Second Look Endoscopy for Bleeding Peptic Ulcers and ESD-induced Ulcer

Kee Don Choi, M.D., Ph.D.
Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Introduction

Endoscopic resection, which includes endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is accepted as a standard treatment for early gastric neoplasm with a negligible risk of lymph node metastasis, because it is minimally invasive and safe, and provides good postoperative quality of life. Although the safety of endoscopic resection has been widely confirmed, adverse events such as perforation and bleeding are still a concern. Of these adverse events, delayed bleeding, manifesting as hematemesis or melena, may occur within 24 h-1 month from the procedure and have been reported to occur in about 3-16% of patients. Whereas immediate bleeding during endoscopic resection can be effectively controlled using various hemostatic techniques, delayed bleeding requires further emergency endoscopic interventions or transfusions. Therefore, prevention of delayed bleeding is a clinically important issue. A recent meta-analysis of patients with peptic ulcer bleeding showed the effectiveness of second-look endoscopy. Rebleeding was significantly decreased by a routine second-look endoscopy (OR 0.55; 95% CI, 0.37-0.81), surgery (OR 0.43; 95% CI, 0.19-0.96), but not mortality (OR 0.65; 95% CI, 0.26-1.62). Nonetheless, the only included trial in which high-dose proton pump inhibitors (PPIs) were used did not show any benefit of second look endoscopy. Because second-look endoscopy was suggested to reduce rebleeding rates in peptic ulcer bleeding, it was thought to be effective at reducing post-ESD bleeding and was empirically performed after gastric ESD. The use of prophylactic hemostasis after ESD was also based on the Forrest classification, extrapolated from peptic ulcer cohorts. The role of the Forrest classification had not been validated in post-ESD ulcer.

Second-look endoscopy after ESD

We evaluated the delayed bleeding rate according to the Forrest classification: the rate of late delayed bleeding when non-bleeding visible vessels were identified (Forrest IIa) but not treated during second-look endoscopy after ESD, in comparison with Forrest IIb, IIc, and III lesions. Between July 2011 and February 2012, 706 lesions in 656 consecutive patients who underwent second-look endoscopy performed on the second day after ESD were prospectively investigated. Proton-pump inhibitor was administered intravenously from the morning of the day of the procedure, followed by an oral proton-pump inhibitor for 4-8 weeks. Post-ESD coagulation
was performed in all cases. All patients underwent second-look endoscopy on day 2 post-ESD. During second-look endoscopy, hemostatic therapy was performed only on Forrest Ia and Ib lesions. If Forrest IIa, IIb, IIc, or III lesions were identified at second-look endoscopy, they were not treated. All patients were evaluated in an outpatient clinic one month after ESD with repeat hemoglobin concentrations measured. Median specimen size was 40 mm. At second-look endoscopy, 8.9% of cases had Forrest I lesions that were treated without any further bleeding post-discharge. Forrest IIa lesions were identified in 8.8%, Forrest IIb in 16.9%, and Forrest IIc/III in 65.5% of cases. Overall, delayed bleeding occurred in 13.4% of cases, whereas late delayed bleeding (after second-look endoscopy, within 1 month of ESD) occurred in 4.1% of cases; all were controlled with endoscopic methods (coagulation/clipping) without any need for surgical interventions. The focus of delayed bleeding did not correspond well to bleeding stigmata in second-look endoscopy; among the 18 lesions with late delayed bleeding, only two lesions with an adherent clot (Forrest IIb) and flat pigmented spot lesions (Forrest IIc) on second-look endoscopy were responsible for the delayed bleeding, and 14 cases occurred in other locations where no bleeding stigmata were seen at the time of the second-look endoscopy. In the other 11 cases, which were assessed in other hospitals, the bleeding site could not be identified because of a lack of data. Most significantly, there was no difference in the late delayed bleeding rate between Forrest IIa (3.2%), Forrest IIb (4.2%), and Forrest IIc/III (4.8%) lesions ($p = 1.00$). Larger specimen size was further confirmed as a risk factor for delayed bleeding. According to univariate analysis, resection size was the only factor that exhibited a trend toward prediction of late delayed bleeding (45 vs. 40 mm, $p = 0.08$). Of the 63 cases with Forrest I lesions, only 11 patients (17.5%) showed clinical manifestations such as melena, hematochezia, hematemesis, dizziness, and diaphoresis. Among eight cases with Forrest Ia lesions, clinical manifestations were noted in five patients (62.5%). This was the first prospective study that supports the hypothesis that prophylactic treatment of non-bleeding visible vessels does not influence delayed bleeding rates post-gastric ESD. These results suggest that the Forrest classification cannot be applied to post-endoscopic resection ulcers for prediction of delayed bleeding.

One prospective randomized clinical trial showed that among 182 patients (74 patients assigned to the second-look endoscopy group and 81 patients assigned to the no second-look endoscopy group), 20 patients (16.2%) in the second-look endoscopy group and 9 (11.1%) in the no second-look endoscopy group experienced post-ESD bleeding (defined as signs of bleeding from 24 h to 4 weeks after the procedure). The frequency of post-ESD bleeding was not significantly different between the two groups ($P = 0.66$). A recent multicenter prospective randomized trial also showed non-inferiority of the non-second-look endoscopy group in terms of post-ESD bleeding. Patients with a solitary gastric neoplasm were enrolled. Exclusion criteria were previous esophagogastric surgery or radiation therapy; perforation and the administration of antithrombotics, steroids or non-steroidal anti-inflammatory drugs. All patients took 10 mg of sodium rabeprazole once daily starting the day before ESD and for at least 4 weeks thereafter. All patients were observed at follow-up clinic visits for 4 weeks post-ESD. The incidences of post-ESD bleeding were 5.4% and 3.8% in the second-look endoscopy and non-second-look endoscopy groups, respectively; non-inferiority of the non-second-look endoscopy group compared with the second-look endoscopy group was confirmed with an absolute risk difference of -1.6% (95% CI -6.7% to 3.5%, one-sided $p < 0.001$). In a comparison between the groups with and without prophylactic coagulation during second-look endoscopy, the proportion of patients with post-ESD bleeding was similar even when prophylactic coagulation was performed. The reasons why de-
layed bleeding occurred proposed by authors included unrecognized arteries that were not coagulated during second-look endoscopy, thick arteries that were not coagulated completely during second-look endoscopy, air insufflation and prophylactic coagulation that may have induced tissue damage during second-look endoscopy.\textsuperscript{6}

One of the major differences between post-endoscopic resection ulcers and peptic ulcers lies in the conditions surrounding the ulcer formation.\textsuperscript{7} Peptic ulcers are usually created under low pH, whereas post-endoscopic resection ulcers are created under relatively high pH due to the proton-pump inhibitor premedication. Post-ESD ulcers would heal faster than peptic ulcers.

**Conclusions**

When bleeding and non-bleeding visible vessels are sufficiently treated during the ESD procedure and perioperative proton pump inhibitors are administered, second-look endoscopy after gastric ESD is not routinely recommended for patients without high bleeding risks. Risk stratification is needed to identify the patients at greatest risk for delayed bleeding in order to develop criteria for second-look endoscopy. Risk factors for delayed bleeding includes larger specimen size (> 40 mm), older age, extended duration of procedures, use of antithrombotic drugs, high grade histology, and the presence of submucosal fibrosis during ESD.\textsuperscript{4,8} A prospective study is warranted for evaluation of the role of second-look endoscopy in patients with high bleeding risk.

**References**