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**Clinical problems with antithrombotic therapy for endoscopic submucosal dissection for gastric neoplasms**

Yoshio T *et al*. Antithrombotic therapy for gastric ESD

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Abstract

Endoscopic submucosal dissection (ESD) is minimally invasive and thus has become a widely accepted treatment for gastric neoplasms, particularly for patients with comorbidities. Antithrombotic agents are used to prevent thrombotic events in patients with comorbidities such as cardio-cerebrovascular diseases and atrial fibrillation. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Dual antiplatelet therapy (DAPT), a representative combination therapy, is frequently used after placement of drug-eluting stents (DES) and has a high risk of delayed bleeding. In patients receiving DAPT, gastric ESD may be postponed until DAPT is no longer required. HBT is often required for patients treated with anticoagulants and has an extremely high bleeding risk. The continuous use of warfarin or direct oral anticoagulants (DOACs) may be possible alternatives. Here, we show that some antithrombotic therapies in high thrombosis-risk patients increase delayed bleeding after gastric ESD, whereas most antithrombotic therapies do not. The management of high thrombosis-risk patients is crucial for improved outcomes.

**Key words:** Antithrombotic therapy; Endoscopic submucosal dissection; Heparin bridge therapy; Dual antiplatelet therapy; Delayed bleeding

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**Core tip:** It is unclear if antithrombotic therapy increases delayed bleeding after endoscopic submucosal dissection (ESD) of gastric neoplasms. With appropriate cessation, antithrombotic therapy does not increase delayed bleeding in low thrombosis-risk patients. However, high thrombosis-risk patients are often treated with combination therapy with antithrombotic agents, such as dual antiplatelet therapy (DAPT), and occasionally require the continuation of antithrombotic agents or heparin bridge therapy (HBT) in the perioperative period. Both patients with DAPT and HBT have a high risk of delayed bleeding. The management of these antithrombotic therapies is important in the perioperative period of ESD.

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**Introduction**

Endoscopic resection of early gastric cancer (EGC) has been developed and applied to many patients since the establishment of criteria for node-negative cancers[1] and the advancement of endoscopic submucosal dissection (ESD)[2,3]. In multicenter studies, we have reported that ESD is a feasible method for the treatment of EGC[4] and that the long-term outcome of gastric ESD is satisfactory[5]. A risk of metachronous gastric cancer exists following ESD or endoscopic mucosal resection (EMR), even when the procedure is curative[6,7]. The cumulative 3-year risk is 5.9%[7]. However, we also demonstrated that nearly all secondary cancers after ESD (97%) were treatable by repeated ESD following scheduled endoscopic surveillance[5]. Consequently, ESD can preserve the entire stomach and improve patient post-operative quality of life. Therefore, ESD has become a more acceptable treatment option for EGC than gastrectomy, particularly for patients with comorbidities[8].

Delayed bleeding is one of the major complications of gastric ESD, and the delayed bleeding rate is 3.1%-6.5%[4,9,10]. In most cases, delayed bleeding is treated successfully by endoscopic hemostasis; however, some patients require transfusion or surgery, and these situations can be fatal[11]. The reported risk factors for delayed bleeding include larger lesions[10], lesions with ulceration[10,12], and longer procedure time[1,13]. The risk is highest for lesions in the middle and lower third[9]. Electronic coagulation of vessels in the ulcer bed after ESD was reported to decrease delayed bleeding[9]. In our analysis, half of delayed bleeding occurred the day of ESD or the next day, and the remainder occurred within 2 wk, with the exception of 1 case that occurred 22 d after ESD[14]. It has been argued that second-look endoscopy after ESD prevents delayed bleeding. However, Goto *et al*[15] showed that second-look endoscopy did not decrease delayed bleeding in a retrospective analysis. A prospective randomized control study also denied a preventive effect of second-look endoscopy for delayed bleeding[16].

Antithrombotic therapy, including antiplatelet agents and anticoagulants, is increasingly used worldwide to prevent cerebro-cardiovascular events[17,18]. These prophylactic agents reduce the risks of thromboembolic events but simultaneously increase the risk of bleeding complications. Most patients with EGC are elderly, and these patients commonly exhibit several comorbidities that require medical treatment, particularly antithrombotic therapy. Risks for delayed bleeding after ESD in patients with antithrombotic therapy depend on the type of endoscopic treatment and the use of antithrombotic therapy.

In this review, we discuss the problems of antithrombotic therapy associated with delayed bleeding after gastric ESD. This review is not a systematic review because of the limited evidence and the variety of patients with various comorbidities receiving many types of antithrombotic agents. However, we searched the entire MEDLINE database to identify the literature on antithrombotic therapy and gastric ESD and included as many studies as possible.

**Effect of Antiplatelet Agents on Gastric ESD**

Antiplatelet agents are used to prevent platelet aggregation for prophylaxis of secondary cerebro-cardioembolic events after the occurrence of stroke or ischemic heart disease[19]. Antiplatelet agents include thienopyridines, protease-activated receptor-1 inhibitors, glycoprotein IIb/IIIa receptor inhibitors, aspirin and non-steroidal anti-inflammatory drugs. When patients exhibit a low risk of thrombosis, antithrombotic agents can be discontinued. Antithrombotic therapy with appropriate cessation is not considered to increase delayed bleeding rates[14,20]. In some high thrombosis-risk patients, it is difficult to discontinue antithrombotic therapy during the perioperative period of ESD. Administration of these antithrombotic agents in combination further complicates the management of these agents. In these patients, the continuous use of minimum antithrombotic agents during ESD is an option.

The recent guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) in 2016[21] and the Japan Gastroenterological Endoscopy Society (JGES) in 2014[22] recommend the continuous use of aspirin during endoscopic procedures in high thrombosis-risk patients, even if the procedures carry a high risk of bleeding. For gastric ESD, a multivariate analysis[23-25] found that the continuous use of aspirin did not increase delayed bleeding, supporting the application of this treatment; however, the delayed bleeding rate was slightly increased (3.6%-21.1%)[23-26]. Moreover, the delayed bleeding rate was considerably higher in patients receiving dual antiplatelet therapy (DAPT) with continuous aspirin and cessation of thienopyridines (35.5%) than in patients who did not receive antithrombotic medications[25].

For patients with coronary artery stents, DAPT with aspirin plus thienopyridines is recommended for 30 days after placement of a bare metal stent and for one year after placement of a drug-eluting stent (DES)[27]. Cessation of these agents within the period resulted in a high risk of stent thrombosis[28]. Thus, according to the consensus statement from the American College of Cardiology Foundation and the American College of Gastroenterology, it is recommended to defer elective endoscopic procedures up to 12 mo from the time of DES placement and perform endoscopic procedures 5 to 7 d after thienopyridine cessation[29]. In addition, aspirin should be continued throughout the perioperative period, and thienopyridine should be resumed once hemostasis is achieved[29]. The timing of ESD for EGC should be decided based on the balance of cancer progression and bleeding risk. EGC often remains in the early stage for a period[30]. Thus, ESD can be delayed in patients with DES placement, provided that the EGC lesion is still considered resectable after the completion of required DAPT.

The management of patients with DAPT for ESD is difficult. A delayed bleeding rate as high as 35.5%[25] was reported when ESD was performed with continuous aspirin and cessation of thienopyridines following the guidelines[21,22,29]. Moreover, patients receiving DAPT for ESD face thrombotic risk from the cessation of thienopyridines, and this thrombotic risk can be increased if delayed bleeding occurs[11,14]. However, it is sometimes necessary to perform ESD in patients with DAPT with continuous aspirin and cessation of thienopyridines who have a risk of delayed bleeding and thrombosis. Care must be taken to identify the initial symptoms of delayed bleeding and thrombotic events. There is insufficient evidence for methods to minimize both bleeding risk and thrombotic risk during DAPT, and we have no data on cases of continuous administration of both aspirin and thienopyridines or cessation of aspirin and continuous thienopyridines.

**Effects of Anticoagulants on Gastric ESD**

Anticoagulants prevent thrombotic events in patients with conditions such as arterial fibrillation (AF) and deep vein thrombosis by interfering with the native clotting cascade. Anticoagulants include oral warfarin, direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, and edoxaban), and heparin derivatives.

The risk of thromboembolism associated with withdrawal of anticoagulants varies considerably. AF is the most common reason for the use of anticoagulant therapy, and the risk of thrombotic events is approximately 1% when anticoagulation is interrupted for 4 to 7 d[31,32]. Thrombotic events can cause serious complications and can be fatal. Thus, all patients on anticoagulant therapy are recommended to be treated as having a high risk of thrombosis[22]. Thus, for the cessation of anticoagulants, heparin bridge therapy (HBT) is required to prevent thrombotic events during the perioperative period[33-35]. However, ESD with HBT carries an extremely high risk of delayed bleeding, with a delayed bleeding rate of 23.8%-37.5% as we previously reported[14,36-38].

DOACs are administered without the need to monitor their effects due to their rapid action and effectiveness in preventing cerebrovascular events[39-42]. Before endoscopic procedures, 1 to 3 d of cessation is recommended in patients without renal dysfunction according to the ASGE guideline[21] based on the half-lives of the agents (8-15 h)[39-42]. According to the British Society of Gastroenterology (BSG) and ESGE guidelines, at least 2 d of cessation is recommended before endoscopic procedures[43]. By contrast, warfarin requires 5 d of cessation to cancel the effect[44], and HBT is required during this period. After the procedure, DOACs should be re-administered without heparin because DOACs achieve their maximum effect shortly (1-4 h) after re-administration, in contrast to warfarin[39-42,45]. Thus, shorter perioperative periods of controlling anticoagulant effects can be applied for DOACs compared with warfarin.

Unfortunately, no study has examined the effect of DOACs on endoscopic procedures except our following conference paper. For gastric ESD for patients, we observed a delayed bleeding rate of 16.7% (3/18) in patients using DOACs, which did not differ significantly from the delayed bleeding rate of 23.5% (4/17) observed in patients using warfarin during the same period[46]. However, the hospitalization period was significantly shorter in patients on DOACs compared with those on warfarin (8 d *vs* 14 d: *p* < 0.01) because the period of HBT was shorter[46]. Further investigations are needed to understand the effect of DOACs on endoscopic procedures.

In high thrombosis-risk patients with comorbidities, combination use of antiplatelet agents and anticoagulants is occasionally required, which also increases delayed bleeding[14].

**Timing of Delayed Bleeding**

Koh et al. reported that antithrombotic therapy was a risk factor for late bleeding (later than post-operative day (POD) 5)[47]. Tounou et al. reported late bleeding (later than POD 8) was significantly more frequent in cases with DAPT but not cases with single aspirin therapy[25]. In cases with HBT, the timing of delayed bleeding was later than in cases without HBT (POD 3.8 ± 4.1 *vs* POD 8.0 ± 5.7, *p* < 0.05)[14]. In cases without HBT, half of delayed bleeding cases occurred on POD 0 and 1; however, in cases with HBT, only 10% of the cases occurred on POD 0 and 1[14].

**Is HBT Feasible for Gastric ESD?**

A recent, randomized control study compared discontinued anticoagulant use with or without HBT in 1884 surgical cases and revealed that HBT did not reduce perioperative arterial thromboembolism but significantly increased major bleeding complications[48]. A meta-analysis of studies of elective invasive procedures or surgeries revealed that warfarin-treated patients receiving bridge therapy with low-molecular-weight heparin appear to be at an increased risk of both overall and major bleeding and exhibited a similar risk of thromboembolic events as non-bridged patients[49].

Another randomized control study involving 681 cases of pacemaker or defibrillator surgery revealed that bleeding complications occurred less frequently in patients with continuous warfarin use than in patients in whom warfarin was discontinued with HBT[50]. Additional meta-analyses supported these results[51].

Considering these findings together, continuous use of warfarin throughout the perioperative period is a better choice than HBT because continuous use of warfarin likely does not increase bleeding complications and exhibits the same risk for thrombosis. None of them are originated of the outcome of endoscopic procedures nor gastric ESD, these results will change our treatment. Tounou et al. reported a case of gastric ESD safely performed with continuous use of warfarin[52]; however, further investigation is needed, such as a randomized study comparing gastric ESD with continuous ESD and with HBT.

For patients requiring HBT, continuous use of warfarin and switching warfarin to DOACs are candidate new strategies, although data to support their use are lacking.

**Analysis of Bleeding Risk in Antithrombotic Therapy by Comparing Patient and Lesion Characteristics**

High thrombosis-risk patients are often at a high risk of delayed bleeding under antithrombotic therapy with multiple agents, particularly patients with HBT and accompanying comorbidities. The antithrombotic therapies, patient comorbidities and EGC characteristics with the highest risks for delayed bleeding remain unclear.

Furuhata *et al*[36] conducted a multivariate analysis of these factors and identified HBT (OR = 10.04), multiple antithrombotic agents (OR = 5.44), the lower third of the stomach (OR = 2.17), and an operation time longer than 100 min (OR = 2.00) as independent risk factors. Matsumura *et al*[37] identified CKD undergoing hemodialysis (OR = 33.86), HBT (OR = 5.77) and a lesion size greater than 40 mm (OR = 3.70) as risk factors (Table 1).

We performed a bleeding risk analysis in 1563 consecutive patients with 1671 gastric neoplasms treated by ESD[53] as an extended analysis of our previous study[11] (unpublished data). This study included 283 (18%) patients receiving antithrombotic agents who all discontinued the agents before ESD. The delayed bleeding rates were similar between patients receiving no antithrombotic therapy and those who discontinued antithrombotic agents without HBT (5.6% *vs* 4.9%); however, the delayed bleeding rate was significantly higher (21.9%) in patients with HBT (*p* < 0.01). Moreover, the delayed bleeding rate increased in proportion to the number of discontinued drugs (two drugs: 15.6%, *p* < 0.01; three drugs: 27.3%, *p* < 0.05). Patients on warfarin or ticlopidine had a significant risk of delayed bleeding compared with patients receiving no antithrombotic agent. In a univariate analysis of tumor and patient factors, tumor size greater than 30 mm, tumor in the middle third of the stomach, tumor with ulceration, patients with CKD and male gender were identified as risk factors for delayed bleeding.

Multivariate analysis showed that HBT (OR = 6.14), lesion in the middle third of the stomach (OR = 2.21), ulceration in tumor (OR = 1.97) and tumor size greater than 30 mm (OR = 1.75) were significant, independent risk factors for delayed bleeding. HBT (OR = 16.43) and CKD (OR = 6.34) were identified as significant risk factors for blood transfusions by multivariate analysis.

The results of these studies show that HBT is the most significant independent factor for delayed bleeding compared with other factors involving patient and lesion characteristics.

**Thrombotic Events**

Few studies of the relationship between thrombotic events and endoscopic procedures have been conducted, and incidence rates of thrombotic events related to gastric ESD of 0%-4.2% have been reported[14,20,23,54]. We observed one patient who developed a thrombotic event[14]. This patient received HBT during the perioperative period and exhibited delayed bleeding on POD 10. After successful endoscopic hemostasis, we restarted heparin, and his activated partial thromboplastin time was sufficiently prolonged on POD 11. However, a cerebral infarction developed on POD 13. This case suggests that delayed bleeding can lead to thrombotic events by reducing intravascular volume and causing hypercoagulability after bleeding. Numata *et al*[11] also reported a case of femoral artery infarction consequent to delayed bleeding after gastric ESD that led to death. These findings suggest that the prevention of delayed bleeding is important for preventing thrombotic events in patients at a high risk for thromboembolism.

**Conclusion**

Most antithrombotic therapies do not increase the risk of delayed bleeding during gastric ESD; however, patients receiving multiple antithrombotic agents, including DAPT, and patients on anticoagulants requiring HBT have a high risk for delayed bleeding. These high thrombosis-risk patients with accompanying comorbidities may have a high risk of delayed bleeding under strong antithrombotic therapy.

To prevent the exposure of these patients to a serious risk of acute ischemic events, new strategies should be developed to replace HBT and to address DAPT. Well-designed prospective and comparative clinical studies are needed to obtain further evidence regarding the management of antithrombotic therapy.

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**Table 1 Multivariate analysis of risk factors for delayed bleeding: antithrombotic therapy and patient and lesion characteristics**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **Risk factor identified by multivariate analysis** | **OR (95%CI)** | **Risk factors identified by univariate analysis** |
| Furuhata *et al*[36] | 1781 | HBT | 10.04 (4.35-23.16) | HBT, multiple antithrombotic agents, tumor size greater than 20 mm, lower third location, UL+ tumors, operation time longer than 100 min, and cardiovascular disease |
| Multiple antithrombotic agents | 5.44 (2.00-14.79) |
| Lower third location | 2.17 (1.32-3.58) |
| Operation time longer than 100 min | 2.00 (1.25-3.20) |
| Matsumura *et al*[37] | 413 | CKD undergoing hemodialysis | 33.86 (4.72-242.74) | HBT, Tumor size over 40 mm, CKD undergoing hemodialysis |
| HBT | 5.77 (1.67-19.96) |
| Lesion size greater than 40 mm | 3.70 (1.09-12.52) |

HBT: heparin bridge therapy.