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Gastrointestinal Tract

Risk factors of the rebleeding according to the patterns of nonvariceal upper gastrointestinal bleeding

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Original Article

ABSTRACT

Background/Aims: Despite of successful endoscopic hemostasis of nonvariceal upper gastrointestinal bleeding (NGIB), rebleeding rate has not decreased. The aim of this study was to identify risk factors for rebleeding after endoscopic hemostasis in patients with NGIB according to bleeding patterns.

Materials and Methods: A retrospective analysis was performed on the consecutive patients with NGIB in whom successful primary endoscopic hemostasis had been achieved at three university hospitals in Korea. All patients underwent endoscopic treatment with hemoclips, epinephrine injection, argon-plasma coagulation, or its combinations within 12 h.

Results: A total of 198 patients were studied. The male-to-female ratio was 3:1. Mean age was 60.7±14.9 years. Rebleeding occurred in 41 cases (20.7%). Median day of rebleeding after endoscopic therapy was 2.0 days. Overall mortality rate was 5.1%. Risk factors for rebleeding were inpatients [odds ratio (OR) 2.61, 95% confidence interval (CI): 1.05-6.46, p=0.038) and Forrest Ib (OR=2.73, 95% CI: 1.15-6.47, p=0.023) by multivariate regression analysis.

Conclusion: Despite of successful emergent endoscopic therapy for NGIB, rebleeding occurred in 17.7% within a week. Endoscopic treatments should be more carefully performed for patients in hospitalization or patients with active oozing.

Keywords: Risk factors, gastrointestinal hemorrhages, therapeutics, endoscopy

INTRODUCTION

The incidence of upper gastrointestinal bleeding has been decreasing over the past two decade (1-3). Peptic ulcer bleeding is most common cause of acute hemorrhage from upper gastrointestinal tract, and carries an overall mortality 5%-11% (3-6). Advances in endoscopic management can provide effective control of bleeding for nonvariceal upper gastrointestinal bleeding (NGIB) (7). Endoscopic therapies including injection, thermal treatment, hemoclips, either alone or in combination with other methods, are superior to intravenous proton-pump inhibitors (PPIs) (8). The risk factors for rebleeding such as hemodynamic instability, comorbidities, active spurting bleeding, history of NSAID intake, and old age have been investigated (9-11). Timing of endoscopy and second-look endoscopy have been considered to decrease the rebleeding after endoscopic hemostasis in NGIB (12,13). However, the rebleeding rates for NGIB after endoscopic therapy reported up to 16.4%, and it has not decreased in past two decades (9,14). Moreover, little is known about the bleeding patterns of the initial endoscopic therapy as a risk factor for rebleeding after successful emergent endoscopic treatment. The aim of this study was to investigate the risk factors for rebleeding after emergent endoscopic hemostasis of NGIB according to the bleeding status.

MATERIALS AND METHODS

Subjects

Consecutive patients with upper gastrointestinal bleeding who presented to three university hospitals in Korea between May 2008 and April 2011 were eligible for the study. All patients were endoscopically

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confirmed to have active or recent bleeding from gastric or duodenal ulcer. We retrospectively reviewed medical records of the clinical factors including age, sex, comorbidities, history of anticoagulants or NSAID intake, admission status (outpatient or inpatient) and initial hemoglobin level. Endoscopic factors such as location and bleeding status, rebleeding, and mortality were also investigated. We excluded the patients with esophageal variceal bleeding, Mallory-Weiss syndrome, malignant ulcers, and peptic ulcers with clean base such as Forrest III. Written informed consent was obtained from all the patients before endoscopic procedures. This study was reviewed and approved by the Institutional review board of DUIH (No. 2009-63).

Endoscopic Hemostasis

All ulcer bleedings were treated by endoscopic procedure with hemoclipping, epinephrine (1:10,000) injection, argon-plasma coagulation or its combination within 12 h of presentation. We regarded spurting or oozing bleeding, visible blood vessels, and adherent blood clots needing endoscopic management (Forrest classification Ia, Ib, IIa, and IIb) as active bleeding and only included the patients with active bleeding ulcers to the study (15). All patients intravenously received standard dose of PPI for 48 h. Then, the patients were treated with a standard dose of oral PPI for 6-8 weeks.

Definitions

Rebleeding was defined as hematemesis, significant decreased in blood pressure (<80 mmHg or 25% decreased in baseline blood pressure), >20% increase in heart rate, >2 g/dL of hemoglobin decrease within 7 days after successful endoscopic therapy and had to be confirmed by second endoscopic examination. Old age was defined as age >65 years. Primary outcome was rebleeding rate within 7 days after successful endoscopic therapy.

Statistical Analysis

We analyzed whether there are differences in terms of patients' baseline demographics, location of ulcer, ulcer bleeding pattern, endoscopic treatment modality and quality, underlying diseases, hemoglobin level, and history of medications between rebleeding group (case) and non-rebleeding group (control). A two-sample t-test was used for the comparison of mean age and the Pearson's chi-square test or Fisher's exact tests was used to compare differences for categorical variables. We estimated the odds ratio (OR) for risk of rebleeding in the different Forrest classification compared to Forrest IIb, in the ulcer located in the antrum or corpus compared to duodenal ulcer, in the different treatment modalities compared to hemoclip monotherapy, and in in-hospital bleeding compared to the outpatient bleeding by chi-square test. To evaluate the significant independent factors for rebleeding, independent variables which had a p value of <0.1 in the univariate tests were entered into a multivariate logistic regression model and adjusted by age, gender, and other variables which may be confounding factors of risks for rebleeding. ORs and 95% confidence intervals (CIs) were determined in the multivariate analysis. All p values are two-sided, and significance is indicated by a p value of <0.05. All statistical analyzes were performed using STATA software, version 10.1 (StataCorp, College Station, TX, USA).

RESULTS

Patient Characteristics

A total of 198 patients were evaluated. Male-to-female ratio was 3:1. Mean age was 60.7±14.9 years (range, 20-98). Baseline hemoglobin was 8.8±2.7 g/dL (range 2.6-17.4).

Cerebrovascular diseases were present in 20 cases (10.1%) and ischemic heart diseases were present in 14 cases (7.0%). Antiplatelet agents were administrated in 45 cases (22.6%).

Rebleeding occurred in 41 cases (20.7%). Median day of rebleeding after endoscopic management was 2.0 days (interquartile range 4 days, range 1-27 days). In-hospital mortality occurred in 10 patients (5.1%), and cause of death was ulcer bleeding in three patients (1.5%). The baseline patients' demographics and endoscopic findings between rebleeding and control group are shown in Table 1. Gastric ulcers were in 135 cases (68.2%) and 76 cases (38.4%) were located in the corpus to fundus. There were no differences in terms of age and gender between the case and control groups.

Endoscopic Hemostasis

The distribution according to the Forrest classification was 16 (8.1%), 44 (22.2%), 98 (49.5%), and 40 (20.2%) cases in the Ia, Ib, IIa, and IIb, respectively. Ulcer with Forrest Ib was significantly associated with rebleeding (p=0.039), whereas the risk of rebleeding was not increased in Forrest Ia, IIa. The risk for rebleeding was not different according to ulcer location, treatment modality, underlying diseases, history of NSAIDs or anticoagulants, and hemoglobin level. Thirty-six patients (16.7%) experienced peptic ulcer bleeding during hospitalization; especially, eight of these (4.1%) occurred during ICU care. The risk for rebleeding was higher in in-hospital bleeding than in outpatient bleeding (p=0.012). In addition, it tended to be lower if the endoscopic managements were performed by attending staff rather than by training fellow (p=0.104).

Risk Factors for Rebleeding

In the multivariate analysis, the risk for rebleeding was significantly increased in patients with in-hospital bleeding (OR=2.61, 95% CI:1.05-6.46, p=0.038). Ulcer bleeding with Forrest Ib was significantly associated with rebleeding (OR=2.73, 95% CI:1.15-6.47, p=0.023) (Table 2).

Table 1. Patients demographics and clinical characteristics: univariate analysis of the risk for rebleeding after endoscopic management

Variables	Rebleeding (n=41)	Control (n=157)	p
Mean age±SD, years	63.2±12.0	60.0±15.6	0.237
Old age, n (%)	21 (51.2)	72 (45.9)	0.540
Gender, n (%)			0.506
Male	29 (70.7)	119 (75.8)	
Female	12 (29.3)	38 (24.2)	
Ulcer location, n (%)			0.251
Duodenum	10 (24.4)	53 (33.8)	
Stomach	31 (75.6)	104 (66.2)	
Ulcer location, n (%)			
Duodenum	10 (24.4)	52 (33.8)	
Antrum, prepylorus	12 (29.3)	45 (29.2)	0.491
Corpus-fundus	19 (46.3)	57 (37.0)	0.162
Forrest classification, n (%)			
Ia	3 (7.3)	13 (8.3)	0.840
Ib	14 (34.1)	30 (19.1)	0.039
IIa	20 (48.8)	78 (49.7)	0.918
IIb	4 (9.8)	36 (22.9)	0.080
Treatment modality, n (%)			
Hemoclip	14 (33.3)	49 (31.2)	0.719
Epinephrine injection	3 (7.3)	15 (9.6)	1.000
Coagulation	6 (14.6)	23 (14.6)	0.998
Combination	20 (48.8)	67 (42.7)	0.486
Underlying disease, n (%)			
CVA	4 (9.8)	16 (10.2)	0.934
CAD	3 (7.3)	11 (7.0)	0.945
Hypertension	6 (14.6)	30 (19.1)	0.651
Diabetes	4 (9.8)	18 (11.5)	1.000
Medication, n (%)			
Antiplatelet agents	7 (17.1)	38 (24.2)	0.336
NSAIDs	4 (9.8)	18 (11.5)	0.757
Place, n (%)			0.012
Outpatient	28 (68.3)	134 (85.4)	
In-hospital*	13 (31.7)	23 (14.6)	
Initial hemoglobin, n (%)			0.460
<8 g/dL	18 (43.9)	59 (37.6)	
≥8 g/dL	23 (56.1)	98 (62.4)	
Quality of procedure, n (%)			
Weekend	7 (17.1)	23 (14.6)	0.807
Night	7 (17.1)	16 (10.2)	0.221
On call	9 (22.0)	34 (21.7)	0.967
By Staff	29 (70.7)	129 (82.2)	0.104

CAD: coronary artery disease; CI: confidence interval; CVA: cerebrovascular disease; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; SD: standard deviation
*included bleeding developed during ICU care

Table 2. ORs for the risk of rebleeding from a multivariate logistic regression model

Variables	ORs*	95% CI	p
Old age	1.14	0.50-2.57	0.758
Male	1.07	0.43-2.62	0.891
Location of ulcer†	1.27	0.80-2.03	0.313
Forrest Ib	2.73	1.15-6.47	0.023
Treatment modality	1.03	0.77-1.38	0.832
In-hospital bleeding	2.61	1.05-6.46	0.038
Hemoglobin < 8 g/dL	1.51	0.69-3.31	0.306
Endoscopist's experience	0.47	0.20-1.15	0.100

CI: confidence interval; OR: odds ratio
*ORs for the risk of rebleeding occurred within a week
†We used three categories of duodenum, antrum to prepylorus, and corpus to fundus

DISCUSSION

Clinical implication of rebleeding is one of the most significant predictors relating to mortality (16). In this study, we confirmed active oozing bleeding (Forrest Ib) and in-hospital bleeding was significantly associated with rebleeding in patients with active ulcer bleeding that needed urgent endoscopic management. The definition of active bleeding ulcer was heterogeneous from study to study, even though there have been several reports regarding the predictive risk factors of rebleeding in patients with active ulcer bleeding. Ulcers with spurting or oozing bleeding on endoscopy was one of the major predictors for rebleeding after initial endoscopic treatment (17). A previous study found that systolic blood pressure <100 mmHg, blood in the nasogastric tube, and visible vessel, which could suggest active bleeding, were independent predictors of rebleeding (18). Ulcers with signs of spurting or oozing bleeding and ulcers with a visible vessel are at high risk of recurrent bleeding, while the role of endoscopic therapy for ulcers with adherent blood clots remains uncertain (19). However, a randomized trial reported that combination endoscopic therapy of adherent clots significantly reduced the rebleeding rate compared with medical therapy alone (20). We performed endoscopic treatment in the most patients with adherent clots (Forrest IIb), and included these cases in the study.

Despite successful endoscopic therapy, overall rebleeding rate was 20.7%, which is similar to the result of the earlier study or somewhat higher than that of other studies (5,10,21). The exclusion of patients who experienced spontaneous hemostasis without endoscopic treatment and those who had inactive ulcers might cause increased rate of rebleeding in our study. Rebleeding was observed in 13 of the 36 patients (31.7%) in admission, and it was much higher than 14.6% of outpatient ulcer bleeding. A recent study showed that seven-day rebleeding rate was 34.6%, and thirty-day rebleeding rate was 51.1% in critically ill patients (22). Another study reported that in-hospital bleeding was one of significant risk factors for recurrent bleeding within 3 days and was the only independent risk factor for

mortality (4). Our finding that showed significantly increased rebleeding rate in in-hospital bleeding versus outpatients bleeding supports these results of earlier studies. The patients with ulcer bleeding occurred during hospitalization have higher risk of rebleeding because of comorbidities and critically ill status, and this higher risk affects clinical course and prognosis in patients with peptic ulcer bleeding. The presence of comorbidities had a higher rebleeding rate than those without comorbid disease, which is comparable to the finding of our study, even though we did not investigate underlying causes of hospitalization (23). As for risk factors for 30-day rebleeding, a large prospectively followed population of 1,264 patients hospitalized with severe peptic ulcer bleedings was conducted (6). The study demonstrated that the ulcer size (≥10 mm), a high-risk stigmata (Forrest Ia to IIb), in-patient start of bleeding, and prior GI bleeding were the risk factors for worse outcome.

The rate of rebleeding after epinephrine monotherapy has been reported relatively high, showing 13%-21% in previous studies (10,24,25). In addition, the number of patients with epinephrine monotherapy had higher in rebleeding group than in control (21). Several reports showed that hemoclip or combination therapy was superior to monotherapy with epinephrine injection or heat probe in reduction of rebleeding rate (26,27). Additional treatment after epinephrine injection reduced further bleeding and mortality when compared to epinephrine monotherapy regardless of which procedure was combined (28). Barkun et al. (8) reported a meta-analysis that compared various methods of endoscopic hemostasis for patients with peptic ulcer bleeding that exhibited high-risk stigmata. They concluded that optimal therapies included thermal therapy or clips, either alone or in combination with other methods. These previous studies are inconsistent with our result that did not show different risk of rebleeding according to treatment modalities. It may be because we preferred using hemoclip or combination therapy for endoscopically more active bleeding rather than adherent blood clots. While we performed hemoclipping alone or combination treatment for all patients with Forrest Ia, epinephrine injection or coagulation monotherapy was not done for those patients. In addition, the ORs for treatment with hemoclips with or without combination therapy were significantly lower in patients with Forrest IIa and IIb compared with Forrest Ia.

Patients aged >65 years did not have increased risk of rebleeding versus younger patients, and it is consistent with a recent study on rebleeding risk of elderly patients (age ≥65 years) compared to young patients (29). However, there have been a few conflicting reports that evaluated whether the risk of rebleeding was increased with greater age (11,30). Because older patients may have a possibility of having a more complicated comorbidity and are vulnerable to recovery from initial hemodynamic instability, they might have high risk for rebleeding and high mortality rate. Thus, further studies are needed to clarify this point. Several studies found that ulcers located on the high gastric lesser curvatures or posterior duodenal bulb had increased risks for rebleeding, which locations could be related to difficulty of accurate focusing during endoscopic management (9,17,31). In our cases, there was no significant difference of rebleeding risk according to location of ulcer. It may be caused by different distribution of treatment modalities among the locations of ulcers in our study and not dividing in detail in terms of location of ulcer due to small sample size.

Forrest Ib was predictive risk factor of rebleeding after hemostasis in present study. This finding was in contrast to the result of other study, which showed that spurting bleeding (Forrest Ia) is only a significant independent predictor of rebleeding in multiple logistic regression (32). Our finding may be related that direct focusing on bleeding site during endoscopic procedure is harder in case of oozing (Ib) bleeding than spurting (Ia). Interestingly, a previous study reported that compared with injection monotherapy, combination with hemoclipping was more effective in treating ulcers with oozing bleeding, while both were equivalent therapies in treating ulcers with spurting bleeding (33). This report is similar to our result in that more effective endoscopic management could be needed for oozing bleeding. In addition, even though there are some differences in the studies, they are consistent in that endoscopically active bleeding and disadvantage in endoscopic procedure increase rebleeding risk.

There are several limitations to this study. First, this is a retrospective study and limited by the small sample size, particularly in the analysis of independent variables divided by more than two categories. Thus, the findings of our study should be confirmed by further large prospective studies. Second, as the part of information relating to the use of NSAIDs or anticoagulants and underlying diseases was obtained from history taking rather than from objective data, these data were vulnerable to recall bias. Third, we performed second-look endoscopy for some patients, especially those with clinical suspicion of rebleeding, rather than for all patients. Even though routine second-look endoscopy with thermal coagulation reduced recurrent ulcer bleeding in a recent meta-analysis, there is no proven evidence of benefit from second-look endoscopy for all patients with peptic ulcer bleeding (34). However, we cannot exclude the possibility of underestimation of rebleeding rate. Fourth, we did not control for ulcer size, initial hemodynamic status, and major comorbidity which were important predictors for recurrent bleeding in other studies (17,23,35). Fifth, the subjects in our study were performed different endoscopic management. Because the rate of rebleeding could be different according to treatment modalities, subgroup studies according to this point were needed. Finally, most information relating to *Helicobacter pylori* infection status and eradication, which were closely associated with recurrence of peptic ulcer bleeding, was not available; this is because the testing was usually not performed at the time of urgent endoscopy, and data relating to second endoscopy and the *H. pylori* testing were insufficient for analysis (36,37).

In conclusion, it is important to exactly perform the endoscopic procedure on correct bleeding focus for prevention of rebleeding. Moreover, endoscopic treatments should be more carefully performed for patients with active oozing bleeding occurred during hospitalization.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board of Dongguk University Ilsan Hospital (Decision Date: 28.01.2010/Decision No: 2009-63).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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