Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for gastric neoplasms

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Background: The discontinuation of antithrombotic drugs is recommended during endoscopic submucosal dissection (ESD) for gastric neoplasms; however, controversy remains as to whether antithrombotic drugs are risk factors for postoperative bleeding.

Objective: To determine the risk factors for post-ESD bleeding.

Design: Single-institution, retrospective review.

Setting: University hospital.

Patients: From June 2000 to December 2010, we treated 1192 gastric neoplasms in 1032 consecutive patients.

Intervention: The ESD procedures were performed by using the standard techniques. Antithrombotic drug therapy was principally interrupted preoperatively and was restarted when hemostasis was confirmed by second-look endoscopy.

Main Outcome Measurements: Risk factors for postoperative bleeding after ESD (early, delayed, and overall [combined] occurrence of bleeding during the first 5 postoperative days or thereafter) were analyzed by using logistic regression analysis.

Results: Among 1166 ESD-induced ulcer lesions, overall postoperative bleeding was evident in 62 lesions (5.3%); early and delayed bleeding occurred in 30 and 32 lesions (2.6% and 2.7%), respectively. Based on a multivariate analysis, a specimen size of >40 mm was the sole independent risk factor for overall bleeding. Moreover, oral antithrombotic drug therapy was selected as independent risk factor for delayed but not early bleeding, according to the multivariate analysis. The delayed bleeding rate in patients who had a specimen size of >40 mm and who used antithrombotic drugs was 11.6%.

Limitations: Retrospective design and single-site data collection.

Conclusion: Interruption of antithrombotic drug therapy may be adequate for preventing early post-ESD bleeding; however, reinitiating antithrombotic drug therapy is a significant independent risk factor for delayed post-ESD bleeding. (Gastrointest Endosc 2013;78:476-83.)

Abbreviations: EGC, early gastric cancer; ESD, endoscopic submucosal dissection; IT, insulation-tipped; JGCA, Japanese Gastric Cancer Association; NSAID, nonsteroidal anti-inflammatory drug.

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In recent years, endoscopic submucosal dissection (ESD) for gastric neoplasms has made remarkable progress, and many preliminary studies have shown the advantage of ESD over conventional EMR.[1] Because the indications for the endoscopic resection of early gastric cancer (EGC) have been expanded based on a nominal risk of lymph node metastasis, as determined from a large number of surgical EGC cases,[2] the number of patients with EGC who undergo ESD treatment has been increasing. Although ESD is now accepted as a standard treatment modality for gastric adenoma and EGC because of its efficacy,[3-5] a higher risk of procedure-related adverse events, such as postoperative bleeding and perforation, remains a serious problem. In particular, postoperative bleeding is the most common adverse event and reportedly occurs at a rate of 0.9% to 15.6%.[5-17]

Antithrombotic agents, including antiplatelet agents (eg, low-dose aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], thienopyridines, cilostazol, and sarpogrelate) and anticoagulants (eg, warfarin, heparin, and low-molecular-weight heparin) reportedly reduce the number of atherothrombotic events in at-risk individuals and are increasingly used at higher rates worldwide.[18-20] Because the most common site of significant bleeding in patients receiving oral antithrombotic agents is the GI tract, recently published expert guidelines recommend discontinuing these agents for 5 to 7 days preoperatively when higher-risk procedures, including ESD, are planned.[21-23] However, no consensus has been reached as to the optimal timing for reinitiating antithrombotic agents after ESD, and controversy exists as to whether these agents are risk factors for postoperative bleeding after ESD.[8-17]

Here, we analyzed risk factors for postoperative bleeding after ESD (early, delayed, and overall [combined] bleeding occurring during the first 5 days postoperatively or thereafter) for gastric neoplasms by using logistic regression analysis. We aimed to provide single-institution retrospective data regarding the risk of postoperative bleeding after ESD in patients receiving antithrombotic agents. This approach permitted the following issues to be addressed: (1) whether interruption of antithrombotic agents and adherence to guideline recommendations decrease the risk of bleeding during and after ESD and (2) whether reinitiation of antithrombotic agents after ESD increases the risk of delayed postoperative bleeding.

Take-home message

- Interruption of antithrombotic agent therapy and following the guideline recommendations appears to decrease bleeding during and after ESD for gastric neoplasms.
- Reinitiation of antithrombotic drug therapy seems to increase the risk of delayed postoperative bleeding.

METHODS

Patients

From June 2000 to December 2010, 1192 early gastric neoplasms (1090 early gastric cancers and 102 gastric adenomas) in 1032 consecutive patients were treated with ESD at the Yokohama City University Medical Center. We retrospectively reviewed the clinical records for all the patients after obtaining approval from the institutional review board.

The indications for ESD were determined based on endoscopic findings, including those from chromoendoscopy with indigo carmine and biopsy. We referred to the following criteria for possible node-negative early gastric cancer, as described by Gotoda et al[2]: (1) differentiated-type mucosal cancer without ulcer findings, irrespective of tumor size; (2) differentiated-type mucosal cancer with ulcer findings <3 cm in diameter; (3) minute (<500 μm from the muscularis mucosae) invasive differentiated-type submucosal cancer <3 cm in diameter; and (4) undifferentiated-type mucosal cancer without ulcer findings <2 cm in diameter. We also performed ESD for gastric adenoma that was difficult to distinguish from adenocarcinoma or that patients strongly desired to have resected. Patients with EGC that did not fall into one of the categories were excluded as candidates for ESD and received surgical resection; however, in patients with a high probability for surgical resection ($n = 21$), ESD was selected as a second choice.

Management and procedure

All patients taking antithrombotic drugs (anti-platelet and anti-coagulant drugs) usually were asked to stop the medication for 7 days before ESD if the patients were considered to be at a low risk for thromboembolism; however, high-risk patients were switched to intravenous heparin (ie, bridging therapy). Intravenous heparin was administered until 6 hours before ESD, restarted soon after ESD, and continued until discharge. The oral antithrombotic treatment was restarted when hemostasis was confirmed by second-look endoscopy. For all patients undergoing dialysis because of chronic kidney disease, the anticoagulant agent was changed to nafamostat mesylate. Patients under treatment with steroidal agents continued to take the drugs through the procedures.

All gastric neoplasms were treated with ESD by using a conventional single-channel endoscope or 2-channel endoscope and an insulation-tipped (IT) knife (KD-610L; Olympus Optical Co, Ltd, Tokyo, Japan) or an IT knife 2 (KD-611L; Olympus) as previously described.[7] Briefly, the markings along the presumed cutting line were defined according to the normal mucosa that surrounded the lesion. This was performed with a standard needle-knife at least 5 mm from the tumor. Along the presumed cutting line, we injected epinephrine solution (0.025 mg/mL in saline solution) into the submucosa, and then made