.59)	0.75
Non-laparoscopic surgery	3.38 (0.44–25.70)	0.24
Combined resection (yes)	1.38 (0.55–3.41)	0.49
Multivariate regression analysis		
Blood loss (every 100 mL increment)	1.13 (1.05–1.23)	$<$0.01
BMI ($\geq$25 kg/m^2)	2.76 (1.10–6.90)	0.03
Age (every 10 years increment)	1.65 (1.01–2.70)	0.046

duration of intravenous antibiotic use was over 24 hours in 59.3% of patients undergoing major surgery in the United States. From this study, we should note that the risk of SSIs, including remote infections, is increased with single-dose intravenous antimicrobial prophylaxis as compared with multiple-dose prophylaxis.

Although numerous studies have analyzed the relationship between the incidence of SSIs and the duration of antibiotic prophylaxis, few have addressed short-term antimicrobial prophylaxis focusing on gastric cancer surgery.[15–20] To the best of our knowledge, there has been only the publication by Mohri *et al*[17] of a prospective randomized trial comparing single-dose versus multiple-dose antimicrobial prophylaxis in patients undergoing gastric cancer surgery. They reported that the incidence of SSIs following elective gastric cancer surgery was similar between patients receiving single-dose and those receiving multiple-dose prophylaxis (9.5% versus 8.6%). Our results are similar to those of Mohri *et al*; however, the two studies differed in a few respects: first, their study was a multicenter trial; second, they permitted two kinds of antibiotics (cefazolin, which is effective for Gram-positive bacteria, and ampicillin-sulbactam, which is also effective against anaerobic pathogens), included bypass operations, and did not regulate the methods of reconstruction (hand-sewn or mechanical anastomosis) and drainage, all of which could potentially influence the risk of development of SSIs. Even though this study was performed in a single institution, we believe that it had several distinct merits that increased the quality of the study; there were no inter-hospital variations, the surgical procedures and preoperative, intraoperative, and postoperative managements related to SSIs were well standardized, and a first-generation cephalosporin (cefazolin) was exclusively used. In addition, only resectional surgery was included.

There may be a criticism that surgical drains may increase the risk of occurrence of SSIs. A recent meta-analysis[21,22] showed that routine placement of drains is not necessary in elective surgery for gastric cancer, because the incidence of postoperative complications is higher and the hospital stay is longer in patients with drain placement. However, the use of drains did not affect the incidence of wound infection or intra-abdominal abscess. At least at the start of the present study, prophylactic placement of abdominal drains after gastrectomy with lymph node dissection for gastric cancer was a standard procedure in Japan,[13] and the closed-suction drain system was used routinely. In this study, no change in the incidence of SSIs associated with drain placement, especially incisional-site infections at the drain sites or organ/space infections around the tips of drains, was encountered. In regard to the development of SSIs following gastric cancer surgery, further research might be needed to clarify the relationship between the use of

prophylactic drains and the duration of antimicrobial prophylaxis.

The incidence of SSIs in both groups (9.1% or 6.9%) was identical to or lower than the figures reported from recent studies.[16–20] Pathogens likely to be encountered in patients undergoing gastric surgery include enteric Gram-negative bacilli and Gram-positive cocci. Gastric bacterial colonization has been reported to occur in patients with gastric cancer.[17] When present, gastric microflora are usually divided between the oral or proximal intestinal aerobes and oral anaerobes. These pathogens are considered to be sensitive to cefazolin, one of the first-generation cephalosporins, which is therefore widely used as the antibiotic of first choice for patients undergoing gastric cancer surgery in Japan. The incidence of detection of multiple-resistant strains such as methicillin-resistant *Staphylococcus aureus* from surgical and remote sites was extremely low in both groups.

We also evaluated the risk factors for the development of SSIs. Multivariate logistic regression analysis identified greater blood loss, BMI in the overweight range (BMI $\geq$ 25.0 kg/m^2), and advanced age as significant risk factors for the development of SSIs. Gastric cancer surgery in overweight patients often takes longer and is associated with greater blood loss than that in lean individuals, as the presence of excessive fat tissue complicates surgical procedures, including lymph node dissection Specifically, the demarcation between the pancreas and the surrounding fat tissue is obscured in the presence of much fat, and it is sometimes difficult to perform lymph node dissection of the suprapancreatic region, which increases the risk of development of pancreatic fistula and the related intra-abdominal abscess. Therefore, there is a close relationship between greater blood loss and BMI in gastric cancer surgery,[23] even though in this study, greater blood loss and BMI in the overweight range independently affected the risk of development of SSIs. Since the sample size in this study was limited, calculated as it was based on the primary endpoint (overall SSI), we could not evaluate the impact of blood loss and BMI on the development of organ/space infection. This issue is of interest and warrants further investigation. Ozalp *et al*[18] studied the risk factors for incisional-site infection after gastrectomy with D2 lymphadenectomy in Caucasians, who tend to have a higher BMI than Japanese, and concluded that BMI in the overweight range increased the risk of incisional-site infection. It is still a matter of debate whether additional doses of antibiotics in antimicrobial prophylaxis, administered irrespective of prolonged operative time, might reduce the risk of SSIs after gastric cancer surgery. Little is known about the blood and tissue concentrations of cefazolin and blood loss in gastric cancer surgery. Swoboda *et al*[24] studied the effect of intraoperative blood loss on the serum and tissue concentrations of cefazolin in spinal instrumentation surgical procedures and concluded that the effect of the antibiotic diminished and an additional dose was necessary when the blood loss exceeded 1500 mL. On the other hand, Sue *et al*[25] reported that the blood loss in cardiac surgery had minimal effect on the elimination of cefazolin; 14% of the cefazolin dose administered was lost as a result of intraoperative bleeding, despite the mean blood loss being 110 mL/h and total blood loss being over a liter, with crystalloid replacement in excess of 3 L. Nevertheless, surgeons should note that minimization of intraoperative blood loss is important to reduce the risk of development of SSIs after elective gastric cancer surgery. Advanced age has also been reported to be a risk factor for the development of SSIs after gastric surgery,[15,26] although the exact reasons are unclear and further investigation is warranted. The results of this study confirmed the aforementioned three factors (age, blood loss, and BMI) previously reported by retrospective studies as risk factors for SSIs. Of importance, it would appear that choosing between single-dose versus multiple-dose prophylaxis may have little impact on the prevention of SSIs after gastric cancer surgery.

In conclusion, this prospective randomized study demonstrated that single-dose antimicrobial prophylaxis was noninferior to multiple-dose prophylaxis in terms of the risk of occurrence of SSIs after elective gastric cancer surgery. Single-dose antimicrobial prophylaxis seems to be a valid means to reduce the risk of occurrence of SSIs, and choosing between single-dose or multiple-dose prophylaxis may have little impact on the prevention of SSIs.

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