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Antibacterial prevention of postcoagulation syndrome during endoscopic removal of colon neoplasms (review and meta-analysis)

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ABSTRACT *AIM: to assess efficacy of antibacterial prevention for postcoagulation syndrome after endoscopic removal of colon neoplasms.*
MATERIALS AND METHODS: literature search and meta-analysis were performed in accordance with the PRISMA guidelines using the PUBMED search system in the Medline electronic database. The systematic review included all studies devoted to antibacterial prophylactic of postcoagulation syndrome after endoscopic submucosal resection neoplasms of colon.
RESULTS: the analysis included 5 studies — 1055 patients, 546 in the antibiotic prevention group and 509 in the group without it. Postcoagulation syndrome was lower in antibacterial prophylaxis group 5,9% vs 16,1% without antibacterial prevention group (OR = 0.30; 95% CI: 0,09–0,96; p = 0.04).
CONCLUSION: antibiotic prophylactic reduces the incidence of postcoagulation syndrome after endoscopic removal of epithelial neoplasms of the colon.

KEYWORDS: *postcoagulation syndrome, antibacterial prophylactic, endoscopic removal of epithelial neoplasms of the colon*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

The most common complication after endoscopic submucosal dissection (ESD) for colorectal villous tumors larger than 30 mm is postcoagulation syndrome (PCS). The manifestations of this syndrome are similar to the clinical picture of peritonitis caused by bowel perforation, which leads to unjustified diagnostic tests and active treatment approach, including abdominal surgery [1]. According to the experience of 1,000 ESD, PCS occurs in 13.6% of cases [2]. The mean hospital stay after dissection is 5 days. However, the PCS lead to an increase in the hospital stay 3 days, which increases the treatment cost [3]. Currently, there is no unified concept of the pathogenesis and prevention of this complication. The only known method of prevention is clipping of a postoperative lesion.

However, a meta-analysis by Liu et al., including 477 patients, did not reveal a significant difference in the rate of postcoagulation syndrome when comparing groups with and without endoscopic clipping OR = 0.75 95% CI: (0.26–2.18), $p = 0.6$ [4]. Considering that this syndrome is accompanied by signs of a systemic inflammatory reaction, attempts have been made to carry out antibiotic prevention. There are conflicting data in the literature regarding the effectiveness of preventive antibiotics before ESD. Taking into account a sufficient number of studies, the meta-analysis of the data was carried out.

MATERIALS AND METHODS

The meta-analysis was performed in accordance with the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA). The meta-analysis includes full-text papers in English that reflect the development of coagulation syndrome after removal of colorectal epithelial tumors by ESD and mucosectomy with and without preventive antibiotics.

A search in the PubMed database for "endoscopic submucosal dissection" and "coagulation syndrome" resulted in 58 studies. Fifty of those studies were identified. In the future, 48 publications devoted to the endoscopic removal of epithelial neoplasms of the large intestine, the technical aspects of performing endoscopic submucosal dissection, as well as risk factors for the PCS are excluded. As a result of an additional search of bibliographic data, among the studies included in the meta-analysis, additionally 3 publications were identified on the antibacterial prevention of PCS after endoscopic removal of colorectal tumors. So, all 5 studies were randomized (Fig. 1).

When searching the eLibrary database for literary sources for the query "postcoagulation syndrome", not a single article was found that highlights the problem of the development of postcoagulation syndrome after endoscopic removal of colorectal neoplasms, as well as its antibacterial prevention.

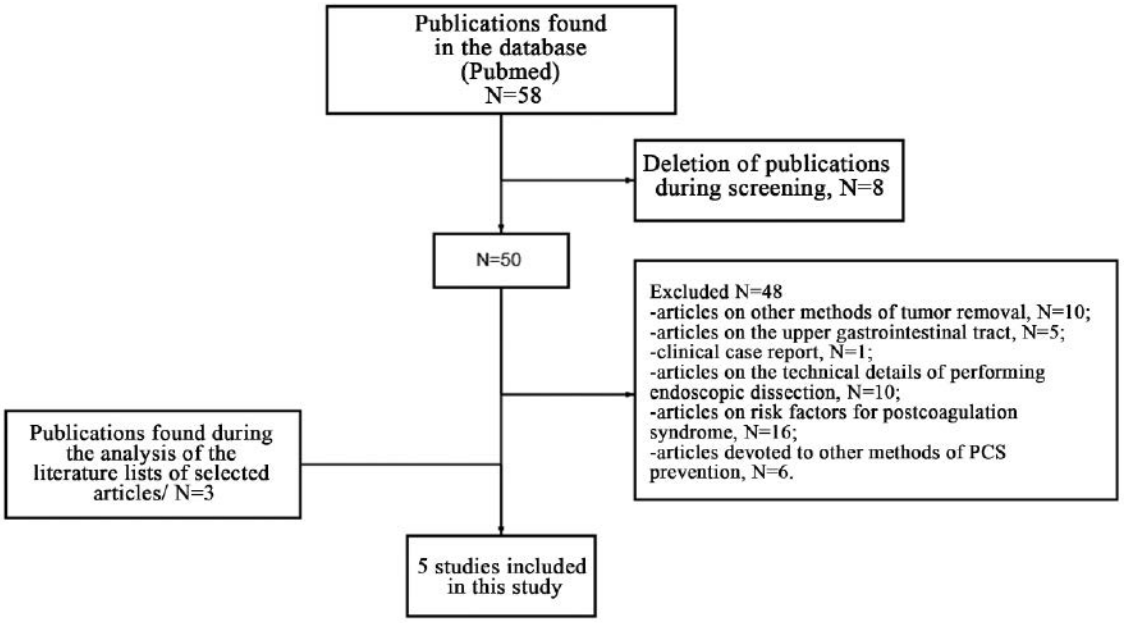

Figure 1. *Search in the MedLine database*

Data obtained from the articles:

Author	Year	Type of research	Surgery type	Rate of PCS development		The antibiotic
				AB–	AB+	
Lee et al.	2017	Random	ESD	8/50 (16%)	1/50 (2%)	Ampicillin/ sulbactam
Shichijo et al.	2021	Random	ESD	14/188 (7.5%)	9/192 (4.7%)	Ampicillin/ sulbactam
Zhang et al.	2015	Random	ESD + EMR	45/107 (42%)	8/107 (7.5%)	Cefuroxime
Shi et al.	2016	Random	EMR	2/38 (5%)	0/77 (0%)	Levofloxacin, ceftazidime
Zheng et al.	2022	Random	EMR	13/126 (10%)	14/120 (12%)	Cefixime

Table 1. *Distribution of patients by gender*

Author	Gender	
	AB–	AB+
Lee et al.	M 68% (34)	M 58% (29)
Shichijo et al.	M 62% (118)	M 61% (115)
Zhang et al.	M 63% (68)	M 58% (62)
Shi et al.	No data	
Zheng et al.	M 52% (63)	M 63% (68)

Table 2. *Distribution of patients by age*

Author	Age	
	AB–	AB+
Lee et al.	60.56 ± 12.71	61.52 ± 12.86
Shichijo et al.	69 (35–80)	68 (32–80)
Zhang et al.	63.1 ± 9.5	68.1 ± 12.5
Shi et al.	No data	
Zheng et al.	51.11 ± 9.52	52.74 ± 8.89

Table 3. *Operative time of endoscopic procedure*

Author	Surgery duration	
	AB–	AB+
Lee et al.	55.56 ± 33.30	61.40 ± 56.55
Shichijo et al.	86.0 (78.3–93.7)	86.1 (77.7–94.5)
Zhang et al.	No data	
Shi et al.	No data	
Zheng et al.	No data	

Table4. *Distribution of neoplasms by location*

Author	Localization of neoplasms	
	AB–	AB+
Lee et al.	Right colon — 30% (15) Left colon — 36% (18) Rectum — 34% (17)	Right colon — 40% (20) Left colon — 28% (14) Rectum — 32% (16)
Shichijo et al.	Right colon — 52% (99) Left colon — 15% (28) Rectum — 33% (61)	Right colon — 53% (101) Left colon — 18% (35) Rectum — 29% (56)
Zhang et al.	Right colon — 25% (27) Left colon + rectum — 75% (80)	Right colon — 24% (26) Left colon + rectum — 76% (81)
Shi et al.	No data	
Zheng et al.	Right colon — 39% (103) Left colon — 42% (111) Rectum — 19% (50)	Right colon — 39% (103) Left colon — 41% (109) Rectum — 20% (56)

Statistical Analysis

The total value of the dichotomous data is described as a ratio of odds (OR) with a 95% coincidence interval (CI). OR was calculated using Mantel-Haenszel's test. In all cases, a random effects model was used for the meta-analysis. Statistical heterogeneity among the studies was assessed using the I^2 test. Heterogeneity was considered significant at $I^2 > 50\%$. Statistical data processing, bias risk verification, and charting were performed in the Review Manager (RevMan) 5.4.1 (Cochrane collaboration software) program (Fig. 2).

RESULTS

The results of endoscopic removal of epithelial neoplasms in 1,055 patients were analyzed, while with high heterogeneity of studies $I^2 = 80\%$, significant differences were obtained in reducing

Table 5. *Distribution of neoplasms by size*

Author	The size of the neoplasms	
	AB–	AB+
Lee et al.	20.42 ± 8.22	20.56 ± 8.90
Shichijo et al.	30 (20–60)	30 (20–60)
Zhang et al.	< 10 mm — 17.8% (19) 10–20 mm — 60.7% (65) > 20 mm — 21.5% (23)	< 10 mm — 20.5% (22) 10 — 20 mm — 56.1% (60) > 20 mm — 23.4% (25)
Shi et al.	< 20 mm	< 20 mm
Zheng et al.	10–20 mm	10–20 mm

the PCS rate with intravenous antibacterial prevention (OR = 0.30; 95% CI: 0.09–0.96, p = 0.04) (Fig. 2).

Considering that the studies included in the meta-analysis are randomized, the quality of these studies was assessed using the CONSORT system. According to the results of the quality assessment, the presence of low-quality studies was revealed, which is a disadvantage of the meta-analysis [5].

DISCUSSION

PCS after ESD is a complication characterized by an inflammatory reaction resulting from damage to the large intestine wall by electrocoagulation. The mechanism of PCS is not fully understood, and it is assumed that thermal damage to the muscle layer during endoscopic resection of the mucous layer and the microbiota of the large intestine acting on the postoperative lesion play a key role [6]. PCS is established in the presence of localized pain in the abdominal cavity corresponding to the site of endoscopic submucosal dissection, and febrile fever or increased inflammatory blood markers and leukocytosis. It should be noted that after endoscopic procedure, abdominal pain should be assessed no earlier than 6 hours after the end of the procedure, since gas insufflated into the intestinal lumen during the surgery can also cause pain similar to the symptoms of PCS [7]. According to the literature, the PCS rate can reach 16% of the total number of ESD performed, which is much more common than after endoscopic polypectomy, in which this syndrome develops in 4.4% [8,9]. Despite the fact that most cases of PCS can be resolved conservatively with systemic antibiotics, in some cases the clinical picture of this syndrome proceeds under the guise of delayed bowel perforation, and can also mimic peritoneal symptoms, which leads to abdominal surgery [10]. Symptoms caused by PCS may change the vector of conservative postoperative treatment. In 66.7% of cases, patients got parenteral antibiotics and nonsteroidal anti-inflammatory agents, which increases the hospital stay by 3 days, the cost of treatment by 15%, and reduces the patient's quality of life in the postoperative period due to a 2-fold prolongation of the fasting period [7,3].

Two types of PCS are classified: type I is without gas in the paracolic tissues; type II is with gas in

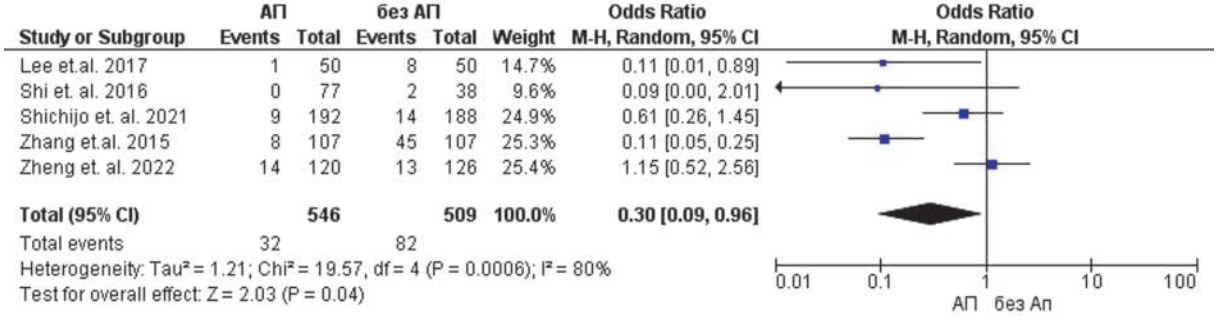

Figure 2. *The effect of antibacterial prophylaxis on the development of postcoagulation syndrome after endoscopic removal of epithelial neoplasms of the colon*

the paracolic tissue. Type II PCS is accompanied by a vivid clinical picture in contrast to type I. It becomes possible to differentiate these types of PCS only when performing abdominal CT; gas in the paracolic tissue may increase the risks of abdominal surgery [6,8].

In the literature, the main risk factors for PCS include: female gender, the operative time > 90 minutes, and the location of the tumor in the right colon [11]. The operation time, according to generally accepted data, is a risk factor for this syndrome, there is a direct correlation between the size of the removed neoplasm, and its localization in the right colon [12]. A study by Arimoto J. et al., including 106 patients, devoted to the search of risk factors for PCS, showed that the time of PCS is more than 90 minutes, and localization in the right colon are independent risk factors for PCS. Such a risk factor as the localization of the tumor in the right colon is explained by a thinner wall, which contributes to a deeper and faster spread of coagulation energy to the muscular layer of the intestinal wall. The operation time of endoscopic surgery can be shortened by improving the skills [12]. The determination of risk factors will make it possible to develop a nomogram and, at the preoperative stage, identify patients with a high risk of PCS and use antibiotic prevention in this cohort.

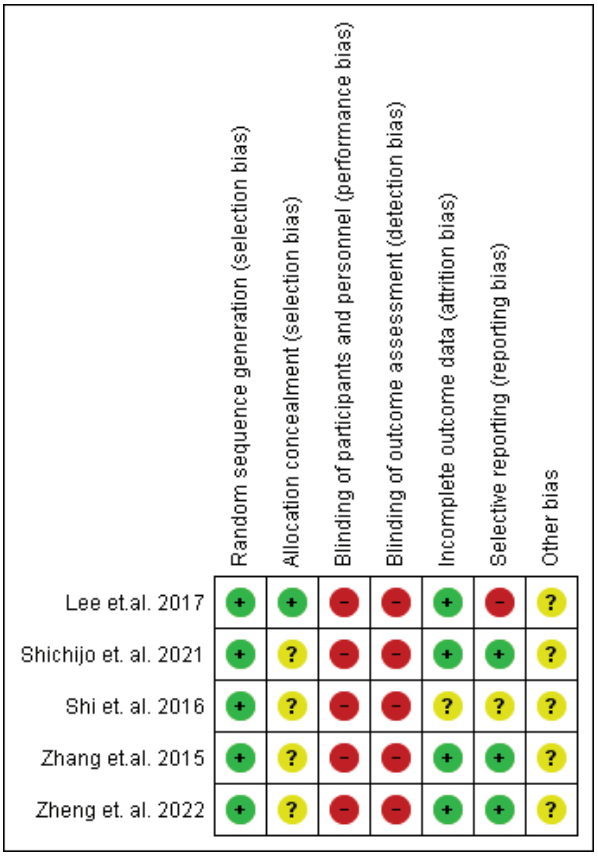

Figure 3. *The quality of the studies included in the meta-analysis*

Recently, available literature contain data only on intravenous antibacterial prevention of PCS after ESD. According to the randomized trial by Lee S.P. et al., where each of 2 groups included 50 people, during which 1.5 grams of ampicillin-sulbactam were administered intravenously 1 hour before, and then 8 and 16 hours after endoscopic submucosal dissection, a significant decrease in the PCS rate was demonstrated in the main group: 1/50 (2%) versus 8/50 (16%), $p = 0.031$ [13]. A randomized trial by Shichijo S. et al., included 380 cases in both groups, during which 3 grams of ampicillin-sulbactam were administered intravenously immediately before, 8 hours after, and the next morning after endoscopic submucosal dissection, showed no significant differences in the groups with and without antibacterial prophylaxis: 9/192 (4.7%) versus 14/188 (7.5%), $p = 0.29$ [14]. In a study by Zhang et al., the PCS was assessed in both patients who underwent ESD and mucosectomy, with 107 patients in the control and main groups each. In the main group, patients were given cefuroxime 1.5 grams intravenously half an hour before and 6 hours after the surgery. The abdominal pain and fever in the antibiotic-treated group was significantly lower than in the control group: abdominal pain 3/107 (2.8%) vs. 16/107 (15%), $p < 0.01$ and fever 1/107 (1%) vs. 9/107 (8%), $p < 0.05$, respectively. The levels of inflammatory blood markers were also significantly lower in the antibiotic-treated group compared with the control group: leukocytosis 2/107 (1.8%) vs. 12/107 (11.2%), $p < 0.01$ and C-reactive protein elevation 2/107 (1.8%) vs. 8/107 (7.5%), $p < 0.05$ [15]. In a study by Shi et al., where 38 patients were included in the control group and 77 in the main group, there were no significant differences in fever and an increase

in the level of inflammatory blood markers after mucosectomy in patients receiving levofloxacin for 3 days at 0.4 grams per day or ceftazidime for 3 days, 1.0 grams per day compared with patients who did not receive antibacterial drugs: 2/38 (5%) versus 0/77 (0%) [16]. In a study by Zheng et al., an analysis of fever and abdominal pain in patients after mucosectomy was also performed. Patients in the main group, including 120 people, were given 1.0 grams of cefixime intravenously 30 minutes before mucosectomy, followed by another dose of antibiotic 6 hours after surgery, and 126 patients in the control group underwent mucosectomy without any antibiotic prevention. There were no significant differences between the main and control groups in the rate of fever, abdominal pain, or the level of inflammatory blood markers: 14/120 (12%) versus 13/126 (10%), respectively [17]. PCS does not really have a radical clinical effect on postoperative period. However, it causes discomfort in patients and requires additional diagnostic invasive and non-invasive tests. Also, when this syndrome occurs, it becomes necessary to prescribe systemic antibacterial agents, due to the high level of septic markers. There is no single concept in the medical community, not only in determining the optimal antibacterial agent, but also in dosage, as well as the route of its administration for the prevention of PCS. Clear criteria are needed for the use of antibiotic prevention before endoscopic removal of colorectal epithelial neoplasms.

This meta-analysis showed a decrease in the rate of PCS due to antibiotic prevention from 16.1% to 5.9%, $p = 0.04$. However, the results of this meta-analysis should be interpreted with caution. Randomized trials were included in this meta-analysis, but the publication data were of poor quality with a high level of heterogeneity $I^2 = 80\%$. At the same time, not all the included studies are devoted only to endoscopic dissection in the submucosal layer. Half of the studies included in the analysis include mucosectomy. ESD is a minimally invasive technique with a low morbidity rate and a short postoperative stay, and intravenous antibacterial agents are associated with a high risk of both local and systemic complications.

A distinctive feature of oral antibiotics is the simplicity and lower cost of this method of prevention. Recently, there are no studies on oral antibacterial prevention of PCS after ESD. There is a need for a study on oral antibiotic prevention of PCS.

CONCLUSION

Intravenous antibacterial prevention of postcoagulation syndrome before endoscopic submucosal dissection has shown efficacy in patients with colorectal epithelial tumors. However, there is no data on oral antibiotic prevention, which requires prospective randomized trials.

AUTHORS CONTRIBUTION

Concept and design of the study: *Nikolay S. Pogosov, Alexey A. Likutov, Ilya V. Nazarov*

Collection and processing of the material: *Nikolay S. Pogosov*

Statistical processing: *Artem A. Balkarov*

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Editing: *Artem A. Balkarov, Alexey A. Likutov, Ilya V. Nazarov*

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