

Postoperative infection of endoscopic submucosal dissection of early colorectal neoplasms: a case controlled-study using a Japanese database

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SUMMARY

What is known and objective: Endoscopic submucosal dissection of early colorectal neoplasms (ESD - ECN) is known to be an operation with risk of contamination, possibly requiring preoperative antimicrobial prophylaxis for prevention of postoperative infection. However, an evaluation of the need for preoperative antimicrobial prophylaxis of ESD – ECN has yet to be reported. The objective of this study was to determine whether preoperative antimicrobial prophylaxis is associated with a reduced incidence of postoperative infection following ESD - ECN.

Methods: The present retrospective case-controlled study utilized a database built from the medical records of 14 university hospitals throughout Japan. Patients who were admitted and discharged from the hospital from April 2012 to October 2013 and who had undergone ESD - ECN were included in the study. Patients who had been undergone any other operation during their course of hospitalization, and patients who were prescribed antimicrobial agents for reasons other than postoperative infection or for prophylaxis were excluded. Characteristics of the study population, preoperative antimicrobial prophylaxis, and antimicrobial therapy for postoperative infection were investigated. In addition, we compared the characteristics of patients with postoperative infection (PI) and

those with no postoperative infection (NPI). Univariate analyses were used to estimate the odds ratios (OR) and 95% confidence intervals (95%CI).

Results and discussion: We obtained the records of 522 patients who had undergone ESD - ECN from the database. After application of exclusion criteria, 421 patients were enrolled. The postoperative infection rate was 1.2%. Peritonitis was found most to be the most common postoperative infection (44%). Preoperative antimicrobial prophylaxis was used for 314 patients (75%), with a median duration of 3.0 (range 1 – 11) days. Cefotiam was most frequently prescribed for preoperative antimicrobial prophylaxis (56%). Antimicrobial therapies were started 1 to 10 days after ESD - ECN for a duration of 1 to 14 days. Preoperative antimicrobial prophylaxis was not associated with postoperative infection rate, with an OR (95%CI) of 0.73 (0.08 – 6.61). However, digestive tract perforation was shown to be associated with postoperative infection, and had an OR (95%CI) of 17.1 (1.66-176.45).

What is new and conclusion: Postoperative infection is an exceedingly rare event following ESD - ECN. Preoperative antimicrobial prophylaxis had no significant effect on postoperative infection following ESD - ECN, and thus may be unnecessary. Instead, prevention of digestive tract perforation may be more critical for the decrease in postoperative infections.

What is known and objective

Endoscopic submucosal dissection (ESD) is a variant of endoscopic mucosal resection (EMR), and is a technique for resection of early gastrointestinal tract cancers. ESD is used primarily in the stomach, but is also increasingly being applied in the colon and rectum¹.². The technique involves identifying the margins of the polyp, submucosal injection, and circumferential dissection of the tumor-bearing mucosa and submucosa using various diathermic knives. The aim of ESD is to achieve an en-bloc resection of a sessile lesion, irrespective of its size. This facilitates histological evaluation and improves the rate of curative resection, even for carcinomas with early submucosal invasion³).

Postoperative infections are a major contributor to healthcare-associated infections. Gastrointestinal procedures are thought to have the highest risk for postoperative infection due to exposure to intraluminal bacteria⁴). Therefore, preoperative antimicrobial prophylaxis is warranted for patients undergoing gastrointestinal surgery involving the colon or rectum. ESD of early colorectal neoplasms (ESD - ECN) is considered to be an operation with risk of contamination, possibly requiring preoperative antimicrobial prophylaxis for the prevention of postoperative infection. Because the ESD procedure requires advanced skill and extensive training to achieve a satisfactory level of ability, the use of this technique has been somewhat limited. Therefore, the evaluation of the need

for preoperative antimicrobial prophylaxis for ESD has not been sufficient. The objective of this study was to determine if preoperative antimicrobial prophylaxis is associated with a reduced incidence of postoperative infection following ESD - ECN.

Methods

Study Design and Data Source

This study was a retrospective case-controlled study utilizing the Platform for Clinical Information Statistical Analysis (CISA) database, which is composed of clinical data from 14 university hospitals throughout Japan. The CISA database contains data on approximately 2.45 million unique patients, a cumulative total of 1.25 million inpatients, a cumulative total of 37.79 million outpatients, 32.86 million prescriptions for inpatients, and 14.50 million prescriptions for outpatients. These data were collected from the medical records from each facility after removing personal information and irreversibly anonymizing the data. At present, data on medical treatment results, such as test results and interviews, information on palpation, and images are not included in the database. Diagnostic codes were established according to both the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and the Japanese Receipt Disease Name Master (JRDNM). Drug codes were established

according to the Anatomical Therapeutic Chemical Classification System (ATC) code. In the present study, only data obtained from April 2012 to October 2013 were analyzed.

Population and Definitions

Data on patients who were admitted and discharged from the hospital from April 2012 to October 2013 and who had undergone ESD - ECN were collected from the CISA database.

To reduce any possible influence of the patients' preoperative conditions, patients who had undergone ESD - ECN more than 4 days after the date of admission were excluded.

Four days was selected because this duration was the most generally period from hospitalization to do ESD – ECN in Japan. Patients who had undergone any other operation other than their first ESD – ECN procedure during their course of hospitalization, such as those who had undergone additional tumorectomy or ESD for the same or different region, were also excluded. Patients who were prescribed antimicrobial agents for treatment of conditions other than postoperative infection were excluded, as were patients who were prescribed antimicrobial agents for purposes other than postoperative infection or prophylaxis. The patients remaining after application of the exclusion criteria was divided into two groups, those who had been postoperative infection (PI) and those who had been not PI (NPI) (Fig. 1).

Codes from the Japanese Receipt Disease Name Master were used for definition of postoperative infection. Codes for infectious diseases were selected by excluding infections originating from regions other than the abdomen, such as pneumonia, from all disease codes of the study population, and defined the remaining as Postoperative Infection Codes (PIC). In the present study, antimicrobial therapy for postoperative infection was defined as antimicrobial therapy administered to patients who were assigned a PIC after undergoing ESD - ECN. Thus, the postoperative infection group (PI) was defined as patients who were treated with antimicrobial therapy for postoperative infection.

Preoperative antimicrobial prophylaxis was defined as antibiotic administration during the first day of hospitalization to the day of ESD - ECN.

Epidemiological Research and Statistical Methods

Characteristics of the study population, use of preoperative antimicrobial prophylaxis, and administration of antimicrobial therapy for postoperative infection were collected from the database for epidemiological evaluation. JRDNM were used for definition of the perforation of the digestive tract. Perforation of the digestive tract was defined as patients who were assigned JRDNM codes that were meaning "perforation of the digestive tract" in the disease name after undergoing ESD – ECN and counted. Additionally, the duration

of hospitalization after ESD – ECN, and the number of patients with malignant tumor-related diseases were collected for comparison between the PI and NPI groups. We compared the PI and NPI groups using the Wilcoxon rank sum test for continuous variables, the chi-square, or Fisher’s exact test for dichotomous variables. Differences were considered significant when $P < 0.05$. Univariate analyses was used to determine independent predictors of postoperative infection and to obtain odds ratios (OR), and the 95% confidence interval (95%CI) for each OR was calculated. Statistical significance was determined by 95% confidence intervals, not including 1.00 for logistic analyses. We introduced preoperative antimicrobial prophylaxis and digestive tract perforations as groups of variables into the model, because these are well known to be associated with postoperative infection.

Ethics statement

Because the data utilized in this study were provided to us already anonymized by the database provider, CISA, the study was exempted from obtaining informed consent from individual patients according to the local ethical guidelines for epidemiological research. This study and the waiver of informed consent were approved by the Nagasaki University Hospital ethics committee (14102796).

Results and discussion

1. Characteristics of the study population:

We obtained data on 522 patients who had undergone ESD - ECN from the CISA database.

After applying the exclusion criteria, 421 patients were enrolled in the present study (Figure 1). The postoperative infection rate was 1.2%. Types of neoplasms observed in the study population are shown in Table 1. The majority of the patients had malignant neoplasms of the colon (45%) or rectum (14%). Perforation of the digestive tract was observed in 2% of patients. The characteristics of postoperative infection of the study population are shown in Table 2. Peritonitis (including generalized, circumscribed, and perforative peritonitis) were the most common postoperative infection (44%). Only two cases were reported to have developed sepsis (0.5%).

2. Characteristics of preoperative antimicrobial prophylaxis:

Preoperative antimicrobial prophylaxis was used for 314 patients (75%). The median dosing period of preoperative antimicrobial prophylaxis was 3.0 (range 1 – 11) days. Table 3 shows the duration of the preoperative antimicrobial prophylaxis per generic name. Cefotiam was the most commonly prescribed preoperative antimicrobial prophylaxis (56%), with a median dosing period of 3.0 days. Cefmetazole were the

second most frequently prescribed prophylaxis (17%), with a median dosing period of 2.5 days.

3. Antimicrobial therapy for postoperative infection:

The median duration of antimicrobial therapy for postoperative infection was 4 days; the characteristics are shown in Table 4. Six agents, including combination therapy, were used for treatment of postoperative infection, and were started 1 to 10 days after ESD - ECN for a duration of 1 to 14 days.

4. Comparison of the PI and NPI groups:

Characteristics of the PI and NPI groups are shown in Table 5, with no significant differences between the two groups. Table 6 shows the duration of the preoperative antimicrobial prophylaxis per generic name of PI. Cefotiam was the most commonly prescribed preoperative antimicrobial prophylaxis (50%) of PI, too. Univariate analyses of PI and NPI is shown in Table 7. Preoperative antimicrobial prophylaxis was not associated with postoperative infection, and had an OR (95%CI) of 0.73 (0.08 – 6.61). However, perforation of the digestive tract was associated with postoperative infection, and had an OR (95%CI) of 17.1 (1.66-176.45).

The present results suggested that there is no significant correlation between preoperative antimicrobial prophylaxis and incidence of postoperative infection after ESD - ECN.

Instead, perforation of the digestive tract was found to increase postoperative infection approximately 17-fold. In present study, it is not possible to perform multivariate logistic regression analysis, because the low number of patients with postoperative infection. So we conducted univariate analyses. Therefore, our results may include the confounding factors.

The postoperative infection rate in the present study was 1.2%, and was lower than that rate previously reported for whole colon surgery (15%)⁵⁾. Sepsis had developed in only 2 patients (0.5%). Similarly, Minn et al. reported a low bacteremia rate (2.5%) associated with ESD or endoscopic mucosal resection (EMR)⁶⁾, suggesting that this was due to the low possibility of direct injection into a blood vessel during submucosal injection⁶⁾. This may also be the case in ESD, which is usually used for resecting a large lesion, and consequently results in a considerable amount of exposed submucosa, requiring a large number of submucosal injections. Therefore, ESD may have a higher risk for postoperative infection than EMR. However, ESD has considerably fewer opportunities of injury to blood vessels compared with general colon surgery. Unlike an open abdominal surgery, ESD does not remove the digestive tract, and does not spill bacteria-laden intestinal contents into the abdomen. Supporting this, the present study found that perforation of the digestive tract was an important contributor to postoperative infection.

The reduced incidence in spilling bacteria-laden intestinal contents into the abdomen may contribute to the lower postoperative infection rate of ESD. The use of second-generation cephalosporin (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended as intravenous antimicrobial prophylaxis for colorectal surgery^{4, 7)}. In the present study, 76% of preoperative antimicrobial prophylaxes were second-generation cephalosporin, and the selection of antibiotics used in the study population was shown to be reasonable. On the other hand, the median duration of antimicrobial prophylaxis was 3.0 (range 1 – 11) days, which was longer than the reported 24-hour duration used in common practice⁸⁾. Nelson et al. reported that there was no need for a second intraoperative dose, or any postoperative doses, when the antibiotic was used for the purpose of prophylaxis of ESD or EMR⁶⁾. However, Japanese guidelines on the management of infectious diseases has reported that antimicrobial prophylaxis for a duration of 2 days was acceptable, but over 3 days increased the risk of infection with antimicrobial resistant bacteria⁹⁾. Therefore, these results suggested overall adherence to the Japanese guidelines for antimicrobial prophylaxis duration. Nearly all antimicrobial agents used for postoperative infection were those selective for anaerobic bacteria. Whether these choices in antibiotics were optimal cannot be determined with confidence due to the lack of cultivation test results in the database, and is one of the limitations of the present study. Furthermore, the present

study was unable to assess treatment result data, such as interviews and palpation information, nor were images available for investigation. Therefore, postoperative infection was defined in a two-step process, first identifying those patients diagnosed with an infectious disease obtained from the case records and then identifying those who were prescribed an antibiotic.

What is new and conclusion

Postoperative infection is an exceedingly rare event following ESD - ECN. Preoperative antimicrobial prophylaxis had no significant effect on postoperative infection following ESD - ECN, and thus may be unnecessary. On the other hand, the prevention of digestive tract perforation is important for decreasing the incidence of postoperative infection.

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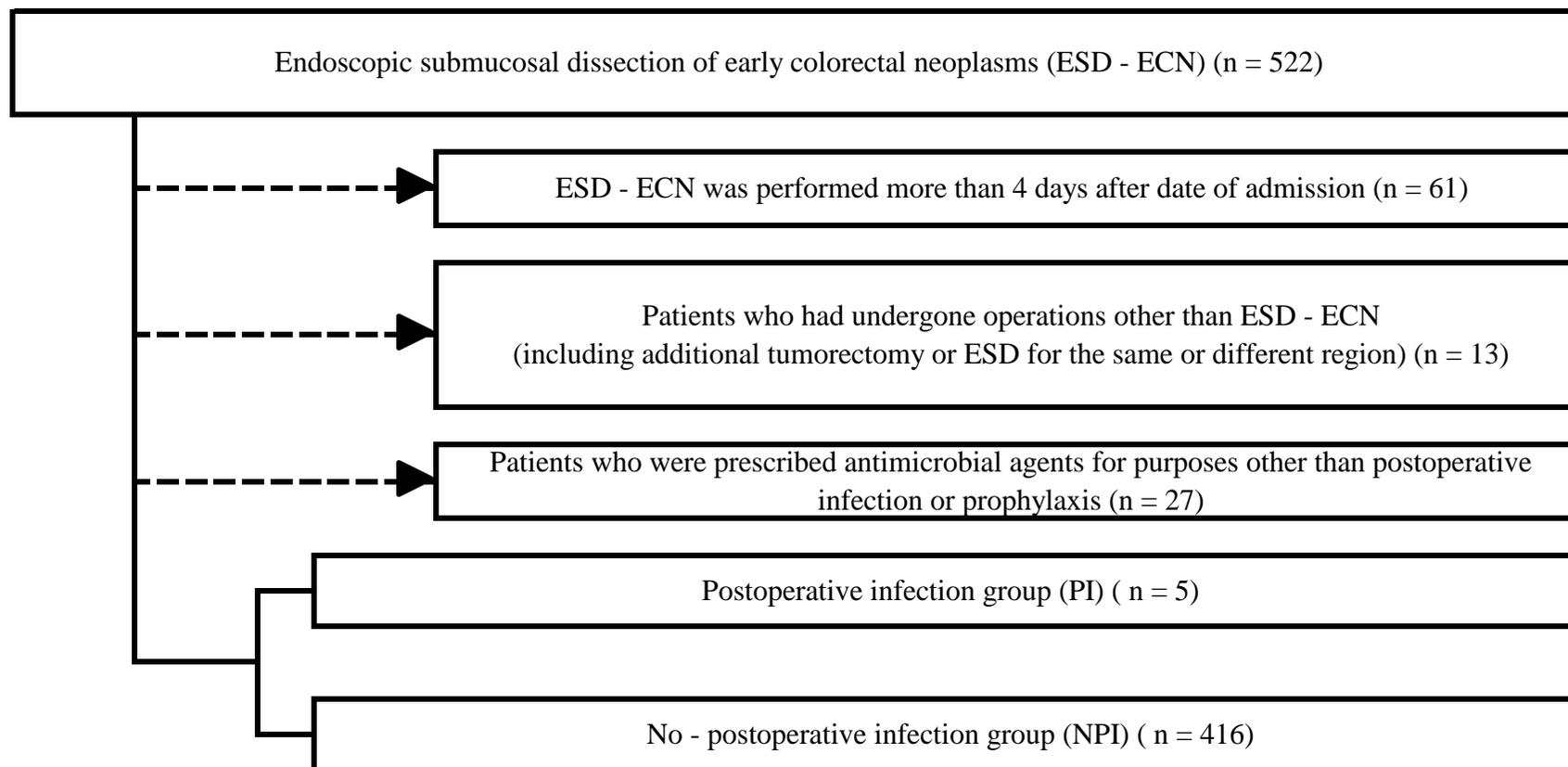


Figure 1 Flow chart for selection of study population

Table 1 Patient neoplasms

ICD10 code	Description	n (%)
C18	Malignant neoplasm of colon	347 (45)
C20	Malignant neoplasm of rectum	109 (14)
C78	Secondary malignant neoplasm of respiratory and digestive organs	52 (7)
C16	Malignant neoplasm of stomach	47 (6)
C34	Malignant neoplasm of bronchus and lung	32 (4)
C25	Malignant neoplasm of pancreas	24 (3)
C79	Secondary malignant neoplasm of other and unspecified sites	19 (2)
C22	Malignant neoplasm of liver and intrahepatic bile ducts	18 (2)
C61	Malignant neoplasm of prostate	14 (2)
C67	Malignant neoplasm of bladder	11 (1)
C80	Malignant neoplasm, without specification of site	10 (1)
C15	Malignant neoplasm of oesophagus	9 (1)
C50	Malignant neoplasm of breast	8 (1)
C91	Lymphoid leukaemia	8 (1)
C77	Secondary and unspecified malignant neoplasm of lymph nodes	7 (1)
C85	Other and unspecified types of non-Hodgkin lymphoma	6 (1)
C19	Malignant neoplasm of rectosigmoid junction	4 (1)
	Others	41 (5)

ICD10: International Statistical Classification of Diseases and Related Health Problems 10th revision
Including multiple primaries and metastases

Table 2 Postoperative infections

PIC number*	Postoperative infection†	n
389004	sepsis	2
8833267	diarrheal disease	2
91023	enteritis	1
5679005	generalized peritonitis	1
5679007	circumscribed peritonitis	1
5679012	perforative peritonitis	1
5679015	peritonitis	1

*: Japanese Receipt Disease Name Master was used for the definition of postoperative infection.

†: Codes for infectious diseases were selected by excluding infections originating from regions other than the abdomen, such as pneumonia, from all disease codes of the study population, and defined the remaining as Postoperative Infection Codes (PIC).

Includes complex infections.

Table 3 Preoperative antimicrobial prophylaxis

ATC level5 name	n* (%)	Duration (d), median (range)
Cefotiam	182 (56)	3.0 (1 - 7)
Cefmetazole	56 (17)	2.5 (1 - 11)
Ampicillin and enzyme inhibitor	46 (14)	3.0 (1 - 7)
Meropenem	10 (3)	5.0 (4 - 6)
Cefazolin	10 (3)	3.0 (1 - 3)
Flomoxef	8 (2)	2.0 (2 - 4)
Ceftriaxone	7 (2)	3.0 (1 - 9)
Cefoperazone, combination	5 (2)	3.0 (2 - 9)
Clindamycin	1 (0)	4.0 (-)

*: including combination therapy

ATC: Anatomical Therapeutic Chemical Classification System

Table 4 Antimicrobial therapy for postoperative infection

ATC level5 name	n*	Start of administration (days after ESD)	Duration (d)
Sulfamethoxazole and trimethoprim	1	7	2
Metronidazole	1	4	14
Doripenem	1	5	4
Cefazolin	1	2	1
Piperacillin and enzyme inhibitor	1	10	5
Cefmetazole	1	1	4

*: including combination therapy

ATC: Anatomical Therapeutic Chemical Classification System

Table 5 Characteristics of the PI and NPI groups

	PI	NPI	P value
N	5	416	-
Age (y), median (range)	73 (54 - 87)	68 (54 - 92)	0.72
Duration of stay after ESD (d), median (range)	8 (5 - 22)	6 (3 - 20)	0.03
Male n (%)	3 (60)	245 (59)	1.00
Classification of Diseases*			
Infectious and parasitic diseases	5	119	0.91
Neoplasms	5	414	
Diseases of the blood and blood-forming organs and disorders involving the immune system	4	108	
Endocrine, nutritional, and metabolic diseases	5	196	
Mental and behavioral disorders	1	55	
Diseases of the nervous system	3	81	
Diseases of the eye and adnexa	2	41	
Diseases of the ear and mastoid process		17	
Diseases of the circulatory system	4	177	
Diseases of the respiratory system	4	103	
Diseases of the digestive system	5	295	
Diseases of the skin and subcutaneous tissue	3	65	
Diseases of the musculoskeletal system and connective tissue	3	99	
Diseases of the genitourinary system	3	74	
Pregnancy, childbirth, and the puerperium		11	
Congenital malformations, deformations, and chromosomal abnormalities	1	7	
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	5	144	
Injury, poisoning, and other consequences of external causes	3	32	
Factors influencing health status and contact with health services		18	
Number of malignant tumor-related diseases n (%)			0.15
	0†	9 (2)	
	1	143 (32)	
	2	3 (60)	135 (11)
	3	1 (20)	44 (7)
	4		29 (4)
	5		16 (4)
	> 5	1 (20)	40 (10)
Preoperative antimicrobial prophylaxis n (%)	4 (80)	310 (75)	0.81
Duration of preoperative antimicrobial prophylaxis (d), median	5 (2 - 9)	3 (1 - 11)	0.07

PI: postoperative infection group; NPI: no postoperative infection group;

*; International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) code, including overlap

†; Patients whose abnormal tissue samples were found to be not cancerous after postoperative pathological examination

We compared the baseline characteristics of the PI and NPI groups using the Wilcoxon rank sum test for continuous variables, the Yates' chi-square, or Fisher's exact test for discrete variables.

Table 6 Preoperative antimicrobial prophylaxis of PI

ATC level5 name	n (%)	Duration (d), median (range)
Cefotiam	2 (50)	5.0 (5 - 5)
Cefmetazole	1 (25)	2.0 (-)
Cefoperazone, combination	1 (25)	9.0 (-)

Table 7 Univariate analyses of PI versus NPI

	PI	NPI	OR	95% CI
Preoperative antimicrobial prophylaxis n, (%)	4 (80)	310 (75)	0.73	0.08-6.61
Perforation of the digestive tract n, (%)	1 (20)	6 (1)	17.1	1.66-176.45

PI: postoperative infection group; NPI: no postoperative infection group;

OR: Odds ratios; 95%CI: 95% confidence interval