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Effects of antithrombotic therapy on bleeding after endoscopic submucosal dissection: A systematic review and meta-analysis

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#### ACCEPTED MANUSCRIPT

#### **Abstract**

**Background and Aims:** Bleeding is the most common adverse event after ESD. Although several studies have been reported about the use of antithrombotic agents and post-ESD bleeding, many issues remain controversial. We conducted a meta-analysis and systematic review to evaluate the effects of antithrombotic therapy for post-ESD bleeding.

**Methods:** Published literature was searched from online databases, and all studies were inclusive until January 2017. Standard forms were used to extract data by 2 independent reviewers. The Newcastle-Ottawa Scale (NOS) score was used to assess the quality of studies. The pooled odds ratio (OR) was computed for the effect of antithrombotic agents. Publication bias was assessed by funnel plots. Heterogeneity was assessed by the Cochran Q test and I<sup>2</sup>-statistic.

**Results:** Sixteen retrospective articles were included. Regardless of discontinuation (OR, 1.66; 95% CI, 1.15-2.39; P = .007) or continuation (OR, 8.39; 95% CI, 4.64-15.17; P < .00001), antithrombotic therapy was significantly associated with post-ESD bleeding, particularly for delayed bleeding (OR, 2.66; 95% CI, 1.42-4.98; P = .002). The bleeding rate was higher in discontinued multiple antithrombotics group (OR, 5.17; 95% CI, 3.13-8.54; P < .00001) than in discontinued a single antithrombotic (OR, 2.23; 95% CI, 1.29-3.85; P = .004) and single antiplatelet group (OR, 2.08; 95% CI, 0.93–4.63; P = .07). In subgroup analysis, resuming antithrombotics within 1 week (OR, 2.46; 95% CI, 1.54-3.93; P = .0002) and using heparin replacement (HR) (OR, 4.20; 95% CI, 1.94-9.09; P = .0003) significantly increased post-ESD bleeding risk. Continued use of low-dose aspirin (LDA) (OR, 1.22; 95% CI, 0.17-8.61; P = .84) did not significantly increase the bleeding risk.

**Conclusions:** Antithrombotic therapy is a risk factor for post-ESD bleeding, especially for delayed bleeding. Using multiple antithrombotic drugs, resuming antithrombotics within 1 week and HR were significantly associated with post-ESD bleeding; but continuous LDA was not. However, much larger prospective studies are required.

#### Introduction

Endoscopic submucosal dissection(ESD) is accepted as an effective treatment for superficial gastrointestinal neoplasms without metastasis because of the high rate of en bloc resection and low local recurrence rate<sup>1</sup>. Taking this into consideration, ESD seems to be more advantageous than conventional endoscopic mucosal resection (EMR). Although the safety and efficacy of this procedure has been substantiated, adverse events such as bleeding remain problematic. The rate of post-ESD bleeding has been reported to range from 1.8% to

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