

## Randomized Controlled Trial

## Antimicrobial prophylaxis in patients with colorectal lesions undergoing endoscopic resection

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antibiotics on clinical adverse events in patients who underwent endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) for colorectal lesions.

**METHODS:** From June 2011 to December 2013, a total of 428 patients were enrolled into the study, of which 214 patients admitted to hospital underwent EMR or ESD procedures. These patients were randomized to an antibiotic group, in which patients were given cefuroxime 1.5 g iv half an hour before and 6 h after surgery respectively, and a control group, in which patients were not given any antibiotic. A further 214 outpatients with small polyps treated by polypectomy were compared with controls that were matched by age and gender, and operations were performed as outpatient surgery. Recorded patient parameters were demographics, characteristics of lesions and treatment modality, and the size of the wound area. The primary outcome measures were clinical adverse events, including abdominal pain, diarrhea, hemotachezia, and fever. Secondary outcome measures were white blood cell count, C-reactive protein and blood culture. Additionally, the relationship between the size of the wound area and clinical adverse events was analyzed.

**RESULTS:** A total of 409 patients were enrolled in this study, with 107 patients in the control group, 107 patients in the antibiotic group, and another 195 cases in the follow-up outpatient group. The patients' demographic characteristics, including age, gender, characteristics of lesions, treatment modality, and the size of the wound area were similar between the 2 groups. The rates of adverse events in the antibiotic group were significantly lower than in the control group: abdominal pain (2.8% vs 14.9%,  $P < 0.01$ ), diarrhea (2.0% vs 9.3%,  $P < 0.05$ ), and fever (0.9% vs 8.4%,  $P < 0.05$ ) respectively. The levels of inflammatory markers also decreased significantly in the antibiotic group compared with the control group: leukocytosis (2.0% vs 11.2%,  $P < 0.01$ ), and C-reactive

### Abstract

**AIM:** To investigate the effect of prophylaxis with

protein (2.0% *vs* 10.7%,  $P < 0.05$ ). Additionally, clinical adverse events were related to the size of the surgical wound area. When the surgical wound area was larger than 10 mm × 10 mm, there were more clinical adverse events.

**CONCLUSION:** Clinical adverse events are not uncommon after EMR or ESD procedures. Prophylactic antibiotics can reduce the incidence of clinical adverse events. This should be further explored.

**Key words:** Antibiotic prophylaxis; Endoscopic mucosal resection; Endoscopic submucosal dissection; Adverse events; Cefuroxime

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**Core tip:** We designed a controlled, randomized study to investigate the effect of prophylaxis with antibiotics on clinical adverse events in patients who underwent endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) procedures for colorectal lesions, and observed the value of surgical wound area as a risk factor. Clinical adverse events (abdominal pain, diarrhea, hematochezia and fever), leukocytosis and elevated levels of C-reactive protein are not uncommon after EMR or ESD procedures. Prophylactic antibiotics can reduce the incidence of clinical adverse events significantly. In addition, when the surgical wound area is larger than 10 mm × 10 mm, more clinical adverse events occur.

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## INTRODUCTION

With the development of endoscopic technique, a growing number of clinicians choose endoscopic treatment as a standard treatment for superficial colorectal neoplasia. The colon, as a polluted environment, induces a risk of infection even bacteremia or sepsis after polypectomy. In general, there is no need for prophylactic antibiotics in the perioperative period for small polyps usually accompanied with a relatively small wound area. However, the larger, flat and sessile polyps tend to have a higher risk of infection after endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) procedures, possibly because of the larger surgical wound areas. There is no consensus yet as to whether the application of prophylactic antibiotics in the perioperative period is needed for EMR or ESD. We have chosen 428 cases of patients for a prospective

controlled study to observe the effect of prophylactic antibiotics in the perioperative period on clinical adverse events such as abdominal pain, diarrhea and fever after ESD or EMR procedures for superficial colorectal neoplasia.

## MATERIALS AND METHODS

### Patients

The study was approved by the ethics committee of the Branch of Shanghai First People's Hospital, and informed signed consent was obtained from all patients. From June 2011 to December 2013, a total of 428 patients were enrolled into the study. Half of them were admitted to our hospital and underwent EMR or ESD procedures for superficial colorectal neoplasia. These selected patients were randomized to 2 groups using opaque sealed envelopes. One was the antibiotic group; patients were given antibiotics intravenously half an hour before surgery (1.5 g cefuroxime + 100 mL saline solution), and infusion was completed within 30 min. Six hours after surgery, another dose was administered intravenously again. The other group was the control group, in which patients were not given any antibiotic. All patients resumed a normal diet step by step after 24 h of fasting.

Patients with diminutive or small (< 10 mm) polyps were gender and age matched with the inpatients enrolled into the study (age ± 2 year, gender 1:1 matched), and operations were performed as outpatient surgery. The first day after surgery blood samples were collected for white blood cell counts (WBC), C-reactive protein (CRP) and blood culture. Meanwhile data on abdominal pain, diarrhea, hematochezia and fever of patients was recorded and the patients were followed up by telephone for 3 d. The surgical wound area was less than 10 mm × 10 mm and no antibiotics were used in these patients. One hundred and ninety-five patients completed this study.

Exclusion criteria were patients with blood disease, coagulation dysfunction, taking anticoagulants, allergic to penicillin, history of previous colorectal surgical resection, or submucosal invasive lesions. Additionally patients with poor bowel preparation were also excluded.

On postoperative day 1, blood samples for WBC, CRP and blood culture were collected for all inpatients. Recorded patients parameters were demographics, characteristics of lesions and treatment modality, and the size of the wound area. The endoscopic morphology of superficial lesions was recorded according to standard Paris classification<sup>[1]</sup>.

### Outcome variables and definition

The primary outcome measure was clinical adverse events, including abdominal pain, diarrhea, hematochezia, fever and length of hospital stay (excluding

events caused by other known reasons). Secondary outcome measures included inflammatory markers such as WBC, CRP and blood culture.

Leukocytosis was defined as a WBC  $\geq 1.1 \times 10^9/L$ . An elevated level of CRP was defined as CRP value  $\geq 2$  times the upper limit of the normal reference value. Usually a hospital stay for inpatients undergoing EMR or ESD procedures did not exceed over 72 h. So length of hospitalization over 72 h was considered as elongated.

The wound area of lesions was recorded after operation visually under endoscopy. A single wound area of lesion was defined as the length times the width, and the wound area of multiple lesions was recorded as the sum of the lengths times the sum of the widths.

### Instruments

The ESD or EMR was performed with electronic colonoscope (Olympus-CF-Q260 AI; Japan), ultrasonic endoscope (Olympus EUM 200), needle (NM-4L-1), hot biopsy forceps (FD-1U-1), endoclip (HX-110LR, HX-610-135), hooking knife (Olympus), insulation-tipped knife (Olympus) and suction cap. The coagulating cutting was carried out with mixed current mode with high frequency electrotomy equipment (ERBE ICC-200; Germany) and argon plasma (ERBE APC 300; Germany). Injection was mixed with 1:10000 adrenaline and 0.5% methylene blue solution.

### Endoscopic procedure

The surgical mode depends on the size and pathologic feature of the lesions. If the lesion was small in diameter ( $< 10$  mm) and pathological diagnosis was non-invasive, it was cut with snare technique by high frequency electrocision. On the other hand, if the lesion was between 10 mm and 20 mm in size, or the lesion was small in size ( $< 10$  mm) but with an invasive pathology, EMR was adopted for complete lesion resection. If the lesion was large in size ( $> 20$  mm), the ESD procedure was chosen. Detailed procedures of EMR and ESD can be found in research by Zhou *et al.*<sup>[2]</sup>. For larger lesions ( $> 3$  cm) with a peduncule, it was cut with a snare for the raised section, followed by EMR or ESD for the residual base.

### Statistical analysis

The statistical package SPSS 18.0 (SPSS Inc., Chicago, Ill., United States) was used for analyzing the data. Mean  $\pm$  SD were given and compared using a two-sided Mann-Whitney *U* test. A  $\chi^2$  or Fisher's exact test was applied to the categorical variables, whenever appropriate. For all comparisons, the criterion for statistical significance was  $P < 0.05$ .

## RESULTS

In total, 409 patients completed this study, with 107 patients in the control group, 107 patients in

the antibiotic group, and 195 cases in the follow-up outpatient group. Baseline demographic, clinical characteristics of lesions, and treatment modality were compared between the control group and the antibiotic group. No significant differences regarding gender or age were observed between the two groups ( $P > 0.05$ ). No significant differences regarding the size, morphology, location and treatment modality of the lesions were observed between the two groups ( $P > 0.05$ ) (Table 1).

Abdominal pain was the most common adverse event; usually the pain was mild or moderate, and could be remitted by sedative drugs or anticholinergic agents. Rarely narcotic analgesics were needed. Among control group patients, abdominal pain occurred in 16 of the 107 (14.9%) patients; in the antibiotic group, only 3 of the 107 patients (2.8%) suffered abdominal pain. The difference was significant ( $P < 0.05$ ). Diarrhea occurred in 2 of the 107 (2.0%) patients in the antibiotic group and in 10 of the 107 (9.3%) in the control group ( $P < 0.05$ ). The range of fever usually was 37.2 °C to 38.5 °C, rarely over 39 °C. In the antibiotic group, the incidence of fever was 0.9% (1/107), also significantly less than 8.4% of control group patients (9/107,  $P < 0.05$ ). As for hematochezia, another common adverse event, this occurred in 5.5% of patients (6/107) in the control group and in 3.7% patients (4/107) in the antibiotic group, and no significant difference was observed.

Leukocytosis and elevated levels of CRP occurred in 11.2% and 10.7% patients from the control group and in 2.0% and 2.0% patients from the antibiotic group respectively; there was a significant difference between the two groups (Table 2,  $P < 0.05$ ). In addition, four patients in the control group showed fever (temperature  $> 38.5$  °C), leukocytosis and abdominal pain and were diagnosed as having local infections. All of the symptoms disappeared quickly after treatment, including fasting and the use of antibiotics. Two patients showed positive blood culture, one was *Escherichia coli*, the other was *Enterococcus faecalis*, and both were cured after anti-infective therapy. No patient had the complication of perforation in this study.

In this study, we found that clinical adverse events were related to the surgical wound area. When the surgical wound area was larger than 10 mm  $\times$  10 mm, there were more clinical adverse events. Every specific event, including abdominal pain, diarrhea, hematochezia, fever, and hospital stay over 72 h in patients with a surgical wound area more than 10 mm  $\times$  10 mm was significantly more frequent than in those patients with a surgical wound area less than 10 mm  $\times$  10 mm; the difference was significant (Table 3,  $P < 0.05$ ).

## DISCUSSION

Surgical site infection is the second most common

**Table 1 Clinical characteristics of inpatients, lesions and treatment modality *n* (%)**

Characteristic	Antibiotic group ( <i>n</i> = 107)	Control group ( <i>n</i> = 107)	<i>P</i> value <sup>1</sup>
Age (yr)	68.1 ± 12.5 (42-86)	63.1 ± 9.5 (39-82)	0.732 <sup>2</sup>
Gender (M:F)	62:45	68:39	0.421
Tumor size			
< 10 mm	22 (20.5)	19 (17.8)	0.602
10-20 mm	60 (56.1)	65 (60.7)	0.488
> 20 mm	25 (23.4)	23 (21.5)	0.743
Macroscopic type			
Pedunculated	14 (13.0)	16 (15.0)	0.694
Subpedunculated	32 (29.9)	30 (28.0)	0.763
Sessile	24 (22.4)	22 (20.6)	0.739
Flat elevated (0-II a)	28 (26.2)	30 (28.0)	0.758
Flat (0-II b, 0-II c)	9 (8.5)	9 (8.5)	1.000
Location			
Rectum and sigmoid	58 (54.2)	61 (57.0)	0.680
Descending	23 (21.5)	19 (17.8)	0.491
Transverse	12 (11.2)	14 (13.1)	0.676
Ascending and cecum	14 (13.1)	13 (12.1)	0.741
Treatment modality			
ESD	45 (42.1)	42 (39.3)	0.676
EMR	62 (57.9)	65 (60.7)	0.676

<sup>1</sup>Fisher's exact test (excluding variable age); <sup>2</sup>Student's *t*-test. ESD: Endoscopic submucosal dissection; EMR: Endoscopic mucosal resection.

iatrogenic infection, and happens in 2%-5% of patients undergoing abdominal aseptic operations and in more than 20% of patients undergoing abdominal operations. Such infection is a major contributor to patient length of stay, mortality, and health care costs<sup>[3,4]</sup>. The 2002 Medicare National Surgical Infection Prevention Project suggested antibiotic prophylaxis should be used during colorectal operations in general abdominal surgery<sup>[5]</sup>. It was reported that bacteremia occurred in 0% to 8% patients undergoing gastroscopy, with or without a biopsy<sup>[6,7]</sup>. The rate of bacteremia during colonoscopy ranges from 0% to 25%. Usually the bacteremia is transient and lasts a short time (< 30 min), and no clinical infectious manifestations have been observed<sup>[8]</sup>. Currently with improvements in endoscopic modality and operational skill, the bacteria associated with conventional endoscopy maneuver are rare, and usually without clinical value. The routine use of antibiotics only to prevent infective endocarditis is no longer recommended; however, administering antibiotics to prevent infections is recommended during some endoscopic procedures, such as percutaneous endoscopic gastrostomy, and esophageal dilation and sclerotherapy<sup>[9,10]</sup>.

EMR or ESD, a new technique for complete resection of gastrointestinal lesions under endoscopy, entails production of a large mucosal defect which is left open, without endoscopic closure. Extensive submucosal exposure to the indigenous bacterial flora in the gastrointestinal tract may cause bacteremia and/or endotoxemia. Though many studies have recorded the occurrence and management of perforation and bleeding after EMR or ESD, only a limited number of

**Table 2 Comparison of adverse events between antibiotic and control groups**

	Antibiotic group ( <i>n</i> = 107)	Control group ( <i>n</i> = 107)	<i>P</i> value <sup>1</sup>
Clinical adverse events			
Abdominal pain	3	16	0.002
Diarrhea	2	10	0.017
Hematochezia	4	6	0.517
Fever	1	9	0.010
Leukocytosis	2	12	0.006
Elevated CRP	2	8	0.050
Blood culture (+)	0	2	0.155
Hospital stay over 72 h	6	21	0.002

<sup>1</sup>Fisher's exact test. CRP: C-reactive protein.

**Table 3 Relationship between the size of wound area and clinical adverse events**

Wound area	< 10 mm × 10 mm ( <i>n</i> = 195) <sup>1</sup>	> 10 mm × 10 mm ( <i>n</i> = 107) <sup>2</sup>	<i>P</i> value <sup>3</sup>
Clinical adverse events			
Abdominal pain	12	16	0.009
Diarrhea	7	10	0.038
Hematochezia	3	6	0.048
Fever	3	9	0.004
Leukocytosis	3	12	0.003
Elevated CRP	2	8	0.003
Blood culture( + )	0	2	0.112

<sup>1</sup>The follow-up outpatients; <sup>2</sup>The control group inpatients; <sup>3</sup>Fisher's exact test. CRP: C-reactive protein.

studies focus on the occurrence and management of postoperative infection. In a pilot study by Kato *et al*<sup>[11]</sup>, bacteremia and endotoxemia after ESD for superficial gastric neoplasia in 50 patients were studied. Four percent (2 patients) of the cases after ESD showed positive blood cultures, but clinical infectious manifestations had not been observed. So they argued that there was no need to apply antibiotic prophylaxis for these patients. In the study by Lee *et al*<sup>[12]</sup>, bacteremia after ESD for upper gastrointestinal lesions was studied in 38 patients. At 10 min post-procedure, 5.3% (2/38) of patients had a positive blood culture. But 4 h after surgery, the blood culture of all patients was negative. Meanwhile no clinical manifestation of infection was observed. Therefore, they concluded that bacteremia accompanied with the ESD procedure was rare and transient.

In a prospective, multicenter, observational study, 479 patients were referred for EMR of sessile colorectal polyps that were 20 mm or greater in size, and seven patients (1.5%) were treated with antibiotics for suspected serositis for 3-5 d until full recovery<sup>[13]</sup>. Kim *et al*<sup>[14]</sup> suggested that post ESD transient bacteremia could be improved with empirical antibiotics in most cases.

Many domestic studies<sup>[15,16]</sup> report antibiotic treatment

after ESD or EMR, but there is no consensus on whether the application of antibiotics in the perioperative period is necessary. Zhou *et al.*<sup>[17]</sup> advocated antibiotic therapy after surgery in an expert consensus on endoscopic submucosal dissection of gastrointestinal mucosa lesions, if the surgical wound area was larger, the duration of the procedure was longer, or potential likelihood for perforation existed. Prophylactic antibiotics are considered for colorectal lesions after ESD within 72 h. However, this proposition lacks the support of evidence-based medicine.

Previous studies, with an emphasis on postoperative perforation and bleeding after EMR or ESD, paid less attention to clinical common adverse events such as abdominal pain, diarrhea, hematochezia and fever. As a matter of fact, non-specific abdominal pain is common after an EMR or ESD procedure. The possible causes include excessive submucosal injection, greater insufflation air during colonoscopy or serositis and perforations<sup>[18,19]</sup>. In our study, clinical adverse events included abdominal pain (19/214, 8.8%), diarrhea (12/214, 5.6%), hematochezia (10/214, 4.7%) and fever (10/214, 4.7%), all of which affects the patients' satisfaction for the operation. We designed this study according to the principle of use of antibiotics during the perioperative period with a randomized control method. The results show that the use of antibiotics during the perioperative period can significantly reduce the incidence of adverse events of abdominal pain, diarrhea and fever after EMR or ESD. In our study, no one in the antibiotic group experienced severe abdominal pain or fever over 38 °C, and patients in the antibiotic group expressed higher satisfaction. We postulated the mechanism referred might be an infection due to a local mucosal defect, which caused enhancement of bowel movement, smooth muscle spasms, and fever. Hematochezia is mainly associated with the endoscopist's experience and techniques, so use of antibiotics had no effect on it.

The second generation cephalosporins, like cefuroxime and cefazolin, are the first choice for surgical antibiotic prophylaxis<sup>[20]</sup>. They have a broad antibiotic spectrum and are active against both Gram-positive and Gram-negative bacteria with low toxicity. In our study the first dose of cefuroxime (1.5 g) was given intravenously half an hour before the ESD or EMR procedure. Another dose was administered six hours after surgery, which is in accordance with international guidelines<sup>[5]</sup>. Use of prophylactic antibiotics for EMR or ESD procedures during the perioperative period significantly reduces the incidence of clinical adverse events and length of hospital stay. The disadvantages, such as burden of healthcare cost and the concern for drug resistance, should be considered. In terms of antimicrobial resistance, prophylactic antimicrobial use carries a selection risk, whether the use is warranted or not. However, by preventing postoperative wound infection, the need for long-term antimicrobial therapy is reduced and this may then contribute to reducing

selection of antimicrobial-resistant bacteria<sup>[21]</sup>.

As a complication of colonoscopy, ischemic colitis is rare, but the incidence can increase when a longer procedure time or other risk factors of ischemia is present<sup>[22,23]</sup>. The procedure time of EMR or ESD is usually a lot longer than the procedure time of a common colonoscopy examination. In order to get a good endoscopic vision, endoscopists require repeated endoscopic lens barrel rotation and repeated inflation and cleaning of the colon lumen, which may lead to increased colonic intraluminal pressure, and excessive stretching or compression of the intestine. All of these factors may lead to the occurrence of ischemic colitis. In patients with ischemic colitis, we recommend using antibiotics. Thus for EMR or ESD potential complications of ischemic colitis, the application of perioperative antibiotics may be beneficial.

Leukocytosis and raised levels of CRP are generally considered the marks of the body's inflammatory reaction. There are two possible reasons for leukocytosis and elevated levels of CRP during the post-EMR or post-ESD. One is postpolypectomy coagulation syndrome, with inflammatory signs including abdominal pain, fever, abnormal levels of inflammatory markers, and peritoneal irritation, which occurs with an incidence of 0.7%-7.1%<sup>[19,24,25]</sup>, and needs antibiotics without surgical treatment. Another reason could be local infection of the wound area after EMR or ESD surgery for colon neoplasia, but more clinical evidence is needed to confirm this scenario. In addition, ischemic colitis complicated by colonoscopy may also be a rare cause. Blood cultures are not sensitive indicators of clinical adverse events; the study included 409 patients, but only two cases of positive blood culture were found, and the reasons may be as follows: (1) a postoperative infection is localized, bacteria do not enter into the systemic bloodstream necessarily; and (2) bacteria enter into the bloodstream transiently and missed the time of sample collecting for blood culture.

The resection of large lesions exposes larger areas of the submucosa and results in deeper wounds, which suggests that more complications are likely to occur. A meta-analysis compared ESD and EMR procedure-related complications, in which bleeding and perforation rates in the ESD group were higher than in the EMR group<sup>[26]</sup>. Previous studies have demonstrated an increased risk of post-polypectomy bleeding after removing large polyps, particularly when the size of polyps was larger than 10 mm<sup>[27-29]</sup>. In addition, the size of polyps was associated with the incidence of postpolypectomy coagulation syndrome<sup>[24,25]</sup>. However the tumor size and the surgical wound area are not entirely related. In flat lesions, tumor size is consistent with the wound area, but the flat lesions accounted for only 30% to 48% of colorectal tumors, and the rest were protruded lesions<sup>[30]</sup>. In protruded lesions, especially pedunculated and subpedunculated lesions, the head of the tumors may be large, but the

stalk is small and the surgical wound area is smaller, and therefore we chose the wound area as a factor affecting postoperative complications as being more appropriate than tumor size. This study shows that: for 195 outpatients whose wound area was less than 10 mm × 10 mm, the total incidence of clinical adverse events was significantly lower than that in the 107 inpatients whose wound area was greater than 10 mm × 10 mm, in which each specific event, such as abdominal pain, diarrhea, hematochezia, fever, elevated white blood cell count and CRP, had a lower incidence.

Clinical adverse events are not uncommon after EMR or ESD procedures, including abdominal pain, diarrhea, hematochezia and fever, especially in those patients with larger surgical wound areas. The application of antibiotics in the perioperative period can significantly reduce the incidence of clinical adverse events after EMR or ESD for colorectal lesions.

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## COMMENTS

### Background

Surgical site infection happens in more than 20% of abdominal operations. Such infection is a major contributor to patient length of stay, mortality, and health care costs, and it can be significantly reduced by administration of prophylactic antibiotics. Antibiotic prophylaxis during colorectal operations and general abdominal surgery has been accepted and administered worldwide. Endoscopic submucosal dissection (ESD) and mucosa resection (EMR), by shaving off the superficial layers of the gut wall, were widely accepted for treating early colorectal cancer and precancerous lesions. Yet to now, there is no data to answer whether prophylactic antibiotics are necessary for EMR or ESD.

### Research frontiers

Surgeons were more interested in improvement of operating techniques related to EMR or ESD. Mostly they paid attention to major complications, such as bleeding and perforation. Other complications like abdominal pain, diarrhea, hematochezia and fever usually were overlooked.

### Innovations and breakthroughs

The authors designed a controlled, randomized study to investigate the effect of prophylactic antibiotics on clinical adverse events in patients who underwent ESD or EMR procedures for colorectal lesions, and to observe the value of surgical wound area as a risk factor. Clinical adverse events (abdominal pain, diarrhea, hematochezia and fever), leukocytosis and elevated level of C-reactive protein are not uncommon after EMR or ESD procedures. Prophylactic antibiotics can reduce the incidence of clinical adverse events significantly. In addition, when the surgical wound area is larger than 10 mm × 10 mm, more clinical adverse events occur.

### Applications

The results of this study can provide evidence-based-medicine support for prophylactic antibiotics in patients with colorectal lesions undergoing EMR or ESD procedures.

### Terminology

Endoscopic resection has certainly revolutionized the management of gastrointestinal neoplasia. Lesions that were routinely referred to surgery in the past can now be removed using EMR and ESD. Both techniques involve careful peeling off the mucosa along with the superficial submucosa of the gastrointestinal tract bearing the neoplastic lesion while preserving the deeper layers. Prophylactic antibiotics indicate administering antibiotic before surgical

incision for clean-contaminated operations, to reduce postoperative surgical wound infections.

### Peer-review

It is a good research paper about the application of antibiotics in the perioperative period during EMR or EMR for superficial intestinal neoplasia.

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