Oral and Parenteral Versus Parenteral Antibiotic Prophylaxis in Elective Laparoscopic Colorectal Surgery (JMTO PREV 07-01): A Phase III, Multicenter, Open-label, Randomized Trial

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Short running head: ABX for laparoscopic colorectal surgery

Mini-Abstract

Our multicenter randomized controlled trial has shown that both the oral and parenteral antibiotic prophylaxis significantly reduces the incidence of surgical site infections compared to parenteral prophylaxis alone in patients undergoing elective laparoscopic colorectal surgery.

Abstract

Objective: To confirm the efficacy of oral and parenteral antibiotic prophylaxis (ABX) in the elective laparoscopic colorectal surgery.

Background: There is no evidence for the establishment of an optimal ABX regimen for laparoscopic colorectal surgery, which has become an important choice for the colorectal cancer patients.

Methods: The colorectal cancer patients scheduled to undergo laparoscopic surgery were eligible for this multicenter, open-label, randomized trial. They were randomized to receive either oral and parenteral prophylaxis (1 g cefmetazole before and every 3 h during the surgery plus 1 g oral kanamycin and 750 mg metronidazole twice on the day before the surgery; Oral-IV group) or parenteral prophylaxis alone (the same IV regimen; IV group). The primary endpoint was the incidence of surgical site infections (SSIs). Secondary endpoints were the incidence rates of *Clostridium difficile* colitis, other infections, and postoperative non-infectious complications, as well as the frequency of isolating specific organisms.

Results: Between November 2007 and December 2012, 579 patients (289 in the Oral-IV group and 290 in IV group) were evaluated for this study. The incidence of SSIs was 7.26% (21/289) in the Oral-IV group and 12.8% (37/290) in the IV group with an odds ratio of 0.536 (95% CI, 0.305–0.940; p = 0.028). The two groups had similar incidence rates of *C. difficile* colitis (1/289 vs. 3/290), other infections (6/289 vs. 5/290), and postoperative non-infectious

complications (11/289 vs. 12/290).

Conclusions: Our oral-parenteral ABX regimen significantly reduced the risk of SSIs following elective laparoscopic colorectal surgery.

Trial registration identifier: NCT00508690.

Keywords: laparoscopic colorectal surgery, antibiotic prophylaxis, chemical bowel preparation, oral antibiotics

INTRODUCTION

Surgical site infections (SSIs) are one of the major causes of morbidity in patients undergoing colorectal surgery. The development of SSIs increases the length of hospital stay and related costs, and decreases the health-related quality of life.[1-3] Recently, laparoscopic surgery has become a practical option for patients with colorectal cancer because of its several advantages over open surgery. Forty-five per cent of operable colon and 19.5% of rectal cancer patients in the United States, and 39.2% of rectal cancer patients undergoing low anterior resection in Japan opt for the laparoscopic surgery.[4, 5] However, the incidence of SSIs in laparoscopic colorectal surgery remains high at around 8–23%.[6-8] Although several guidelines have been published for antibiotic prophylaxis (ABX) in case of colorectal surgery,[9-11] no previous studies have determined the optimal regimen for laparoscopic colorectal surgery. Given that patients undergoing laparoscopic colorectal surgery are allowed to stop intravenous fluids as soon as oral intake becomes possible, we hypothesized that the optimal prophylaxis regimen would be based on the short duration of oral as well as parenteral administration.[12] Some studies as well as the Cochrane meta-analysis have shown that both oral and parenteral ABX is effective in open colorectal surgery,[13-15] but no consensus has been reached on the optimal regimen. In case of laparoscopic surgery, many factors can theoretically contribute to a reduction of SSI rates, such as the need for a shorter surgical incision, involvement of less tissue trauma and contamination, and elimination of mechanical abdominal wall retraction.[16]

Thus, we conducted a multicenter, non-blinded, randomized, controlled trial to assess the efficacy of an oral and parenteral ABX regimen for specifically in laparoscopic colorectal surgery.

METHODS

Study design and participants

The Japan-Multinational Trial Organization (JMTO) conducted a multicenter, non-blinded, randomized controlled trial at five hospitals in Japan between November 1, 2007 and December 31, 2012. The patients satisfying all of the following criteria were selected for the study: (a) undergoing elective laparoscopic colorectal surgery for colorectal cancer or adenoma; (b) aged 20 years or older, (c) having good oral intake, and (d) having adequate organ function.

The patients with any of the following conditions were excluded from the study: (a) bowel obstruction; (b) preoperative infections; (c) antibiotic use within two weeks before the surgery; (d) preoperative steroid use; (e) neoadjuvant radiation and/or chemotherapy; (f) uncontrolled diabetes mellitus; (g) pregnant or lactating woman; and (h) severe allergy.

The trial protocol was approved by the JMTO Ethics Committee in February 2007 and also by the institutional review boards of all of the participating hospitals. All patients provided

written informed consent before randomization. This trial was registered with ClinicalTrials.gov, Number NCT00508690.

Randomization and masking

The investigators recruited eligible patients for this trial from those scheduled to undergo laparoscopic colorectal surgery, and communicated the details of the patients to the JMTO data center by fax. The data center entered these details into the computer to check the patients' eligibility, completed the registration if appropriate, and randomly allocated them to either to the intravenous (IV) group or the Oral-IV group. The treatment allocation was then communicated to the appropriate investigating surgeon by fax. We used Pocock and Simon's minimization method for the minimization of imbalance between the two treatment groups with respect to the following three stratifying factors: trial center, surgery types (colectomy, anterior resection or abdominoperineal resection), and the presence of diabetes mellitus. Neither the patients nor investigators were masked to the treatment assignment. The JMTO data center was responsible for assigning the interventions, data management, and central monitoring.

Procedures

All patients underwent mechanical bowel preparation (MBP) with 75 mg of sodium

picosulfate and 34 g of magnesium citrate along with 180 ml of water on the day before the surgery. The patients assigned to the Oral-IV group were given two oral doses of 1 g of kanamycin and 750 mg of metronidazole at 13 h and 9 h before the surgery. This was a modification of a previously reported oral regimen.[17] The IV group received no oral antibiotics. One gram of cefmetazole (a cephamycin antibiotic) was administered intravenously to both the groups 30 min before the skin incision, and an additional dose was given every 3 h during the surgery. After the surgery, no additional antibiotics were given to either of the groups. Except the oral antibiotic administration in the Oral-IV group, the perioperative treatment protocol was identical for both the groups.

We followed the US Centers for Disease Control and Prevention's (CDC) guidelines for the prevention of SSIs.[18] The hairs present around the surgical site were removed with a surgical clipper after the induction of anesthesia. Laparoscopic surgery was performed on all patients in both the groups, and no patients had a diverting stoma created at the time of this initial surgery. The incision site through which a specimen had been taken out was protected with a disposable wring drape during the procedure. We used synthetic absorbable sutures to close the fascia. After the subcutaneous space had been irrigated with saline, either absorbable subcuticular sutures or surgical staples were used to close the skin. The surgical site was covered with sterile dressing for about 48 h and then left dressing-free.

The tolerability and adverse effects of MBP, administration of intravenous and oral antibiotics,

and details of the intraoperative procedures in the patients were recorded on the case report form to check their adherence to the protocol.

Measures of study outcome

The primary outcome of the study was the incidence of SSIs. We used the CDC guidelines to diagnose SSI.[18] SSIs were classified as being either incisional or organ/space. The incisional SSIs were further divided into those involving only skin and subcutaneous tissue (superficial incisional SSI) and those involving deeper soft incisional tissues (deep incisional SSI). The organ/space SSIs involved any part of the anatomy (eg, organ or space) other than the incised body wall layers that had been opened or manipulated during the surgery. Whenever SSIs were suspected or confirmed, clinically relevant microbiological samples were cultured.

The secondary outcomes of the study were the incidence rates of enteritis/colitis/diarrhea, infectious diseases except SSIs, and other postoperative complications, as well as the frequency of isolating specific organisms (Methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*).

The surgeons and nurses assessed these outcomes daily during the patient's hospital stay of the patients. After discharge, all patients were followed up at an outpatient clinic for 30 days from the surgery to check for the occurrence any of the events mentioned above. All events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria

(CTCAE v 3.0), and CTCAE Grade ≥2 events were taken as the secondary outcomes. If the patients developed enteritis/colitis/diarrhea, their stool samples were taken to be tested for *Clostridium difficile* toxins.

Statistical analysis

We planned to enroll 566 patients during the trial design. This sample size would provide an 80% power with a two-sided significance level of 0.05 to demonstrate the superiority of the Oral-IV group in the reduction of SSI rate. The incidence of SSI was anticipated in 10% of the patients in the IV group and 4% in the Oral-IV group. The planned accrual period was 2.5 years but was extended by two years due to a delay in patient enrollment. We conducted the analysis on an intention-to-treat basis. We expressed continuous numerical data as medians and interquartile range (IQRs) and distribution of dichotomous data was done in percentages. The primary outcome was analyzed with a χ^2 test. The secondary comparisons between the two groups were analyzed with the χ^2 test and Fisher's exact test. All *p* values of less than 0.05 were deemed significant.

The subgroups were analyzed with logistic regression for the assessment of statistical interactions between the treatments in various subgroups. The subgroup comparisons were exploratory in nature; hence, we reported the test results without multiplicity adjustments for type I error. We did all analyses in SPSS version 18 (SPSS Inc., Chicago, IL) and SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Role of the funding source

This study was funded by JMTO, a general incorporated association established in 1999 to support clinical trials, especially multicenter or multinational randomized controlled trials, for the diagnosis, treatment and prevention of the diseases. The sponsor had no involvement in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the report. The corresponding author had full access to the study data and final responsibility in submitting the report for the purpose of the publication.

RESULTS

Figure 1 shows the trial profile. Between November 1, 2007 and December 31, 2012, 584 patients from five hospitals were randomly grouped into two groups: 291 to the IV group and 293 to the Oral-IV group. One patient in the Oral-IV group withdrew consent, and one in the IV group and three in Oral-IV group were found to be ineligible after randomization. Therefore, 290 and 289 patients in the IV and Oral-IV groups, respectively, received allocated treatment and were analyzed for the primary and secondary outcomes. At one of the five trial centers, 36 patients in the Oral-IV group took two oral doses of 500 mg of kanamycin and 250 mg of metronidazole, which were half or less the doses specified in the protocol, at 13 h and 9

h before the surgery; they used IV ABX without any deviation from the protocol. All patients underwent laparoscopic surgery, except 12 (six patients in each group) who underwent open surgery. Table 1 shows the baseline characteristics of the study participants. The two groups were well-balanced at the baseline.

The SSIs occurred in 21 of 289 (7.26%; 95% confidence interval [CI]: 4.26–10.3) patients in the Oral-IV group compared to 37 of 290 (12.8%; 95%CI: 8.90–16.6) patients in the IV group (Table 2). As the primary outcome, the oral and parenteral prophylaxis significantly reduced the incidence of SSIs in patients undergoing elective laparoscopic colorectal surgery (odds ratio [OR] = 0.536; 95% CI: 0.305–0.940; p = 0.028). For the reference, the p-value of the Cochran-Mantel-Haenszel (CMH) test stratified by tumor location was found to be 0.0278.

Table 3 summarizes the secondary outcomes. The incidence rates of enteritis/colitis/diarrhea and *C. difficile* toxins in the stool samples in the Oral-IV group (1.0% and 0.3%, respectively) were numerically (but not significantly) lower than those in the IV group (3.1% and 1.0%, respectively). The incidence of remote infections mainly urinary tract infection was 2.1% (6/289) in the Oral-IV group and 1.7% (5/290) in the IV group. The postoperative non-infectious complications were of identical frequency but their profiles were slightly different between the two groups. The cultures of the surgical site in infected patients yielded growth of 21 and 37 organisms in the Oral-IV and IV groups, respectively (Table 4). The frequencies of isolating specific organisms were similar for the two groups. We did a post-hoc

subgroup analysis to identify the potential interactions between the treatment and background factors (Fig. 2). The incidence of SSIs in the Oral-IV group was lower than that of the IV group in case of patients who underwent colon surgery (OR = 0.379; 95% CI: 0.170–0.848; p = 0.023), and were aged less than 67 years (OR = 0.44; 95% CI: 0.204–0.948; p = 0.041). With regard to the intraoperative factors, a significant risk reduction for SSIs in the Oral-IV group was seen in the following subgroups: (a) patients having a shorter operation time (<5 h) (OR = 0.379; 95% CI: 0.181–0.792; p = 0.009); (b) patients with blood loss less than 100 ml (OR = 0.524; 95% CI: 0.279–0.984; p = 0.039); and (c) patients without surgical drain insertion (OR = 0.487; 95% CI: 0.253–0.942; p = 0.035).

DISCUSSION

The prevalence of laparoscopic colorectal surgery has increased rapidly in the recent years. However, larger randomized controlled trials have reported comparable high incidence rates of SSIs following laparoscopic and open surgery, such as (a) LAPKON II trial: 17.2%; and (b) CLASICC trial: 8% in colon and 23% in rectal surgery.[6,7] Although the current guidelines recommend the use of several antimicrobial agents, no specific regimen has been studied in case of the laparoscopic colorectal surgery.[9-11] In case of open colorectal surgery, only 36% of colorectal surgeons reported using oral-parenteral ABX in 2010 in comparison with 92% in 1990,[19,20] despite the recently proven efficacy of oral-parenteral prophylaxis in randomized

trials and meta-analyses.[13-15] Our multicenter, randomized, controlled trial has shown that in patients undergoing elective laparoscopic colorectal surgery, the oral and IV ABX significantly reduced the incidence of SSIs compared to the IV prophylaxis alone (OR = 0.536; 95% CI: 0.305–0.940; p = 0.028).

The recent randomized controlled trials showed distinct superiority of new prophylaxis regimens in terms of their ability to prevent superficial infections but not organ/space infections.[21,22] Similarly, in our trial, the incidence of superficial incisional infections was 26/290 (9.0%) in the IV group and 15/289 (5.2%) in the Oral-IV group while the incidence of organ/space infection was 10/290 (3.4%) and 7/289 (2.4%) in the respective groups. These data are consistent with the finding in a recent meta-analysis study stating that ABX cannot prevent anastomotic leakages but can effectively reduce the number of contaminating bacteria causing superficial SSIs.[23]

It has been reported that oral non-absorbable ABX increases the risk of *C. difficile* colitis.[24] In our trial, all the patients were assessed for the development of enteritis/colitis/diarrhea, and every patient who developed any of these symptoms had his/her stool samples tested for *C. difficile* toxins. The incidence rates of enteritis/colitis/diarrhea and *C. difficile* toxins in the stool samples of the Oral-IV group (1.4% and 0.3%, respectively) were rather lower than those in the IV group (3.1% and 1.0%, respectively), and were also lower than those reported previously.[24] One possible reason for the successful protection against *C. difficile* infection

after oral ABX was the use of an IV antibiotic just before and during the surgery in our regimen; prolonged antibiotic use is also reported as a risk factor for *C. difficile* colitis.[25] The frequencies of isolating specific bacterial species of concern were similar for the two groups, indicating that oral ABX is unlikely to induce the emergence of resistant organisms. *Bacteroides* species were the most common species isolated in our study but were only isolated in the IV group. Given that cefmetazole, a parenteral antibiotic administered to both the groups, was inactive against some *Bacteroides* species, oral metronidazole might play an additional role in preventing the contamination with *Bacteroides* species.

In the recent years, a controversy has arisen over the benefit of MBP for elective colorectal surgery. In our trial, all the patients received MBP with 75 mg of sodium picosulfate and 34 g of magnesium citrate taken with 180 ml of tap water. A pivotal study reported shortly after the commencement of our trial showed that MBP before elective colorectal surgery could safely be abandoned[26] while other randomized trials and meta-analyses demonstrated that a lower SSI rate was associated with MBP in combination with oral ABX.[13, 16, 26, 27] However, as these trials excluded patients who underwent laparoscopic surgery, a recent meta-analysis concluded that research on MBP in patients submitted to laparoscopic colorectal surgery was warranted.[27] Hence, it was considered unlikely that the MBP affected the effect of our oral-parenteral ABX regimen.

Perioperative hyperglycemia is reported to be associated with increased rates of SSI. [28] In this

trial, the influence of hyperglycemia on SSI is unpredictable because the perioperative glycemic control was not specified in the protocol and was left to the usual hospital management. The patients were stratified by their diabetes status at the time of registration. However, there was a little difference in the incidences of SSI in the nondiabetic (51/515; 9.9%) and diabetic patients (7/64; 10.9%). On the other hand, the positive trend of the effect of our oral-parenteral ABX regimen was observed equally in both the groups by a post hoc analysis. (Fig.2)

We did not record the incidence of hypothermia, though perioperative hypothermia has been reported as the risk factor for SSI.[29] In this trial, the patients were managed to maintain normothermia by the routine methods followed by each hospital. Despite the absence of environmental exposure of the abdominal viscera, the incidence of hypothermia in laparoscopic surgery was similar to that of the open surgery.[30] Thus, perioperative hypothermia might affect the overall incidence of SSI. However, the effect of our oral-parenteral ABX regimen over parenteral ABX did not change because it may have similar influence on both the groups.

Our trial has several limitations. First, this was a non-blinded study. We did not use a placebo in this trial, and the surgeons were not masked to allocated treatment. However, the surgical sites of all patients were evaluated daily during the period of hospitalization by several medical staff members who were not involved in this trial, and this would considerably reduce

the risk of bias in assessing the primary endpoint. Second, 36 patients allocated to the Oral-IV group at one of the five trial centers were given smaller doses of oral prophylactic antibiotics than specified in the protocol because the investigator surgeon used an incorrect prescription set that was created with the smaller doses at the start of the trial. This could have led us to underestimate the true effect size (ie, the difference in the incidence of SSIs between the two treatment groups). Third, the protocol was amended to extend the study period from 2.5–4.5 years to achieve the planned sample size. This was because the chief surgeon shortlisted the trial centers to maintain the quality of the trial that resulted in much time consumption in recruiting subjects for the trial.

In conclusion, our oral-parenteral ABX significantly reduced the incidence of SSIs in the patients undergoing elective laparoscopic colorectal surgery.

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trials, especially multicenter or multinational randomized controlled trials, for the diagnosis, treatment and prevention of diseases.

References

1. Eagye KJ, Nicolau DP. Deep and organ/space infections in patients undergoing elective colorectal surgery: incidence and impact on hospital length of stay and costs. *Am J Surg.* 2009;198:359-367.

2. Anthony T, Long J, Hynan LS, et al. Surgical complications exert a lasting effect on disease-specific health-related quality of life for patients with colorectal cancer. *Surgery.* 2003;134:119-125.

3. Kashimura N, Kusachi S, Konishi T, et al. Impact of surgical site infection after colorectal surgery on hospital stay and medical expenditure in Japan. *Surg Today.* 2012;42:639-645.

4. Matsubara N, Miyata H, Gotoh M, et al. Mortality after common rectal surgery in Japan: a study on low anterior resection from a newly established nationwide large-scale clinical database. *Dis Colon Rectum.* 2014;57:1075-1081.

5. Kang CY, Halabi WJ, Luo R, et al. Laparoscopic colorectal surgery: a better look into the latest trends. *Arch Surg.* 2012;147:724-731.

6. Ozkan OV, Semerci E, Yetim I, et al. Delayed diagnosis of traumatic diaphragmatic hernia may cause colonic perforation: a case report. *Cases J.* 2009;2:6863.

7. Guillou PJ, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet.* 2005;365:1718-1726.

8. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. *Am Surg.* 2011;77:1290-1294.

9. Antimicrobial prophylaxis for surgery. *Treat Guidel Med Lett.* 2012;10:73-78; quiz 79-80.

10. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm.* 2013;70:195-283.

11. Bratzler DW, Houck PM, Surgical Infection Prevention Guideline Writers W. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Am J Surg.* 2005;189:395-404.

12. van der Pas MH, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *Lancet Oncol.* 2013;14:210-218.

13. Lewis RT. Oral versus systemic antibiotic prophylaxis in elective colon surgery: a randomized study and meta-analysis send a message from the 1990s. *Can J Surg.* 2002;45:173-180.

14. Rein DB, Wittenborn JS, Weinbaum CM, et al. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. *Dig Liver Dis.* 2011;43:66-72.

15. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev.* 2014;5:CD001181.

16. Arezzo A, Passera R, Scozzari G, et al. Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis. *Surg Endosc.* 2013;27:1485-1502.

17. Wolff BG, Beart RW, Jr., Dozois RR, et al. A new bowel preparation for elective colon and rectal surgery. A prospective, randomized clinical trial. *Arch Surg.* 1988;123:895-900.

18. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control.* 1999;27:97-132; quiz 133-134; discussion 96.

19. Markell KW, Hunt BM, Charron PD, et al. Prophylaxis and management of wound infections after elective colorectal surgery: a survey of the American Society of Colon and Rectal Surgeons membership. *J Gastrointest Surg.* 2010;14:1090-1098.

20. Solla JA, Rothenberger DA. Preoperative bowel preparation. A survey of colon and rectal surgeons. *Dis Colon Rectum.* 1990;33:154-159.

21. Itani KM, Wilson SE, Awad SS, et al. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med.* 2006;355:2640-2651.

22. Fujita S, Saito N, Yamada T, et al. 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. *Arch Surg.* 2007;142:657-661.

23. Bellows CF, Mills KT, Kelly TN, et al. Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infections after colorectal surgery: a meta-analysis of randomized controlled trials. *Tech Coloproctol.* 2011;15:385-395.

24. Wren SM, Ahmed N, Jamal A, et al. Preoperative oral antibiotics in colorectal surgery increase the rate of Clostridium difficile colitis. *Arch Surg.* 2005;140:752-756.

25. Carignan A, Allard C, Pepin J, et al. Risk of Clostridium difficile infection after perioperative antibacterial prophylaxis before and during an outbreak of infection due to a hypervirulent strain. *Clin Infect Dis.* 2008;46:1838-1843.

26. Contant CM, Hop WC, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet.* 2007;370:2112-7.

27. Guenaga KF, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev.* 2011:CD001544.

28. Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. *Ann Surg.* 2013;257:8-14.

29. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med.* 1996;334:1209-1215.

30. Luck AJ, Moyes D, Maddern GJ, et al. Core temperature changes during open and laparoscopic colorectal surgery. *Surg Endosc.* 1999;13:480-483.

Figure legends

Figure 1: Trial profile. IV: intravenous, Oral-IV: Oral and intravenous.

Figure 2: Subset analysis of the surgical site infections. Significance was calculated with Fisher's exact test. Odds ratios were calculated by logistic regression. IV: intravenous, Oral-IV: Oral and intravenous.

Table. 1 Baseline characteristics of patients

	Intravenous prophylaxis (n=290)	Oral-intravenous prophylaxis (n=289)
Age (years)	67.5 (60.0–75.0)	67 (60.5–75.0)
Sex		
Male	175 (60.3%)	153 (52.9%)
Female	115 (39.7%)	136 (47.1%)
Body-mass index	22.5 (20.3–24.8)	22.8 (20.4–24.8)
Tumor site		
Colon	188 (64.8%)	188 (65.1%)
Rectum	102 (35.2%)	101 (34.9%)
Surgery type		
Colectomy	188 (64.8%)	188 (65.1%)
Anterior resection	91 (31.3%)	92 (31.8%)
APR	11 (3.8%)	9 (3.1%)
Operative time (min)	259 (219–317)	255 (217–305)
Blood loss (mL)	20 (0–66)	20 (0–40)
Drainage tube		
Yes	63 (21.7%)	46 (15.9%)
No	227 (78.3%)	243 (84.1%)
Conversion to open surgery		
Yes	6 (2.1%)	6 (2.1%)
No	284 (97.9%)	283 (97.9%)
Transfusion		
Yes	1 (0.3%)	1 (0.3%)
No	289 (99.7%)	288 (99.7%)
Diabetes mellitus		

Yes	31 (10.7%)	33 (11.4%)
No	259 (89.3%)	256 (88.6%)

Data are n (%) or median (interquartile range).

Table 2

Table. 2 Primary outcome

	Intravenous prophylaxis (n=290)	Oral-intravenous prophylaxis (n=289)	Odds ratio (95% CI)	p value χ^2 test
Primary outcome				
Surgical site infection	37(12.7%)	21(7.3%)	0.536 (0.305–0.940)	p = 0.028☆
Superficial incisional	26	15	0.556 (0.288–1.073)	p = 0.077
Deep incisional	1	1	1.003 (0.062–16.120)	p = 0.996
Organ or space	10	7*	0.695 (0.261–1.852)	p = 0.465
With anastomotic leakage	6	5		
Without anastomotic leakage	4	2		

Odds ratio was calculated by logistic regression

☆The p-value of Cochrane-Mantel-Haenszel test stratified by tumor location was p = 0.0278.

*Two patients had superficial and organ/space surgical site infection

Table 3

Table. 3 Secondary outcomes

	Intravenous prophylaxis (n=290)	Oral–intravenous prophylaxis (n=289)	Odds ratio (95% CI)	p value Fisher exact test
Enteritis/colitis/diarrhea	9 (3.1%)	4 (1.4%)	0.438 (0.133–1.439)	p = 0.174
Clostridium difficile toxin	3 (1.0%)	1 (0.3%)	0.332 (0.034–3.212)	p = 0.341
Remote site infection	5 (1.7%)	6 (2.1%)	1.208 (0.365–4.005)	p = 0.757
Urinary tract	3 (1.0%)	3 (1.0%)		
Prostate	1 (0.7%)	1 (0.3%)		
Lung	1 (0.3%)	1 (0.3%)		
Unknown	0	1 (0.3%)		
Postoperative non–infectious complication	12 (4.1%)	11 (3.8%)	0.916 (0.398–2.112)	p = 0.993
Ileus	5 (1.7%)	1 (0.3%)		
Bowel obstruction	4 (1.4%)	3 (1.0%)		
Bleeding	1 (0.3%)	2 (0.7%)		
Pancreatitis	1 (0.3%)	1 (0.3%)		
Pancreatic fistula	1 (0.3%)	0		
Anastomotic stricture	0	1 (0.3%)		
Atrial fibrillation	0	1 (0.3%)		
Skin rash	0	1 (0.3%)		
Reoperation for residual tumor	0	1 (0.3%)		

Significance was calculated with Fisher’s exact test. Odds ratios were calculated by logistic regression.

Table 4

Table. 4 Microbiology of Infections with Documented Causative Pathogens

	No. of Isolates (n=58)			
	Intravenous prophylaxis (n=37)	Oral-intravenous prophylaxis (n=21)	Odds ratio (95% CI)	p value Fisher exact test
Methicillin-resistant *Staphylococcus aureus*	2	4	4.11 (0.685–24.7)	p = 0.176
Pseudomonas aeruginosa	3	5	3.54 (0.752–16.7)	p = 0.124
Bacteroides spieces	10	0		
Bacteroides fragilis	3	0		
Bacteroides non-fragilis	7	0		
Enterococcus spieces	9	2		
Coaglase-negative *Staphylococcus aureus*	8	3		
Staphylococcus aureus (methicillin-sensitive)	6	2		
Corynebacterium spieces	4	0		
Escherichia coli	3	2		
Peptostreptococcus spieces	2	0		
Enterobacter cloacae	1	0		
Streptococcus spieces	1	1		
Prevotella spieces	1	0		

Neisseria spieces	1	0
Bifidobacterium spieces	1	0
Enterobacteriaceae	1	0
Candida spieces	0	1

Significance was calculated with Fisher's exact test. Odds ratios were calculated by logistic regression. Analysis of only Methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* was pre-specified.

Figure. 1

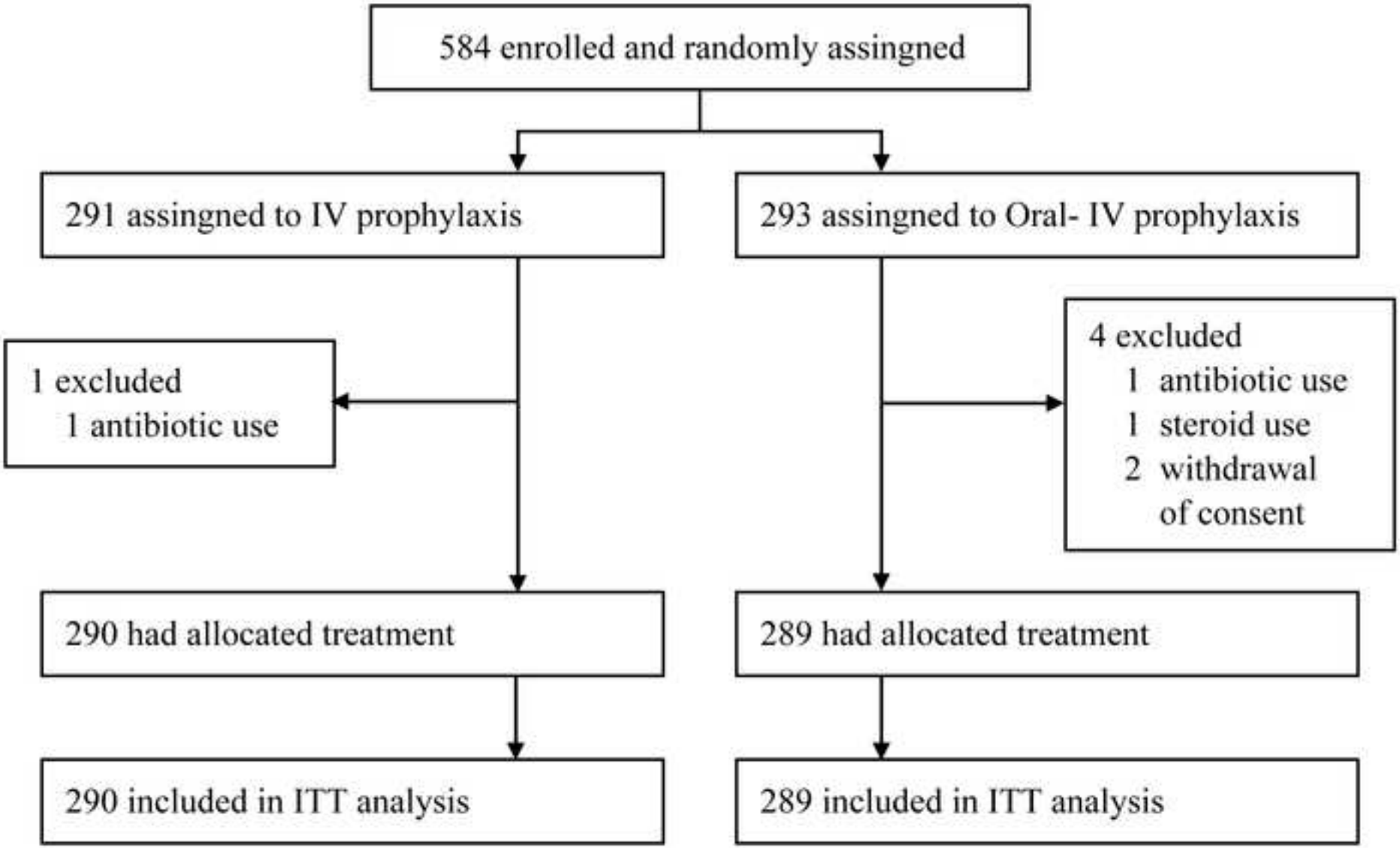

Figure2

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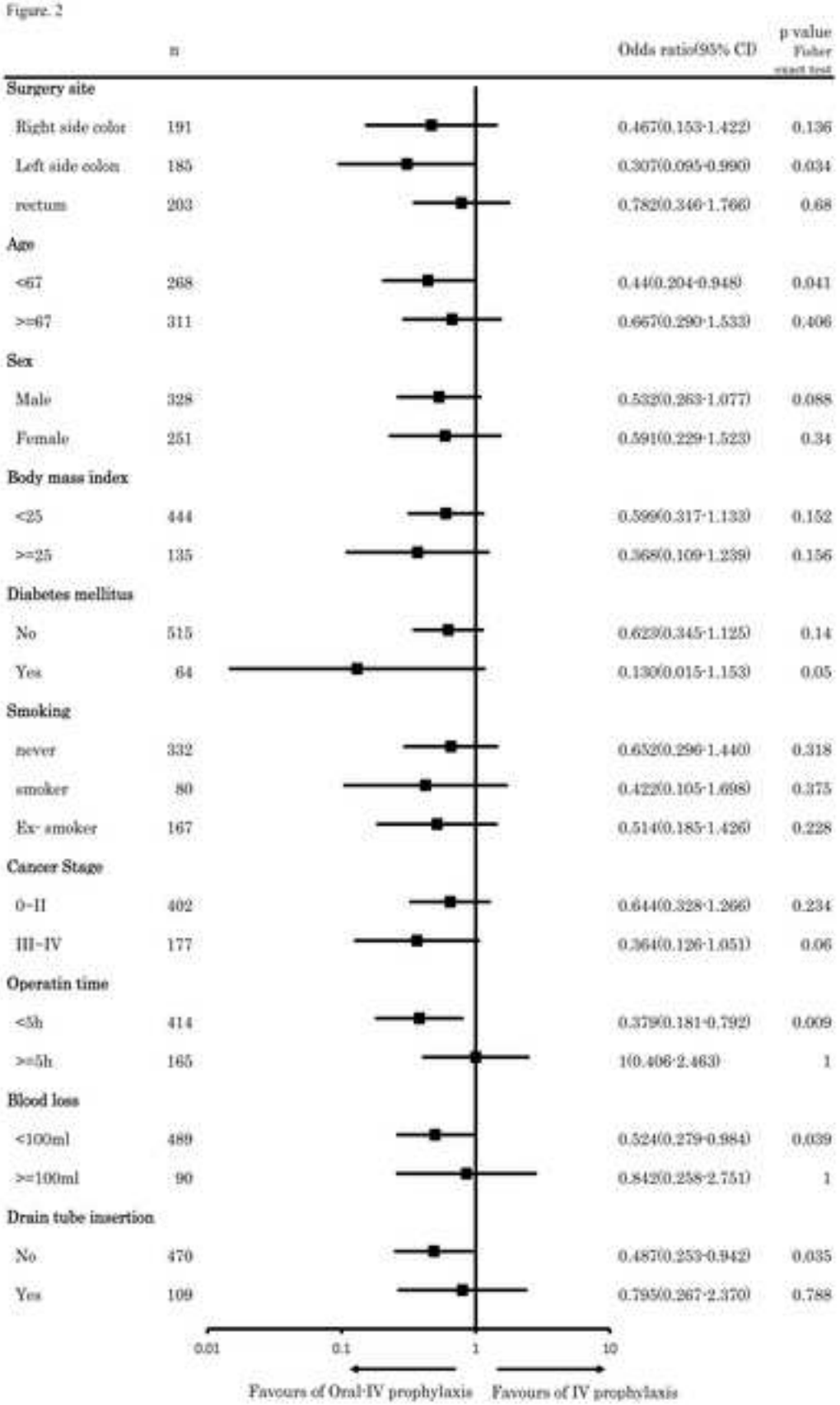
Figure. 2



Authors contribution

The authors' contributions were as follows:

Study concept and design: all authors; drafting/revising the study protocol: Hiroaki Hata, Suguru Hasegawa, and Yoshiharu Sakai; data collection/analysis: Hiroaki Hata and Takeharu Yamanaka; drafting the manuscript: Hiroaki Hata and Takeharu Yamanaka; revising the draft and approving the final version of the manuscript: all authors.