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Gastrointestinal Tract

Continued use of low-dose aspirin may increase risk of bleeding after gastrointestinal endoscopic submucosal dissection: A meta-analysis

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Original Article

ABSTRACT

Background/Aims: Endoscopic submucosal dissection has been widely accepted. At present, the number of antiplatelet (APT) users has been growing. Moreover, because of high risks of thromboembolism, some patients need to continuously receive APT agents. The relationship between hemorrhage and continuous therapy with low-dose aspirin (LDA) remains controversial.

Materials and Methods: A systematic search was conducted; studies were screened out- if data of no-anticoagulant/APT drugs use and interrupted and continued-LDA use were reported separately. The Newcastle-scale was chosen to assess the quality of the included studies. Review Manager 5.2 was used for quality assessment statistical analysis, and the odd ratio (OR) and 95% confidence interval (CI) were calculated.

Results: Pooled data suggested a significantly higher bleeding ratio in the LDA-continued group compared to both the LDA-interrupted group (OR=2.05, 95% CI=1.05-3.99) and no-anticoagulant/APT group (OR=2.89, 95% CI=1.86-4.47). However, the LDA-interrupted group did not differ significantly from the no-anticoagulant/APT group. The en bloc resection rates of the LDA-continued group versus the LDA-interrupted group, the LDA-continued group versus no-anticoagulant/APT group, and the LDA-interrupted group versus the no-anticoagulant/APT group were similar (OR=0.82, 95% CI=0.21-3.24, p=0.78; OR=0.80, 95% CI=0.24-2.65, p=0.71; OR=1.41, 95% CI=0.38-5.24, p=0.60, respectively).

Conclusion: There is an extremely high ratio of bleeding in the LDA-continued group compared to both the LDA-interrupted group and no-anticoagulant/APT group. All groups had similar ratios of en bloc resection.

Keywords: Endoscopic submucosal dissection, gastrointestinal neoplasms, antiplatelet agents, gastroenterological hemorrhage, meta-analysis

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a normal therapeutic technology that allows en bloc excision and complete excision for early gastrointestinal cancers or dysplastic lesions (1-6). One of the complications of gastrointestinal ESD is postoperative hemorrhaging.

Some researchers have shown that the average rate of post-ESD bleeding of colorectal carcinoma is 1.8% (5). However, in gastric carcinoma, the rate of post-ESD bleeding ranged from 5.3% to 15.6% (7). The use of antiplatelet (APT) agents has a far-reaching impact on gastrointestinal post-ESD bleeding (7-9). Although some researchers believe that patients on APT agents or anticoagulants may increase the chance of gastrointestinal post-ESD bleeding, others have shown the opposite result (8-11). Low-dose aspirin (LDA) is commonly used for cerebrovascular and cardiovascular diseases (12-14). At present, several international organizations in the USA and Europe have made an effort in drafting guidelines to manage the use of anticoagulant and APT agents for patients during and after ESD (15-17). In Japan, the guidelines recommend perioperative continuation of LDA for patients undergoing ESD procedures that have high bleeding risks (18). However, the data and literature are limited. Whether the continuous

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use of LDA increases the bleeding risk after gastrointestinal ESD remains controversial; this issue needs to be resolved (19). Therefore, a systematic search on the databases and a meta-analysis were conducted to determine whether patients undergoing ESD for gastrointestinal tumors are at risk of bleeding after continued use of LDA.

MATERIALS AND METHODS

Search Method and Methodological Quality Assessment

Ethics committee approval was obtained and the study was in adherence with the Declaration of Helsinki. We do not have the informed consent. Because we do not use the original data from patients, we just summary the data from others published literatures. Our search analyzed data from PubMed and Cochrane library updated in October 2015 and included a matching essay on the effect of aspirin after gastrointestinal ESD. The algorithms used in the search included "Aspirin" [Mesh] OR "Platelet Aggregation Inhibitors" [Mesh] OR "Dalteparin" [Mesh] AND "Stomach Neoplasms" [Mesh] OR "Colorectal Neoplasms" [Mesh] AND "ESD." The references in the searchable results were selected manually. The data were obtained by two separated evaluators.

The collected literature compared the risk of bleeding from continued-LDA use or from interrupted-LDA use with the risk from no-LDA use. Patients diagnosed with cancer or precancerous lesions were included, and reviews, case reports, abstracts, and letters were excluded. The Newcastle-Ottawa scale was used to assess the quality of the included studies and the funnel plot scale to assess the publication bias (20,21).

Data Extraction

The patients' basic information incorporated the main APT agents, size and location of the lesions, length of the procedures, en bloc resection, bleeding, and perforation rate. The location of lesions and bleeding after ESD were defined according to the literature (22,23).

Statistical Analysis

For all data, we computed the odds ratio (OR) and 95% confidence interval (CI). The Collaboration's RevMan 5.3 software (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analysis. The forest plot was used to confirm the rates of en bloc resection and bleeding in each group. Chi square and I^2 tests were used to examine the statistical heterogeneity. If $I^2>50\%$ and $p<0.1$, the random effects model was chosen; if there was no heterogeneity, the fixed-effects model was applied.

RESULTS

Assessment of the Selected Studies

A total of 305 relevant papers were collected using the key search words. Five full-text studies were chosen for the final analysis (10,11,24-26) (Figure 1). The Newcastle-Ottawa scale was used to assess the quality of the included studies (Table 1).

Detailed Information of the Selected Studies

The five selected publications included four historical cohort studies and one case-control study (10,11,24-26). Four studies involved gastric cancer and one involved colorectal cancer; four studies described tumor location and tumor size and two mentioned operation time and rate of perforation; all the studies were published from 2012 to 2015 (10,11,24,26) (Table 2). The information on age was introduced in five publications. The median age of the patients in the no-anticoagulant/APT group, LDA-continued group, and LDA-interrupted group ranged from 61.6 to 67 years, 66.8 to 75.9 years and 64.5 to 72.7 years, respectively. The ratios of males to females in the five papers were as follows: 1627 to 671 in the no-anticoagulant/APT

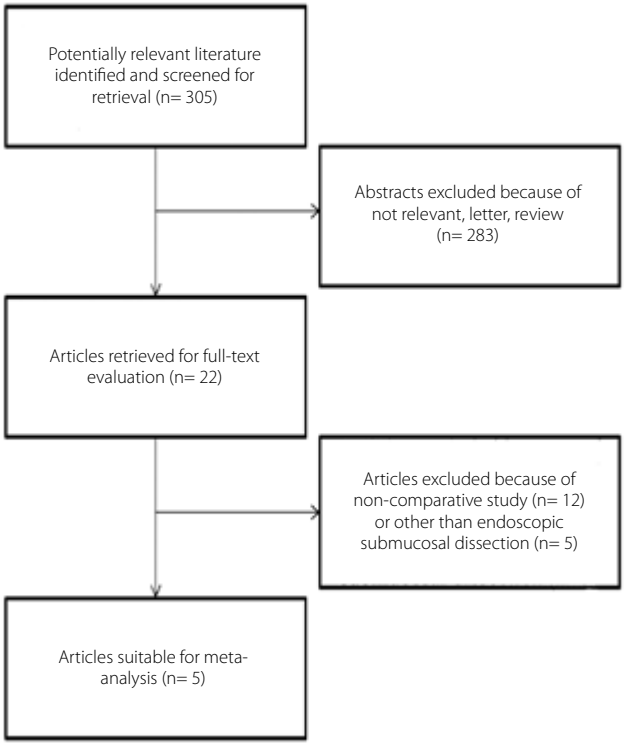

Figure 1. The PRISMA flowchart of literature review

Table 1. Quality assessment of bias in the included studies

	Selection					Outcome/ exposure		
Author	**1**	**2**	**3**	**4**	**Comparability**	**1**	**2**	**3**
Sanomura et al. (24)	★	★		★	★★	★		
Ninomiya et al. (11)	★	★		★	★	★		
Lim et al. (10)	★	★		★	★	★	★	★
Matsumura et al. (25)	★	★			★★	★	★	
Cho et al. (26)	★	★		★	★	★		

Quality assessment of bias in the included studies was evaluated based on the Newcastle-Ottawa quality assessment scale

Table 2. Details of included studies

Author	Study design	Disease	Study groups	Main APT agents	Patient ages, mean±SD or median (range)	Male/ Female	Tumor location (U/M/L or right/left/ rectum)	Tumor size (mm, median)	Operation time (min)	En bloc resection (n)	Perforation (n)
Sanomura et al. (24)	Historical cohort study	Early gastric cancer	LDA-continued group (n=28)	Aspirin, ticlopidine, clopidogre, cilostazol	75.9±8.2	20/5	8/4/16	18.3	49.6	28	0
			LDA-interrupted group (n=66)		72.7±9.1	44/12	11/20/35	16.6	45.3	63	3
Ninomiya et al. (11)	Historical cohort study	Colorectal tumors	LDA-continued group (n=31)	Aspirin, clopidogre, Ticlopidine	67.0±11.1	19/9	15/8/8	35.4±18.9	83.6±59.0	30	2
			LDA-interrupted group (n=13)		66.9±11.2	12/1	5/1/7	35.7±18.9	86.3±63.8	13	1
			No-anticoagulant/ APT group (n=565)		67.0±11.1	379/163	236/120/209	35.5±18.8	85.2±63.5	538	28
Lim et al. (10)	Historical cohort study	Early gastric cancer	LDA-continued group (n=172)	Aspirin, clopidogre, cilostazol	67.60±7.807	135/37	20/56/96	47.8±15.02	-	-	-
			LDA-interrupted group (n=102)		66.45±7.341	85/17	15/21/66	45.9±11.25	-	-	-
			No-anticoagulant/ APT group (n=1317)		61.61±9.321	923/394	116/428/773	45.5±13.91	-	-	-
Matsumura et al. (25)	Case-control study	Gastric cancer	LDA-continued group (n=21)	Aspirin	-	-	-	-	-	-	-
			LDA-interrupted group (n=41)		-	-	-	-	-	-	-
Cho et al. (26)	Historical cohort study	Gastric cancer	LDA-continued group (n=19)	Aspirin, clopidogre, other APTs	66.8±9.6	16/3	12/3/4	15	-	17	-
			LDA-interrupted group (n=56)		64.5±8.8	44/12	43/11/2	15	-	54	-
			No-anticoagulant/ APT group (n=439)		61.7±9.3	325/114	330/73/36	15	-	417	-

SD: standard deviation; L: lower; M: middle; U: upper; LDA: low-dose aspirin; APT: antiplatelet

group, 190 to 54 in the LDA-continued group, and 185 to 42 in the LDA-interrupted group.

Bleeding Complication

Five studies with data available on bleeding included 271 patients who received LDA-continued treatment for thromboembolic events before and after ESD therapies; they also included 278 controls who received LDA-interrupted treatment (10,11,24-26). The average incidence of bleeding in the LDA-continued group was up to 11.8% but was 5.4% in the LDA-interrupted group. One study introduced a higher rate of bleeding in the LDA-continued group, whereas the remaining four studies indicated no significant difference in the proportion of bleeding. We chose the fixed-effects model for pool analysis because of the low heterogeneity among the five studies ($p=0.54$; $I^2=0\%$) (19,11,24-26). The result illustrated that there

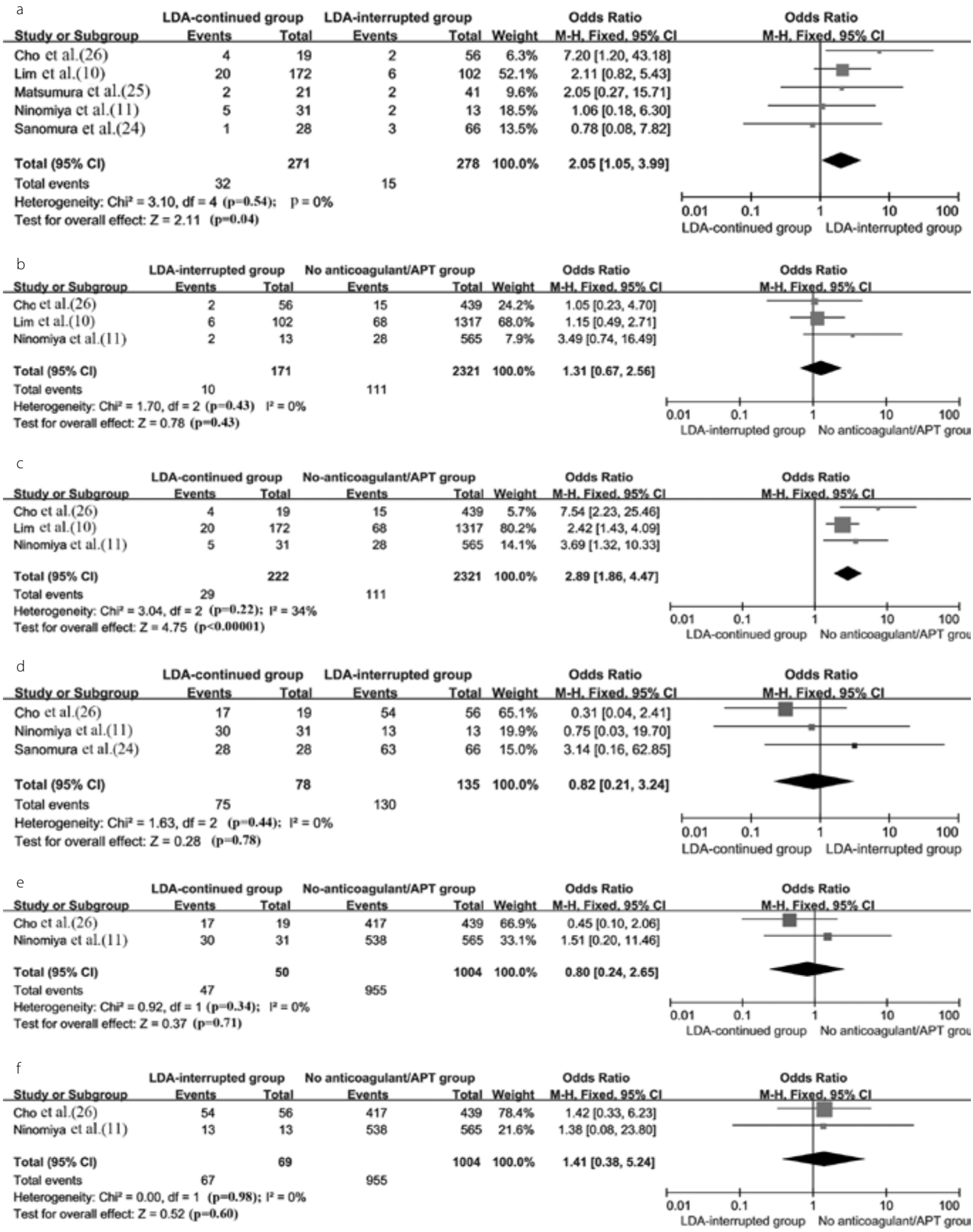

Figure 2. a-f. Forest plots were used to verify the relative effects of en bloc resection and adverse events of bleeding in each group. Results regarding the rate of post-ESD bleeding (a-c) and rate of en bloc resection are shown (d-f)

ESD: endoscopic submucosal dissection; CI: confidence interval; W: weight; OR: odds ratio; LDA: low-dose aspirin; APT: antiplatelet

was a significantly higher bleeding ratio in the LDA-continued group than in the LDA-interrupted group (OR=2.05, 95% CI=1.05-3.99, p=0.04; Figure 2a). According to the results of the funnel plots, there was no publication bias (Figure 3a).

Three of the trials with data available on bleeding included 171 patients who perioperatively received LDA-interrupted treatment and 2321 controls who did not use anticoagulant/APT agents (10,11,26). In the no-anticoagulant/APT group, the incidence of bleeding was 4.8%, but was 5.8% in the LDA-interrupted group. The fixed-effects model was used for pool analysis because of the low heterogeneity among the three studies (p=0.43; I^2=0%). There was no significant difference between the bleeding ratio in the LDA-interrupted group and no-anticoagulant/APT group (OR=1.31, 95% CI=0.67-2.56, p=0.43; Figure 2b). This result suggests that the incidence of bleeding in the LDA-interrupted group was similar to that in the no-anticoagulant/APT group. According to the result of the funnel plots, there was no publication bias (Figure 3b).

Data on bleeding were available for three trials, and they included 222 patients who received continued-LDA treatment

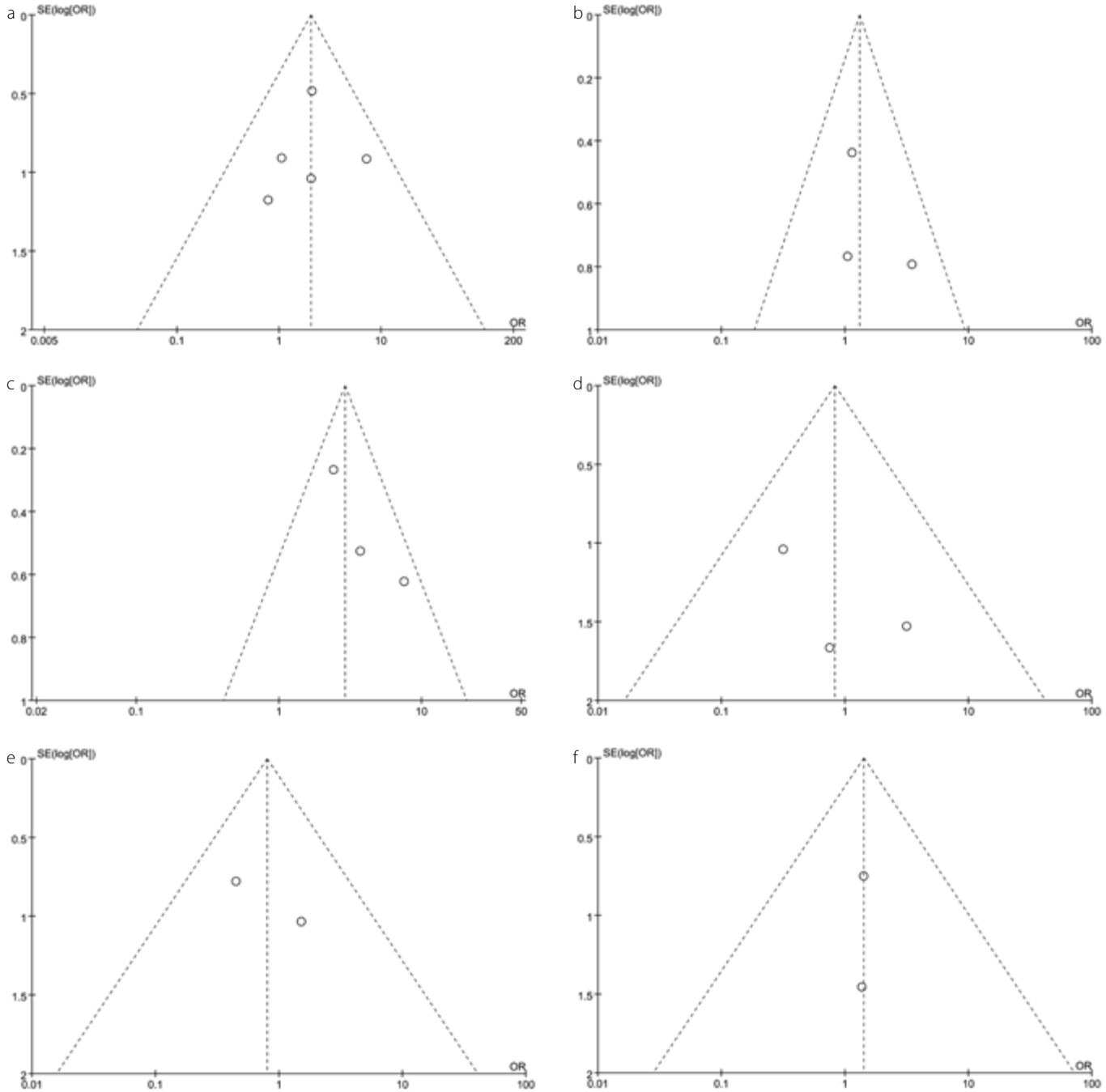

Figure 3. a-f. Funnel plots were used to obtain evidence of publication bias. The results regarding the rate of post-ESD bleeding (a-c) and the rate of en bloc resection (d-f) are shown

for thromboembolic events during the period of ESD therapies and 2321 controls who did not use anticoagulant/APT treatment (10,11,26). The incidence of bleeding in the LDA-continued group was up to 13.1%, but was 4.8% in the no-anticoagulant/APT group. Significant heterogeneity did not exist among those publications (p=0.22; I^2=34%); hence, the fixed-effects model was chosen for pool analysis. The result illustrated that there was a significantly higher bleeding ratio in the LDA-continued group compared to the no-anticoagulant/APT group (OR=2.89, 95% CI=1.86-4.47, p<0.00001; Figure 2c). According to the result of the funnel plots, there was no publication bias (Figure 3c).

En Bloc Resection

The incidence of en bloc resection was reported in three studies (11,24,26). These reported 213 lesions (n=78 in the LDA-continued group and n=135 in the LDA-interrupted group). Significant heterogeneity did not exist among studies (p=0.44; I^2=0 %); therefore, the fixed-effects model was used for pool analysis. No significant difference was found in the en bloc resection rate between the continued-LDA group and the interrupted-LDA group (OR=0.82, 95% CI=0.21-3.24, p=0.78; Figure 2d). According to the result of the funnel plots, there was no publication bias (Figure 3d).

Two reports compared the incidence of en bloc resection between the continued-LDA group and the no-anticoagulant/APT group (11,26). The fixed-effects model was used for pool analysis because of the low heterogeneity between the two studies (p 0.34; I^2=0%). There was no significant difference in the en bloc resection ratio between LDA-continued group and no-anticoagulant/APT group (OR=0.80, 95% CI=0.24-2.65, p=0.71; Figure 2e). This result suggests that the incidence of en bloc resection of the LDA-continued group was similar to that of the no-anticoagulant/APT group. According to the result of the funnel plots, there was no publication bias (Figure 3e).

Two reports with data available on en bloc resection included patients who perioperatively received LDA-interrupted treatment and who did not use anticoagulant/APT agents (11,26). The fixed-effects model was used for pool analysis because of the low heterogeneity between the two studies (p=0.98; I^2=0%). There was no significant difference in the en bloc resection ratio between LDA-continued group and no-anticoagulant/APT group (OR=1.41, 95% CI=0.38-5.24, p=0.60); Figure 2f). This result indicates that the incidence of en bloc resection of the LDA-continued group was similar to that of the no-anticoagulant/APT group. According to the result of the funnel plots, there was no publication bias (Figure 3f).

DISCUSSION

Endoscopic submucosal dissection is an advanced, complex endoscopic technique that is currently used for early gastrointestinal cancers or dysplastic lesions. Bleeding is a major procedural complication during ESD. Although the chance of bleeding after ESD is low, particular caution is necessary because some delayed bleeding could result in severe adverse events, such as cardiovascular events and hypovolemic shock. At present, the users of APT drugs have been growing because of prevention of thrombotic complications. Moreover, some patients cannot interrupt anticoagulants because of the high risk of thromboembolism. Clinical trials have shown that long-term use of anticoagulants decreases the risk of cardiovascular events, but at the expense of an increased risk of delayed bleeding. However, there are no published multicenter studies showing the relation between APT agents (such as aspirin) and post-ESD bleeding; there are only a few expert opinions and one single-center retrospective study. Therefore, this meta-analysis was devised to investigate whether continuous LDA use could increase the risk of post-ESD bleeding and to obtain evidence for APT users based on evidence-based medicine.

The meta-analysis conclusively shows that the incidence of post-ESD bleeding in gastrointestinal tract has no difference between patients with no-LDA use and those with interrupted-LDA use; however, the incidence is higher in continued-LDA users. In contrast, continued-LDA use, interrupted-LDA use, and the absence of LDA use show equal rates of en bloc resection.

Regarding connection between the use of antithrombotic drugs and the hazard for post-ESD bleeding, the results are complicated. Some researchers have shown that patients are at higher risk of bleeding during or after ESD with continuous LDA use (9,26,27). Others have shown the opposite result, indicating that using the LDA continuously does not increase the hazard of bleeding (10,24). We conducted a comprehensive and multicenter literature search and found that using LDA continuously may enhance the risk of bleeding, corresponding to the reported observations of Cho et al. (26).

At present, some studies indicate that using aspirin may lead to post-ESD bleeding, but it does not increase long-term morbidity or mortality; patients at high risk of cardiovascular and cerebrovascular complications need to take aspirin continuously (26). Among the five articles included in this meta-analysis, two reported complications of thromboembolism when patients stopped taking aspirin (10,24). One study reported that two patients experienced cerebrovascular infarction and two experienced acute myocardial infarction when LDA was stopped in patients before ESD (24). In the Lim JH study, after discontinuing the use of aspirin for 5 days, a patient experienced serious cerebral infarction and atrial fibrillation (10). Moreover, a multicenter survey showed that among the Japanese patients, incidence of cerebral infarctions was higher than that of severe post-ESD bleeding upon discontinuation of aspirin (28). The aforementioned studies indicate that the discontinuation of aspirin intake may lead to some serious events compared to its

continuation. The main reason for this phenomenon is that a patient who experienced cardiovascular and atherothrombotic diseases may be more likely at severe risk of acute ischemic events with the cessation of aspirin. Therefore, an individualized approach that fully considers patients' risk and benefit should be applied (29). Aspirin use should be stopped when a person has a low risk for thromboembolic disease. However, when a person has a high risk for thromboembolism, continuous aspirin use should be advised, despite the high risk of post-ESD bleeding. This is because thromboembolic events are more serious than post-ESD bleeding, which can decrease a patient's quality of life (26). ESD has an advantage over endoscopic mucosal resection for en bloc resection (30). With regard to the result of gastrointestinal ESD, the en bloc resection rates were quite high in all three groups included in this meta-analysis, suggesting no effect of aspirin on en bloc resection.

Some studies reported that bleeding was associated with lesion size and tumor location; for example, the hazard of post-ESD bleeding was higher when the lesions were located in the cecum, but it was difficult to stratify patients by these factors in our meta-analysis (31,32). There were also some unanswered questions regarding the bleeding of post-ESD and aspirin use. A recent study showed that the ratio of bleeding after ESD was higher in the anticoagulant agents group than in the nonanticoagulants agent group, 23.3% and 2%, respectively; however, the study did not examine the methods of drug use or which antithrombotic drugs may increase the rate of bleeding (27). In another study, the use of heparin caused a higher risk of delayed bleeding after gastric ESD (33). Takeuchi found that combining LDA with warfarin and longer ESD operations increased the rate of post-ESD bleeding (27). Moreover, Satoshi showed that taking thienopyridine derivatives with aspirin increased the hazard of bleeding after ESD, particularly in gastric ESD (34). These issues warrant further studies.

This meta-analysis has several drawbacks. First, this paper included only five nonrandomized controlled studies. No randomized controlled study comparing the hazard of bleeding after gastrointestinal ESD between interrupted aspirin use and continuous aspirin use has been published. Second, the results of any meta-analysis are influenced by the quality of the individual studies. Based on a quality assessment of the trials included in our meta-analysis, it has been determined that they were not free from systematic bias. Some trials drew a negative conclusion that was potentially due to small sample size. Third, some patients may have used more than one type of antithrombotic drug; the combination of APT and anticoagulation drugs may produce a slight bias. Further controlled trials are needed using larger, high-quality randomized samples.

Through a multicenter study, this meta-analysis showed that continuous aspirin use may increase the risk of bleeding after gastrointestinal ESD. Thus, patients treated with APT should be carefully monitored for post-ESD bleeding.

Ethics Committee Approval: Ethics committee approval was received for this study from ethics committee of Renmin Hospital of Wuhan University (Decision Date: 25.09.2015/Decision No: 2015152).

Informed Consent: N/A.

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