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Originals

Randomized Controlled Trial on the Necessity of Chemical Cleaning as Preoperative Preparation for Colorectal Cancer Surgery

Toru Horie

Department of Gastroenterological Surgery, Dokkyo Medical University, Mibu, Tochigi, 321-0293, Japan

SUMMARY

The use of preoperative oral antibiotics for the preparation of elective colorectal surgery remains controversial. We examined the necessity of chemical preparation using oral antibiotics compared with mechanical preparation, to achieve the further reduction of infection rates in colorectal resection. Consecutive 91 patients were included in this prospective clinical trial of colon preparation. 45 patients received mechanical preparation alone with the polyethylene glycol lavage solution (group A), while 46 patients received mechanical preparation and chemical bowel preparation with 1.5g Kanamycin for 3 days orally before surgery (group B). Cefotiam hydrochloride was administered for 3 consecutive days after surgery in both groups. Specimens for culture were obtained pre-, intra- and post-operatively.

In the specimens of intraoperative colonic mucosal swabs, Escherichia coli (E. coli) was significantly less cultured in group B than in group A. Postoperative diarrhea was observed in 7 patients of group A (15.5%) and in 20 patients of group B (43.5%) ($p < 0.05$). The surgical site infection (SSI) rate was 20.0% in group A and 36.9% in group B ($p = 0.1041$). Although there was no significant difference, SSI rate tended to be higher in group B than in group A.

In conclusion, chemical preparation with oral intake of 1,500 mg Kanamycin for 3 days before surgery did not add any advantages to mechanical preparation and is considered unnecessary to perform colorectal surgery.

Key Words : Surgical site infection, Chemical preparation, Mechanical preparation, Kanamycin

INTRODUCTION

Recently although the morbidity and mortality rates of colorectal surgery have been decreased all over the world, there are still several problems unsolved, including postoperative infectious complications and diarrhea[1,2], and preoperative colon preparation by mechanical preparation with or without oral antibiotics is considered important to reduce surgical site infection (SSI)[1,3～14].

Kanamycin, which is a broad spectrum bactericidal antibiotic, first isolated in 1957, has been used for chemical preparation because of being absorbed in negligible amounts after oral administration[15～18]. However, oral antibiotics administration may be associated with intracolonic overgrowth of staphylococci and induce a risk of enteritis due to methicillin-resistant Staphylococcus aurerus (MRSA)[1,19]. While mechanical preparation is performed by use of polyethylene glycol lavage solution since the 1980s. Polyethylene glycol

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Reprint requests to : Toru Horie
Department of Gastroenterological Surgery, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan

lavage solution has a better cleaning effect than conventional preparation (variety of laxatives and enemas)[20~23]. In addition to mechanical preparation, chemical preparation by oral intake Kanamycin for 3 days before colorectal surgery has been occasionally employed in Japan[24]. However, the use of preoperative oral antibiotics for the preparation of elective colorectal surgery remains controversial. Many surgical centers in Japan prefer mechanical to chemical preparation, consisting of 3-days Kanamycin. However, no solid evidence regarding the superiority of the mechanical preparation has been postulated.

In the present study, in order to assess the value of oral antimicrobial agents, we carried out a prospective clinical trial in patients undergoing elective colorectal surgery, paying particular attention to the influence of these agents on colonic flora, intraoperative bacterial contamination, and the postoperative infection rate, and diarrhea.

PATIENTS AND METHODS

Patients

The participating hospital was the Department of Gastroenterological Surgery, Dokkyo Medical University. Ninety-one patients who were admitted to our hospital for elective surgery of colorectal cancer between April 1, 2002 and December 31, 2006, entered the study after obtaining informed consent. We carried out a prospective randomized clinical trial of colon preparation. The patients were divided into two groups by minimization method with stratification factors, including gender, age, Body Mass Index (BMI), and disease site. Group A received the mechanical bowel preparation alone, while group B received the mechanical bowel preparation with oral antibiotics.

Protocol

Any patients with a colonic obstruction, experience of abdominal operation, and resection of other organs synchronously were excluded. All patients took clear liquids, and then the 2000 ml of polyethylene glycol lavage solution 16 hours before surgery. Only patients who passed watery and non-yellowish stool before operation, were defined as well-prepared by the mechanical bowel preparation, and were enrolled in the study. Group A received the mechanical bowel preparation alone, and in addition, group B received oral antibiotics bowel preparation with 1,500 mg of Kanamycin per day for 3 consecutive days before operation. Prophylactic antibiotics were also given intravenously to all patients. One gram of Cefotiam hydrochloride was administered after the induction of anesthesia, and was administered again two times a day for 3 consecutive days after operation.

Surgical procedures

A midline incision was employed, and abdominal wound was protected with surgical drape. The bowel was divided using occlusion clamps, and the bowel stumps were cleaned with chlorhexidine swabs. Bowel continuity was restored with two layers anastomosis. Double stapling techniques were used for the anterior resection of the rectum. The abdominal cavity was washed out with copious amounts of saline before closure. All gloves were also changed. The wounds were inspected daily until the patients were discharged from the hospital. Wound infection was indicated by the presence of pus or discharge resulting in a positive bacteriological culture.

Specimens for culture

Six specimens consisting of preoperative stool, colorectal mucosal swabs during operation, saline of peritoneal irrigation obtained after 3 liter lavage, saline of fascia irrigation at the closure of the wound, a postoperative stool, and exudates from the infected sites were collected and cultured, respectively. Colonic mucosal swabs were obtained to determine the impact of the antimicrobial preparation on the fecal flora. Peritoneal and fascia fluids were obtained to determine the degree of intra operative microbial contamination. The cultures were performed using a number of media for incubation in aerobic and anaerobic conditions.

Definition of complications

Complications were classified into two categories : surgical site infection, and diarrhea. SSI included wound infection and anastomotic leakage. Wound infection was indicated by presence of pus or discharge resulting in a positive bacteriological culture. Diarrhea was listed as a complication when a patient had at least 5 watery stools a day during the post-operative 7

Table 1 Patient characteristics

		Group A N = 45	Group B N = 46	
Median age		64.7 (39-86)	69.0 (16-85)	n.s
Sex ratio	M	29	25	n.s
	F	16	21	
BMI		23.3 (17.0-34.5)	23.0 (17.8-31.5)	n.s
Haemoglobin (g/dl)		11.9 (6.2-17.0)	11.5 (7.5-15.3)	n.s
Total serum protein (g/dl)		6.6 (5.2-8.0)	6.5 (5.2-8.0)	n.s

n.s : not significant

Table 2 Localization of carcinomas

	Group A N = 45	Group B N = 46	
Localization			
Ascending colon	10	12	n.s
Transverse colon	5	6	n.s
Descending colon	0	2	n.s
Sigmoid colon	18	14	n.s
Rectum	12	12	n.s
Tumor size			
< 5 cm	24	24	n.s
5 cm ≦	21	22	n.s

n.s : not significant

days.

Statistical comparisons were made using the chi-squared test, in which P values of 0.05 or less were interpreted as indicating a significant difference.

RESULTS

A total of 91 patients entered this study during the 56-month period of the trial. Forty-five patients were assigned to group A, and 46 patients were assigned to group B. The age distribution, sex, BMI, and disease site were similar in the two groups (Tables 1, 2). And there were no significant differences in tumor size between the two groups.

Before applying the preparation, E. coli was found in 36 of 45 (80.0%) patients of group A and in 37 of 46 (80.4%) patients of group B in the stool. There were no significant differences in the detection rates of all kinds of bacteria between the two groups (Table 3). Culture of mucosal swab obtained during operation showed that in groups A and B the detection rates of gram-positive bacteria were decreased in the same degree and furthermore in group B the detection rates of gram-negative bacteria were decreased. In particular, there were statistically significant differences in the detection rates of E. coli and Klebsiella between the two groups (Table 4). Culture of peritoneal fluid and fascia fluid obtained during operation showed small detection rates of bacteria in both groups without any significant differences (Table 5). In the stool obtained postoperatively, both gram-positive and gram-negative bacteria restored to the pre-operative conditions in terms of detection rates in group A, while in group B gram-positive bacteria restored in the same manner but the detection rates of E. coli and Klebsiella remained low (Table 6). There were significant differences in the detection rates of the two bacteria between the two groups. Furthermore, fecal colonization of MRSA was detected in 2 patients in group B and in no patients in group A (Table 6).

Postoperative complications with detected bacteria were summarized in Table 7. Wound infection was observed in 5 patients of group A and in 10 patients of

Table 3 Bacteria cultured from preoperative stool

	No. of patients with positive culture		
	Group A (n = 45)	Group B (n = 46)	
Gram-positive bacteria			
Streptococcus	22 (48.9 %)	21 (45.7 %)	n.s
Enterococcus	17 (37.8 %)	18 (39.1 %)	n.s
Staphylococcus	12 (26.7 %)	17 (37.0 %)	n.s
Gram-negative bacteria			
E. coli	36 (80.0 %)	37 (80.4 %)	n.s
Klebsiella	10 (22.2 %)	10 (21.7 %)	n.s
Bacteroides	20 (44.4 %)	25 (54.3 %)	n.s
Pseudomonas aeruginosa	1 (2.2 %)	3 (6.5 %)	n.s

n.s : not significant

Table 4 Bacteria cultured from mucosal swabs during operation

	No. of patients with positive culture		
	Group A (n = 45)	Group B (n = 46)	
Gram-positive bacteria			
Streptococcus	3 (6.7 %)	2 (4.3 %)	n.s
Enterococcus	16 (35.6 %)	12 (26.1 %)	n.s
Staphylococcus	2 (4.4 %)	2 (4.3 %)	n.s
Gram-negative bacteria			
E. coli	35 (77.8 %)	11 (23.9 %)	$p < 0.001$
Klebsiella	10 (22.2 %)	1 (2.2 %)	$p = 0.0036$
Bacteroides	16 (35.6 %)	17 (37.0 %)	n.s
Pseudomonas aeruginosa	0 (0 %)	1 (2.2 %)	n.s

n.s : not significant

Table 5 Bacteria cultured from intra-operative peritoneal fluid, fascia fluid

	Group A (n = 45)	Group B (n = 46)	
Peritoneal fluid	3 (6.7 %)	0 (0 %)	n.s
E. coli	1 (2.2 %)	0 (0 %)	n.s
Klebsiella	2 (4.4 %)	0 (0 %)	n.s
Fascia fluid	1 (2.2 %)	1 (2.2 %)	n.s
Enterococcus	1 (1 %)	1 (2.2 %)	n.s

n.s : not significant

group B. There was no difference between the two groups. Anastomotic leakage occurred in 4 patients of group A and in 7 patients of group B. And anastomotic leakage was observed in 6.1 % of colon cancer and 16.7 % of rectal cancer in group A, while it was found in 8.8 % of colon cancer and 33.3 % in rectal cancer in group B. There was no difference, either. Although Citrobacter, Steno maltophilia and Proteus, which had not been detected preoperatively, were detected, there were no differences in the detection rates between the two groups. MRSA was detected in one patient each of the two groups. Diarrhea occurred in 7 patients (15.5 %) in group A, and in 20 patients (43.5 %) in group B. The difference was statistically significant between the two groups ($p = 0.0055$). Furthermore, diarrhea was observed in 21.2 % of colon cancer and in no case of

Table 6 Bacteria cultured from post-operative stool

	No .of patients with positive culture		
	Group A (n = 45)	Group B (n = 46)	
Gram-positive bacteria			
Streptococcus	11 (24.4%)	5 (10.9%)	n.s
Enterococcus	25 (55.5%)	19 (41.3%)	n.s
Staphylococcus	14 (31.1%)	20 (43.5%)	n.s
(MRSA)	(0) (0%)	(2) (4.3%)	n.s
Gram-negative bacteria			
E. coli	34 (75.6%)	8 (17.4%)	$p < 0.001$
Klebsiella	11 (24.4%)	3 (6.5%)	$p = 0.0216$
Bacteroides	25 (55.5%)	21 (45.7%)	n.s
Pseudomonas aeruginosa	5 (11.1%)	4 (8.7%)	n.s

n.s : not significant

Table 7 Post-operative complications

	Group A n = 45	Group B n = 46	
Colon	33 (73.3%)	34 (73.9%)	
Rectum	12 (26.6%)	12 (26.1%)	
SSI	9 (20%)	17 (37%)	P = 0.1041
Wound infection	5 (11.1%)	10 (21.7%)	n.s
Leakage	4 (8.9%)	7 (15.2%)	n.s
Colon	2/33 (6.1%)	3/34 (8.8%)	n.s
Rectum	2/12 (16.7%)	4/12 (33.3%)	n.s
Enterococcus	0 (0%)	3 (6.5%)	n.s
Staphylococcus	2 (4.4%)	3 (6.5%)	n.s
(MRSA)	(1) (2.2%)	(1) (2.2%)	n.s
Bacteroides	1 (2.2%)	5 (10.9%)	n.s
P. aeruginosa	2 (4.4%)	3 (6.5%)	n.s
Klebsiella	2 (4.4%)	1 (2.2%)	n.s
Citrobacter	2 (4.4%)	0 (0%)	n.s
Enterobacter	1 (2.2%)	0 (0%)	n.s
E. coli	1 (2.2%)	0 (0%)	n.s
Steno maltophilia	0 (0%)	1 (2.2%)	n.s
Proteus	0 (0%)	1 (2.2%)	n.s
Diarrhea	7 (15.5%)	20 (43.5%)	P = 0.0055
Colon	7/33 (21.2%)	15/34 (44.1%)	P = 0.0819
Rectum	0/12 (0%)	5/12 (41.7%)	P = 0.0444

n.s : not significant

rectal cancer in group A, whereas diarrhea occurred in 44.1% of colon cancer and 41.7% of rectal cancer in group B. Occurrence of diarrhea in colon cancer tended to be higher in group B than in group A ($p = 0.0819$), and, in rectal cancer, was significantly higher in group B than group A ($p = 0.0444$). Overall, although there was no statistical difference in the SSI rate between the two groups ($p = 0.1041$), SSI rate tended to be higher in group B than in group A.

DISCUSSION

Since the use of preoperative oral antibiotics during the preparation for elective colonic surgery remains controversial[4~6], we performed this prospective randomized trial by assigning patients either into the mechanical preparation group or into the mechanical and

chemical preparation group. Several factors such as ischemia, age, malignant disease, surgical technique, anemia, shock, peritoneal sepsis, intervening pathological conditions, nutritional status, and drugs influence the incidences of SSI. The great variety of factors that may influence the complications makes it difficult to determine the most important factor. This study was aimed to determine the value of chemical preparation, while controlling other factors that might affect the rate of infectious complications. The two groups were similar in terms of gender, age, type of surgery, surgical technique, and postoperative administration of prophylactic antibiotics.

In our patients, preoperative culture of the stool showed the same bacterial flora in the two groups. However, even in patients with mechanical preparation, culture of mucosal swabs showed that the positive-culture rates of gram-positive bacteria had been decreased, while the positive-culture rates of gram-negative bacteria were unchanged. In addition to these findings, in patients with both mechanical and chemical preparation, the positive culture rates of E. coli and Klebsiella had been decreased significantly. The rates were also statistically significant between the two groups. Our data suggested that bacterial flora in the stool had been changed even by mechanical preparation alone and this change was significant by mechanical preparation with oral antibiotics. In fact, it was described that when given up to 5 days, administration of oral non-absorbable antibiotics resulted in the intracolonic unbalanced overgrowth of staphylococci[25]. Nichols et al.[1] reported that the preparation of the intestine by Kanamycin to control growth of Bacteroides has been a failure. Bacteroides is Gram-negative bacteria and has been found to be an important causal agent in wound infections. In our study, although the detection rates of E. coli, Klebsiella and Pseudomonas aeruginosa had been decreased, the detection rate of Bacteroides remained almost unchanged, indicating that the Kanamycin preparation of the colon also failed in controlling Bacteroides. On the other hand, it was demonstrated by prospective, randomized study that short-term oral administration of antibiotics such as neomycin and erythromycin is effective for reducing infectious complications[3,6]. To be effective against postoperative wound infection, the level of antibiotics in the tissue around the surgical wound should be sufficient at the time of bacterial contamination. Because a single dose of antibiotic appeared to be as effective as multiple doses, it is justified to argue that antibiotic prophylaxis should be used as a single dose or short time to reduce the toxicity, cost and possibility of developing resistant bacteria[8].

During surgery, specimens for culture were obtained from intra-operative peritoneal fluid and fascia fluid. The positive-culture rates were small in the two groups without any significance. Since the abdominal cavity was lavaged with saline, most contaminated bacteria might have been washed out and could not be detected in most cases with SSI. In fact, Furukawa et al.[26] reported that intra-abdominal bacterial contamination is associated with SSI. Bacteria attaching and permeating to the wound fat tissue or threads may cause SSI. Unfortunately, in this study, culture of wound fat tissue was not performed.

In our patients, although there was no significant difference, SSI tended to have occurred more frequently in group B than in group A. In particular, gram-negative bacteria including Bacteroides, P. aeruginosa and Klebsiella were detected as causal bacteria in SSI samples more frequently in group B than in group A. This fact might have been attributed to the change of bacterial flora by Kanamycin administration. This change was still present during the first post-operative week demonstrated by stool culture.

Diarrhea observed within the first postoperative week may be associated with the change of bacterial flora. Nicholas et al.[1] reported that diarrhea developed in many patients as a result of Staphylococcal overgrowth. Nakamura et al.[27] reported that bacterial translocation was confirmed using a postoperative MRSA enteritis mouse model, and careless antibiotic administration may cause MRSA enteritis. In our patients, the incidences of diarrhea were significantly higher in group B than in group A. It was suggested that chemical preparation using oral antibiotics suppresses E. coli, and destroys normal colorectal flora, consequently, resulting in the significantly higher occurrence of postoperative diarrhea in group B. Although there was no significant difference, fecal colonization of MRSA was detected only in 2 patients of group B. While positive culture rate of E. coli in group

A was unchanged from pre-operation to post-operation terms. E. coli is the most important bacteria that keeps normal colorectal flora. In group A, colorectal flora is kept in better condition than in group B. Furthermore, Nichols et al.[1] reported that staphylococcal overgrowth is a dangerous problem, not only as a major factor causing fulminant enteritis, but also as a factor causing wound infections. It is speculated that destroyed normal colorectal flora develops bacterial translocation. In our study, although SSI rate tended to be higher in group B than in group A, it could not be determined whether bacterial translocation had occurred or not. More data will be required for clarifying the clinical implications of these findings.

Overall, in this prospective randomized trial there were no deaths, but there were higher incidences of complication in group B than in group A. Thus chemical preparation could not achieve further reduction of infection rates, whereas rather better results were obtained in patients without chemical bowel preparation.

In conclusion, chemical preparation with oral intake of 1,500 mg Kanamycin for 3 days before surgery did not add any advantages to mechanical preparation and is considered unnecessary to perform colorectal surgery.

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