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Continued versus interrupted aspirin use and bleeding risk after endoscopic submucosal dissection of gastric neoplasms: a meta-analysis

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Abstract

Background Balancing the risk of bleeding and thromboembolic events for patients who use aspirin and need to undergo endoscopic submucosal dissection (ESD) for gastric neoplasms is a delicate process. The current guidelines from different associations provide inconsistent recommendations.

Methods MEDLINE and EMBASE databases were searched through August 2017 for studies that compared the risk of post-ESD bleeding in patients who continued aspirin vs. those who discontinued aspirin preoperatively. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random-effect model, generic inverse variance method. The between-study heterogeneity was quantified using the *Q* statistic and I^2.

Results A total of five studies that included 700 patients were identified. Our meta-analysis could not demonstrate a significantly increased risk of post-ESD bleeding among the aspirin-continued group compared to the aspirin-interrupted group, the pooled OR being 1.81 (95%CI 0.85-3.83). The statistical heterogeneity was insignificant, with an I^2 of 25%. Nine thrombotic events occurred in the aspirin-interrupted group whereas none occurred in the aspirin-continued group.

Conclusions This meta-analysis could not demonstrate that continuation of aspirin significantly increases the risk of post-ESD bleeding. However, the analysis was restricted by the small sample size and the observational nature of the primary studies. Randomized controlled trials are still needed to clarify this risk.

Keywords Antiplatelet, aspirin, bleeding, endoscopic submucosal dissection, gastric neoplasms

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Introduction

Stomach cancer is a major public health issue, as it is the fourth most common cancer in the world [1]. Endoscopic submucosal dissection (ESD) is an advanced technique used to remove superficial gastric neoplasms [2]. It provides a higher rate of *en bloc* resection and a lower rate of cancer recurrence compared to an endoscopic mucosal resection [3]. The National Comprehensive Cancer Network recommends ESD because of its therapeutic potential in early gastric cancer in addition to the diagnostic information it provides [4]. Postprocedural bleeding is one of the most common complications of ESD, with a reported incidence of 5.1% [5].

Aspirin is one of the most commonly prescribed medications worldwide. It is used for the treatment and prevention of several cardiovascular diseases, including ischemic stroke, myocardial infarction, and peripheral arterial disease [6]. According to a

recent report, low-dose aspirin is used for either primary or secondary cardiovascular disease prevention in about 30% of the United States adult population [7]. Balancing the bleeding and thromboembolic risks for patients who use aspirin and need to undergo an invasive procedure with a high risk of bleeding, such as ESD, is a delicate process. The recommendations regarding the periprocedural management of aspirin vary considerably across the guidelines from different national associations. For instance, the American Society of Gastrointestinal Endoscopy recommends continuing aspirin periprocedurally, regardless of thrombotic risks [8], whereas the European Society of Gastrointestinal Endoscopy recommends that aspirin discontinuation should be considered for patients whose risk of hemorrhage outweighs the risk of thrombotic events [9]. The Japan Gastroenterological Endoscopy Society recommends continuation of aspirin in patients with high thrombotic risk and discontinuation of aspirin for 3-5 days in patients with low thrombotic risk [10]. The aim of this systematic review and meta-analysis is to evaluate the risk of post-ESD bleeding among patients who continue aspirin compared to those who discontinue aspirin prior to the procedure.

Materials and methods

Search strategy

Two authors (PU and VJ) independently searched published articles indexed in Ovid/MEDLINE and EMBASE databases from inception to August 2017 using a search strategy that comprised the terms for "aspirin" and "endoscopic submucosal dissection", as detailed in Supplementary Table 1. No language restriction was applied. Reviews, case reports, and letters were excluded. References of selected retrieved articles were also reviewed manually.

Eligibility criteria

We included observational studies that met the following inclusion criteria: 1) adult patients (≥18 years of age) with gastric neoplasms; 2) undergoing gastric endoscopic submucosal dissection; 3) aspirin was stopped prior to the procedure in one group of patients, while the other group continued aspirin periprocedurally; and 4) the number of bleeding events and thrombotic events after the procedure were reported in both groups.

Two authors (PU and VJ) independently reviewed and evaluated the eligibility of the retrieved articles. The quality of each study was also independently evaluated by the same two authors using the Newcastle-Ottawa quality assessment scale, which assessed each study in three areas, including: i) the selection of the study subjects; ii) the comparability of the groups; and iii) the ascertainment of the outcome of interest [11]. Any difference in the determination of the eligibility of each study was resolved by conference with all authors.

Data extraction

The following data were abstracted from each study using a standardized study record form: first author name, study location, year of publication, study design, number of participants, participants' baseline characteristics, aspirin interruption strategy, number of bleeding events, and number of thrombotic events. The data were extracted independently by the same two authors to ensure accuracy.

Statistical analysis

Point estimates and standard errors from individual studies were combined using the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study based on its variance [12]. In light of the high likelihood of between-study variance, a random-effect model was used. The heterogeneity of effect size estimates across the studies was quantified using the Q statistic and I^2 ($P<0.10$ was considered significant). A value of I^2 of 0-25% indicates insignificant heterogeneity, 26-50% low heterogeneity, 51-75% moderate heterogeneity, and 76-100% high heterogeneity [13]. Publication bias was assessed using a funnel plot [14]. Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom).

Results

The initial search yielded 3929 potentially relevant articles (2383 articles from EMBASE and 1546 articles from MEDLINE). After the exclusion of 1508 duplicated articles, 2421 articles underwent title and abstract review. A total of 2387 articles were excluded at this stage, as they clearly did not fulfill the eligibility criteria, leaving 34 articles for full-length review. Twenty-nine articles were excluded after the full-length review, for the following reasons: 7 studies were reviews, case reports, or letters; 4 studies did not perform ESD; 6 studies performed ESD outside the stomach; 7 studies did not recruit our subjects of interest; and 5 studies did not report the outcome of interest. Therefore, 5 studies (all cohort studies) [15-19] that included 700 patients (266 in the aspirin-continued group and 434 in the aspirin-interrupted group) were included in the meta-analysis. Supplementary Fig. 1 outlines the search methodology and study selection process. Table 1 describes the detailed characteristics and quality assessment of the included studies. Two studies are from South Korea and three studies are from Japan. The definition of post-ESD bleeding is bleeding in the interval after the procedure until 2-4 weeks postprocedurally. The aspirin interruption period ranged from 3-7 days prior to the procedure in the aspirin-interrupted group.

A significantly greater risk of post-ESD bleeding among the aspirin-continued group compared with the aspirin-

Table 1 Characteristics of the included studies

Study	Cho *et al* [15]	Lim *et al* [17]	Sanomura *et al* [18]	Tounou *et al* [19]	Igarashi *et al* [16]
Country	South Korea	South Korea	Japan	Japan	Japan
Year	2012	2012	2014	2015	2016
Study design	Cohort study	Cohort study	Cohort study	Cohort study	Cohort study
Study subjects	Patients who took daily aspirin and underwent ESD for EGC at the National Cancer Center Hospital between November 2008 and January 2011	Patients who took daily aspirin and underwent ESD for gastric neoplasms at Seoul National University Hospital between April 2005 and April 2010	Patients who took daily aspirin and underwent ESD for EGC at Hiroshima University Hospital between April 2005 and June 2012	Patients who took daily aspirin and underwent ESD for gastric neoplasms at Shin-Tokyo Hospital between January 2007 and July 2013	Patients who took daily aspirin and underwent ESD for gastric neoplasms at Shizuoka Cancer Center between January 2009 and October 2014
Definition of postprocedural bleeding	Fall in Hgb of at least 2 g/dL with melena or hematemesis that occurred within 4 weeks after ESD	Fall in Hgb of at least 2 g/dL, GIB, or requirement of endoscopic hemostasis that occurred within 2 weeks after ESD	Fall in Hgb of at least 2 g/dL, melena or hematemesis	Hematemesis, melena or hypotension confirmed with urgent endoscopy that occurred within 4 weeks after ESD	Melena or hematemesis that required endoscopic hemostasis, which occurred within 4 weeks after ESD
Average age (years)	66.8	62.6	73.7	71.8	72.4
Female (%)	25.1	51.8	17.9	26.6	22.3
Continued ASA users	19	172	28	14	33
Interrupted ASA users	56	102	66	39	171
ASA interruption strategy	7 days prior to ESD	7 days prior to ESD	5-7 days prior to ESD	3 days prior to ESD	3-7 days prior to ESD
Dosage of ASA	N/A	N/A	LDA	LDA	N/A
Second-look endoscopy	No	No	Yes within 24 h	Yes within 24 h	Yes within 24 h
Quality of study	Selection 3 stars Comparability 1 star Exposure 3 stars	Selection 3 stars Comparability 1 star Exposure 3 stars	Selection 3 stars Comparability 2 stars Exposure 3 stars	Selection 3 stars Comparability 1 star Exposure 3 stars	Selection 3 stars Comparability 2 stars Exposure 3 stars

ACS, acute coronary syndrome; ASA, aspirin; CVA, cerebrovascular accident; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; Hgb, hemoglobin; LDA, low dose aspirin; N/A, not applicable

interrupted group was not observed in this meta-analysis, with the pooled odds ratio (OR) being 1.81 (95% confidence interval [CI] 0.85-3.83). The statistical heterogeneity was insignificant, with an I^2 of 25% (Fig. 1). A funnel plot was used for evaluation of publication bias (Fig. 2). The plot was symmetric and did not provide suggestive evidence of publication bias, although the small number of studies may have compromised this analysis.

On the other hand, a total of 9 thrombotic events (2.1%) occurred in the aspirin-interrupted group (6 cerebral infarction/transient ischemic attack and 3 acute coronary syndrome) whereas no thrombotic events were observed in the aspirin-continued group.

Sensitivity analyses

To confirm the robustness of the results, several sensitivity analyses were conducted. The first was performed by excluding one study at a time from the full meta-analysis to see if it had a significant influence on the result of the meta-analysis (i.e., jack-knife sensitivity analysis). We found that exclusion of any study from the meta-analysis did not significantly alter the pooled result, as we continued to see that the risk of bleeding was not significantly lower or higher with continuation of aspirin (pooled OR 1.52 and 95%CI 0.78-2.98 after exclusion of the study by Cho *et al* [15]; pooled OR 2.16 and 95%CI 0.84-5.56 after exclusion of the study by Igarashi *et al* [16]; pooled OR

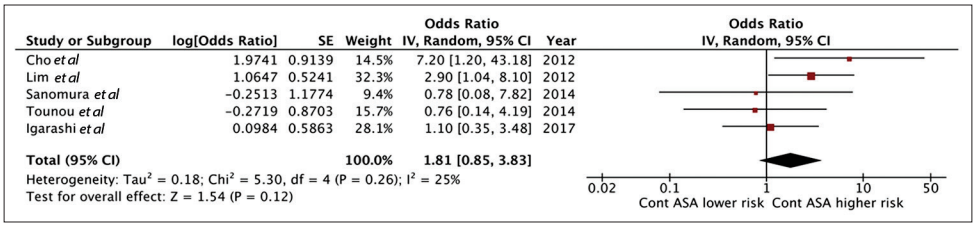

Figure 1 Forest plot of the included studies comparing the risk of bleeding between the aspirin (ASA)-continued group vs. the aspirin-interrupted group. A diamond data marker represents the overall odds ratio and 95% confidence interval (CI) for the outcome of interest

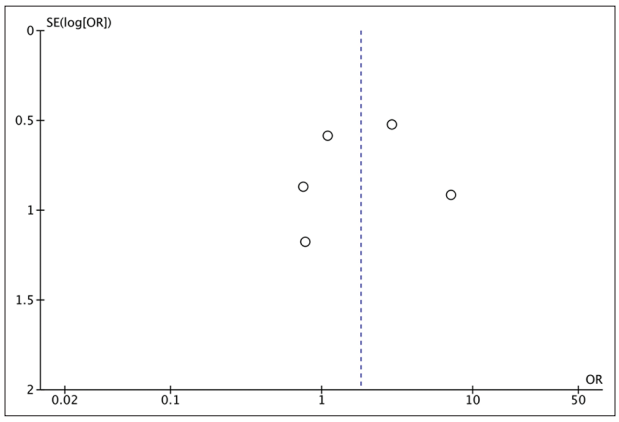

Figure 2 Funnel plot of the included studies. Circles represent observed published studies

1.45 and 95%CI 0.55-3.81 after exclusion of the study by Lim *et al* [17]; pooled OR 1.98 and 95%CI 0.84-4.62 after exclusion of the study by Sanomura *et al* [18]; pooled OR 2.12 and 95%CI 0.93-4.87 after exclusion of the study by Tounou *et al* [19]).

The second analysis was subgroup analysis by quality of study. A total of 2 studies had a perfect Newcastle-Ottawa score of 8 [16,18] whereas the other 3 studies each scored 7 [15,17,19]. Subgroup analysis showed a pooled OR of 1.03 (95%CI 0.37-2.88) for the studies with a score of 8 and a pooled OR of 2.45 (95%CI 0.86-7.49) for those with score of 7. The results of both subgroups were not significantly different from the full analysis.

The third analysis was subgroup analysis according to study protocol, as there were 3 studies that systematically performed second-look endoscopy on the day after ESD [16,18,19] while 2 studies did not [15,17]. Interestingly, while the result for the subgroup of studies that systematically performed second-look endoscopy was similar to the full analysis (pooled OR 0.95; 95%CI 0.39-2.29), subgroup analysis of the studies that did not perform second-look endoscopy showed a significantly higher risk of post-ESD bleeding among those who continued aspirin, with a pooled OR of 3.30 (95%CI 1.49-8.85).

Discussion

With the aging of the global population, the incidence of gastric cancer and cardiovascular disease has been increasing worldwide [20]. The use of aspirin has become more prevalent, posing a challenge to clinicians to balance the risk of bleeding and the benefit of periprocedural thrombotic prevention. The current guidelines for ESD from various national associations [7,9,6] provide inconsistent recommendations, as the safety of continuing aspirin periprocedurally is still not known. Our meta-analysis, which summarized all available evidence from five studies, could not demonstrate a significantly higher risk of post-ESD bleeding among patients who continued aspirin compared to those who discontinued aspirin prior to ESD.

On the other hand, interruption of low-dose aspirin use for secondary prevention is known to pose a significant risk of recurrence of cardiovascular diseases [21,22]. In this meta-analysis, we found the number of thromboembolic events was higher in the aspirin-interrupted group than the aspirin-continued group (2.1% vs. 0%). Nonetheless, it should be noted that a formal analysis to compare the incidence of thromboembolic complications between the two groups could not be performed, as no thromboembolic event occurred in the aspirin-continued group across the five included studies.

A recent meta-analysis of five studies found twofold increased odds of postprocedural bleeding in patients who continued aspirin compared to those who discontinued aspirin prior to the ESD [23]. However, the inclusion criteria for that meta-analysis were fairly broad, as it also included a study of ESD for other gastrointestinal neoplasms apart from the stomach [24]. Moreover, one included study did not compare the incidence of post-ESD bleeding between patients who continued aspirin and those who discontinued aspirin prior to ESD. That study compared the incidence of post-ESD bleeding between patients who continued aspirin and those who discontinued any antithrombotic agents prior to ESD [25]. Therefore, this study did not actually meet the eligibility criteria and should not have been included in the meta-analysis.

Whether post-ESD second-look endoscopy should be performed routinely remains controversial. The potential advantage is that endoscopists can evaluate the status of post-ESD ulcers and can take additional hemostatic measures if necessary [26]. Although few previous retrospective studies have reported its usefulness for prevention of delayed bleeding [27,28], subsequent randomized controlled trials failed to show any clinical benefits, including postprocedural bleeding and morbidity [29-31]. However, these trials assessed the outcomes in patients with average bleeding risk and did not specifically investigate the outcomes in patients who took aspirin. Interestingly, our meta-analysis found a significantly higher risk of post-ESD bleeding in the aspirin-continued

group than in the aspirin-interrupted group in studies that did not routinely perform second-look endoscopy. In contrast, the risk of bleeding did not differ significantly between the groups in studies that routinely performed second-look endoscopy. This may indicate the possibility of a greater bleeding risk in the aspirin-continued group compared to the aspirin-interrupted group and second-look endoscopy may reduce that risk. Whether second-look endoscopy has a role in preventing bleeding in these patients with aspirin use needs further investigation.

This meta-analysis has some limitations that may have jeopardized the validity of the results. First, although this study took advantage of the meta-analysis approach to combine all existing data, the number of included patients was still rather small. Therefore, the study could be underpowered to demonstrate any difference between the two groups. Second, all of the included studies were observational and retrospective in nature. The patients were assigned to continue or discontinue aspirin at the discretion of their endoscopists; thus, the distribution of effect modifiers/confounders may not be even between the two groups. Third, the generalizability of the results to other populations could be limited as all of the included studies were from just two Asian countries.

Summary Box

What is already known:

- Aspirin is one of the most commonly prescribed medications worldwide
- Balancing the bleeding and thromboembolic risks for patients who use aspirin and undergo gastric endoscopic submucosal dissection (ESD) is a delicate process
- The recommendations regarding the periprocedural management of aspirin vary considerably across the guidelines from different national associations

What the new findings are:

- Our meta-analysis of five studies could not demonstrate a significantly higher risk of post-ESD bleeding among patients who continued aspirin compared to those who discontinued aspirin prior to ESD
- A total of 9 thrombotic events (2.1%) occurred in the aspirin-interrupted group whereas no thrombotic events were observed in the aspirin-continued group
- To confirm the robustness of the results, a sensitivity analysis was conducted. We found that exclusion of any study from the meta-analysis did not significantly alter the pooled result

In summary, our meta-analysis could not demonstrate that continuation of aspirin significantly increases the risk of post-ESD bleeding. However, the analysis was limited by the small sample size and the observational nature of the primary studies. Randomized controlled trials are still needed to clarify this risk.

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