



Study of Hemorrhagic Gastroduodenal Ulcers Treated by Emergency Endoscopic Hemostasis: Comparison between the Current Situation and that before 10 Years

Nobuhiro Dan*, Kazuhisa Yamaguchi, Takafumi Otsuka, Kazuhiro Fuchinoue, Kazunori Hijikata, Tomoko Kobayashi, Yoshiro Yamamoto, Takahito Toba, Yoshinori Kikuchi and Yoshinori Igarashi

Department of Internal Medicine, Division of Gastroenterology and Hepatology, Toho University Omori Medical Center, Japan

Abstract

Objective: To conduct a comparative study of changes in terms of the endoscopic hemostasis methods used over the past 10 years and patient characteristics, in cases of Gastroduodenal ulcer treated by emergency upper gastrointestinal endoscopy in our hospital.

Methods: Patients who had undergone emergency upper gastrointestinal endoscopy in our hospital from January 2004 to December 2006 and January 2014 to December 2016 were categorized into Group A and Group B, respectively, based on the time period. The two groups were compared retrospectively by extracting the patient characteristics, hemostasis method, and various risk factors.

Results: The number of cases that required hemostatic treatment tended to decrease with time (138 cases vs. 75 cases). The mean age of patients increased in Groups A and B (59.4 years vs. 66.7 years, $p < 0.01$). *Helicobacter pylori* infection rate showed a slight declining tendency (90.0% vs. 85.0%, $p = 0.33$), but there was an increase in the number of patients taking oral nonsteroidal anti-inflammatory drugs (17.0% vs. 36.0%, $p < 0.01$) and oral antithrombotic agents (12.0% vs. 23.0%, $p = 0.02$). The endoscopic clipping method was reduced (67.0% vs. 29.0%, $p < 0.01$). The number of local ethanol injections decreased markedly (40.0% vs. 4.0% $p < 0.01$). However, there was a marked increase in the number of cases subjected to cauterization using hemostatic forceps (4.0% vs. 80.0%, $p < 0.01$).

Conclusion: While changes that took place over time did not affect *H. pylori* infection, cases treated using local injections of ethanol or clipping decreased in number, whereas cases subjected to hemostasis methods using high-frequency coagulation increased.

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*Correspondence:

Nobuhiro Dan, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Toho University Omori Medical Center, 6-11-1 Omorinishi, Ota-ku, Tokyo, 143-8541, Japan, Tel: 81-3-3762-4151; Fax: 81-3-3763-8542; E-mail: scary0118@yahoo.co.jp

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Introduction

Upper gastrointestinal bleeding is a condition commonly encountered in routine clinical practice and is believed to have an annual incidence of approximately 100 per population of 100,000. In particular, hemorrhagic Gastroduodenal ulcers are still frequently encountered in emergency endoscopy. Furthermore, Gastroduodenal ulcers have been reported to be the main cause of *Helicobacter pylori* (*H. pylori*) infection, besides the use of steroids, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and antithrombotic agents [1-4]. *H. pylori* infection causes inflammation of the gastric mucosa, is responsible for the deterioration of defense mechanisms and decreased gastric acid secretion, and causes gastric and duodenal ulcers. A number of clinical studies have demonstrated that eradication of *H. pylori* improves inflammation of the gastric mucosa, thereby removing the factor that contributes to the development of ulcers, and as a result, markedly inhibits the recurrence of ulcers. Thus, the advent of Proton Pump Inhibitors (PPI) [5] and the spread of *H. pylori* eradication treatment [6,7] are predicted to be accompanied by a decrease in upper gastrointestinal bleeding. While *H. pylori* eradication therapy has been widespread, the aging of society has led to a tendency towards an increased morbidity of underlying diseases, increased morbidity of brain and cardiovascular diseases, and increased incidence of orthopedic disorders. Various comparative tests have previously been conducted to compare the techniques used in endoscopic hemostasis, but thus far, it has been impossible to know which techniques are superior and which ones are inferior. Particularly considering initial hemostasis and re-bleeding, comparisons between the epinephrine local injection method, the pure ethanol local injection method, the heater probe method, and the

clipping method have shown no differences in terms of treatment effect [8,9]. Thus far, the clipping method has been the mainstream technique for endoscopic hemostasis. However, due to recent advances in endoscopic treatments, such as Endoscopic Submucosal Dissection (ESD), hemostasis using high-frequency coagulation for the prevention of postoperative bleeding is often used as a simple and reliable treatment method. Therefore, as times change, the characteristics of patients with hemorrhagic Gastroduodenal ulcers and the clinical features of hemostatic treatments are also presumed to change. Thus, in this study, we conducted a retrospective comparative study examining whether changes have occurred over the past 10 years in terms of the characteristics of patients with Gastroduodenal ulcer who underwent emergency upper gastrointestinal endoscopy in our hospital (age, oral medications), as well as the endoscopic hemostasis techniques.

Materials and Methods

Patients who had been tested using emergency upper gastrointestinal endoscopy in our hospital over a 3-year period from January 2004 to December 2006 and another 3-year period from January 2014 to December 2016 were categorized into two separate groups based on the treatment period. The groups comprised 562 and 467 cases in 2004-2006 and 2014-2016, respectively. The study included patients with hemorrhagic Gastroduodenal ulcers who were treated by endoscopic hemostasis, comprising 138 cases (Group A, 2004-2006) and 75 cases (Group B, 2014-2016). In this study, emergency endoscopy was defined as an endoscopy that was performed outside predetermined consultation hours and performed by the personnel on duty. The characteristics of the bleeding from peptic ulcers were classified on the basis of the Forrest Classification, namely Forrest Ia: spurting bleeding, Ib: oozing bleeding, IIa: exposed blood vessels (non-bleeding visible vessels), IIb: adherent blood clot, IIc: presence of black spots as traces of bleeding on an ulcer base, and III: clean ulcer base. Those with stage IIa and higher were treated by endoscopic hemostasis. The two groups were compared retrospectively on the basis of patient characteristics and endoscopic hemostasis methods. The study examined patient characteristics, such as age, sex, the presence or absence of *H. pylori* infection, usage or non-usage of NSAIDs, usage or non-usage of steroids, usage or non-usage of antithrombotic agents, usage or non-usage of gastric medications other than PPIs, usage or non-usage of oral PPIs, presence or absence of heart disease, presence or absence of diabetes mellitus, presence or absence of chronic renal failure, and the endoscopic hemostasis technique that was used. In our hospital, at least two endoscopists are available on call and when emergency endoscopy is thought to be necessary due to blood test results, computed tomography imaging findings, and the patient's general condition, emergency endoscopy is performed within 12 h of the hospital visit. The endoscopic hemostasis technique was selected at the discretion of the surgeon, and comprised a mechanical method, namely the endoscopic clipping method, and methods using local injections, namely local injection of pure ethanol and local injection of Hypertonic Sodium Epinephrine (HSE), argon plasma coagulation, or coagulation hemostasis using a core grasper. All patients were started on an intravenous drip infusion of a PPI or an H2-receptor antagonist (H2-RA) immediately before or after surgery. In cases where patients had been taking oral steroids, NSAIDs, or antithrombotic agents, the latter were discontinued. Statistical analysis was performed using the Mann-Whitney U-test and the Fisher's exact test, and a p-value of 0.05 or less was considered to be statistically significant. This retrospective study was conducted

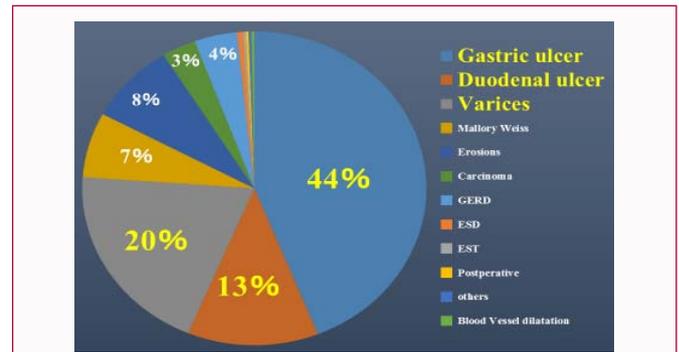


Figure 1: Pie chart showing the frequencies of diseases that caused upper gastrointestinal bleeding between 2004 and 2006. The cases of upper gastrointestinal bleeding between 2004-2006 (N=562).

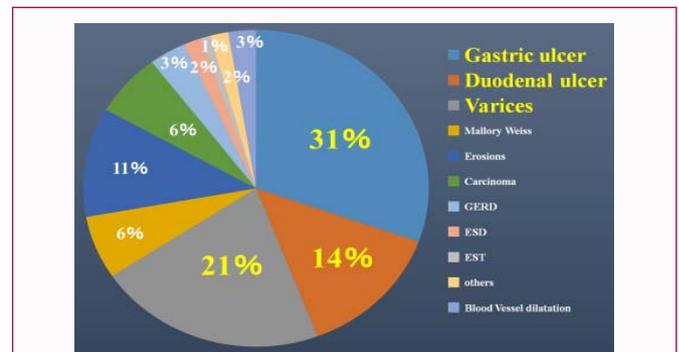


Figure 2: Pie chart showing the frequencies of diseases that caused upper gastrointestinal bleeding between 2014 and 2016. The cases of upper gastrointestinal bleeding 2014-2016 (N=467).

in accordance with the ethical principles of the Declaration of Helsinki and approved by the institutional review board of XXX Hospital and the XYZ. All patients provided signed informed consent before Endoscopy (approval number M17317).

Results and Discussion

The overall number of cases subjected to emergency endoscopy was higher during the 2004-2006 period (562 cases vs. 467 cases). In both groups, diseases consisted of gastric ulcers, esophageal varices, and duodenal ulcers in the descending order of frequency (Figure 1 and 2). The percentage of patients that required hemostatic treatment was 24.6% between 2004 and 2006 (Group A: 138 cases) and 16.1% between 2014 and 2016 (Group B: 75 cases), showing a tendency to decrease ($p < 0.05$). Comparison between Group A and B in terms of Gastroduodenal ulcers subjected to hemostatic treatment showed that Group B patients tended to be older (Table 1) (age: 59.4 years vs. 66.7 years, $p < 0.01$). In terms of sex, the proportion of women increased from Group A to Group B (22.0% vs. 36.0%, $p = 0.04$). Comparison of the two groups in terms of the bleeding sites showed that overall, gastric ulcers accounted for 77.0% in Group A and 71.0% in Group B, showing a tendency to decrease. Duodenal ulcers accounted for 23.2% and 29.3%, in Group A and B, respectively, showing a tendency to increase, but there was no significant difference. There was no difference between the two groups in terms of the lesion sites located in the upper, middle, or lower portion of the stomach (Table 2). Comparison of patient characteristics in terms of risk factors showed that the *H. pylori* infection rate tended to be lower in Group B (90.0% vs. 85.0%, $p = 0.33$), but there was no significant difference. Similarly, no change was found in terms of comorbidities, namely diabetes

Table 1: Patient characteristics (including orally-administered medications)/Background.

	Group A (N=138)	Group B (N=75)	p-value
Age(range)	59.4(13-89)	66.7 (26-88)	<0.01*
Men	108 (78%)	48 (64%)	0.03
Women	30(22%)	27(36%)	
<i>H. pylori</i>	124(90%)	64(85%)	0.33
Diabetes	19(14%)	11(15%)	0.86
Chronicrenal failure	13 (9%)	6 (8%)	0.73
Hemodialysis	9 (7%)	2 (3%)	0.37**
PPIs	6 (4%)	17 (23%)	<0.01
NSAIDs	24 (17%)	27 (36%)	<0.01
Antithrombotic drugs	16 (12%)	17 (23%)	0.02
Steroids	8 (6%)	5 (7%)	0.51**

*Mann-Whitney U-test; **Fisher's exact test

Table 2: Bleeding sites/Location.

Location	Group A (N=138)	Group B (N=75)	p-value
Stomach	106 (77%)	53(71%)	0.33
Location of lesion			
Upper	31(23%)	14(19%)	0.59
Middle	31(23%)	14(19%)	
Lower	44(31%)	25(33%)	
Duodenum	32(23%)	22(29%)	0.33

mellitus (14.0% vs. 15.0%, $p=0.86$) and chronic renal failure (9.0% vs. 8.0%, $p=0.73$), or in terms of the proportion of patients on dialysis (7.0% vs. 3.0%, $p=0.37$) (Table 1). Regarding oral medications, patients taking oral PPIs (4.0% vs. 23.0%, $p<0.01$), oral NSAIDs (17.0% vs. 36.0%, $p<0.01$), and oral antithrombotic agents (12.0% vs. 23.0%, $p=0.02$) tended to be higher in Group A than in Group B. No difference was found regarding oral intake of steroids (6.0% vs. 7.0%, $p=0.51$) (Table 1). In terms of the endoscopic hemostasis technique, hemostatic clipping (67% vs. 29%, $p<0.01$) and local injections of ethanol showed a marked decrease (40.0% vs. 4.0%, $p<0.01$) in Group B compared to Group A, but local injections of HSE solution remained unchanged (41.0% vs. 41.0%, $p=0.99$). Cauterization using hemostatic forceps showed a marked increase (4.0% vs. 80.0%, $p<0.05$) in Group B compared to Group A. Partly due to the widespread use of hemostasis by cauterization, the duration of the endoscopic hemostasis procedure tended to be shorter (37.7 min vs. 28.6 min, $p<0.01$), and the frequency of rebleeding tended to decrease (2/138 [8.7%] vs. 3/77 [3.9%], $p<0.01$) in Group B (Table 3). From the earlier to later time period, the number of cases of upper gastrointestinal bleeding that stopped tended to decrease, and in the latter group, patients tended to be older and the proportion of women increased. This may be due to the decrease in the *H. pylori* infection rate among Japanese patients, as well as the increase in the proportion of women in the Japanese population as a result of the increase in life expectancy of Japanese women. *H. pylori* infection is considered a risk factor for ulcer development [2-4]. In our study, the *H. pylori* infection rate tended to decrease but there was no significant difference. This could have affected the decrease in the incidence of ulcers, but in our study the contributing factor may have been the fact that we examined only cases which had actually been subjected to hemostatic treatment.

Table 3: Hemostasis method.

Result Hemostasis method	Group A	Group B	p-value
Clip	92 (67%)	22(29%)	<0.01
HSE*	57(41%)	31(41%)	0.29
Ethanol	56(40%)	3(4%)	<0.01
Cauterization	5(4%)	60(80%)	<0.01
Time (average range)	37.7(12-95)	28.6(9-85)	<0.01
Rebleeding	12(8.7%)	3(3.9%)	<0.01

Previous reports have shown that diabetic patients have decreased gastric acid secretion, and Gastroduodenal ulcers were frequent in diabetic patients due to the involvement of aggressive factors, such as microcirculatory disorders affecting defense factors, neuropathy, and mucus secretion disorders [10]. However, no difference has been found. In addition, no difference was found in terms of patients with chronic renal failure or those receiving dialysis, who are said to have a 10-fold higher risk of developing upper gastrointestinal bleeding as a complication [11].

In terms of the oral medications taken by the patients, a higher number of Group B patients were taking oral PPIs, NSAIDs, and antithrombotic agents. The increase in the number of patients taking oral PPIs may reflect the widespread use of PPIs and may have contributed to the decrease in the total number of cases of Gastroduodenal ulcers. However, our study failed to demonstrate that there was a decrease in the risk of developing ulcers requiring hemostatic treatment. The increase in the number of patients taking oral NSAIDs and antithrombotic agents (which are considered as risk factors for ulcer development) suggests that the need to prescribe these medications has increased due to the aging population. According to a number of reports published by various authors, the risk of developing ulcers is 5.5 times higher in elderly individuals using NSAIDs, which is more elevated than that found in young individuals (1.5 times) [12-14]. Previous reports on antithrombotic agents [15-18] have also indicated that the risk of gastrointestinal bleeding was approximately 5.5 times higher in the elderly. Patients taking oral antithrombotic agents and NSAIDs have been said to account for approximately 50% of patients with gastrointestinal bleeding in recent years [19,20], similar to the findings of our study. Patients taking oral NSAIDs and antithrombotic agents need to be placed under careful observation due to the possibility of peptic ulcer development. Endoscopic hemostasis is the first-line therapy for gastrointestinal bleeding [8], and the success rate of hemostasis in upper gastrointestinal bleeding is said to be 90% or higher. In our study, the number of patients treated using the endoscopic clipping method as a technique for endoscopic hemostasis decreased markedly, and the number of cauterization cases using hemostatic forceps increased noticeably. Hemostatic treatments using clip forceps are highly reliable methods in which the bleeding is stopped mechanically by directly applying the clip forceps. However, given that it takes time and effort to charge the device, and given that patients taking oral antithrombotic agents are more at risk of bleeding depending on the site of the clip, it can be concluded that the device is not suitable for patients showing impaired frontal view or for patients with a solid and highly fibrosed ulcer base. Furthermore, the device should only be handled by a skilled surgeon. Cauterization using hemostatic forceps [21] is also a mechanical method for hemostasis in which the surgeon holds high-frequency hemostatic forceps. Cauterization

has been increasingly used in recent years due to its simplicity and reliability. Furthermore, our study found that the time required for hemostasis was significantly shorter and the number of cases of rebleeding tended to decrease. The technique is believed to allow less experienced surgeons to achieve a highly reliable hemostatic effect [22]. In the future, it could be a technique centered on endoscopic hemostasis. Regarding treatment by local injections, the frequency of ethanol injections decreased but that of local HSE solution injections remained unchanged. The advantages of HSE solution are that it has only a weak tissue-damaging effect, it can be frequently administered through local injections, and it can also be used in the duodenum. These factors could be the reason as to why the procedure is still being performed nowadays. In a previous study of endoscopic hemostasis of upper gastrointestinal bleeding divided into a first phase consisting of a 6-year period from 2003 to 2008 (197 cases) and a second phase consisting of a 6-year period from 2009 to 2014 (305 cases), Yamaguchi et al. [22] reported changes in patients with Gastroduodenal ulcer who had been treated by endoscopic hemostasis. The *H. pylori* infection rate decreased markedly in the second phase (69.5% vs. 46.2%) highlighting a difference between their findings and those of our study. In contrast, patients taking oral antithrombotic agents increased, similar to our study (34.0% vs. 40.5%), whereas patients taking oral NSAIDs remained unchanged (79.2% vs. 80.3%). Unlike the findings of our study, diabetes (15.7% vs. 22.3%) and chronic renal failure (8.6% vs. 17.4%), which are comorbidities, were reported to show an increasing trend. As our study was conducted on cases found in the Tokyo metropolitan area and Yamaguchi et al. conducted their studies in Saga prefecture, the differences between our findings may have been due to regional differences in terms of the average age of the population, as well as differences in terms of the data collection period. However, while the *H. pylori* infection rate tended to decrease, a number of findings, such as the increase in the number of patients taking oral antithrombotic agents, were also consistent between their study and ours, indicating that those are items that should be recognized as risk factors. Regarding the method used for hemostasis, their findings were virtually the same as ours. Similar to the findings in this report, Yamaguchi showed that the proportion of patients treated using the endoscopic clipping method had decreased markedly (69.0% vs. 21.0%), and those treated by cauterization using high frequency electrical current had increased markedly (11.7% vs. 71.1%). The development and spread of devices using high-frequency hemostatic forceps may have been the factor that contributed to the similar trends observed. With future advances in endoscopic equipment and technology, as well as the development of new devices, better hemostatic outcomes could potentially be achieved with a wide range of strategic hemostatic approaches, including endoscopic hemostasis techniques used alone or in combination with other methods. Therefore, the combination of currently developed methods of hemostasis can improve the accuracy of hemostasis, and it will further improve in the future if the technique of the surgeon improves and new hemostasis methods emerge. The current study is associated with some limitations. First, this study had a small sample size. Second, due to its retrospective, single-center nature, there is limited external validity to this study. Therefore, the possibility of unintentional selection bias cannot be fully excluded.

Conclusion

In this study, changes that took place over time had little effect on *H. pylori* infection, but the increase in the number of patients taking oral antiplatelet agents and NSAIDs, as well as the increase

in comorbidities, reflected the aging of the population. Regarding the selection of the method of endoscopic hemostasis, the number of cases treated using local injections and clipping decreased, whereas hemostasis methods using high-frequency coagulation have become mainstream. When using endoscopic hemostasis methods for emergency endoscopy, the surgeon should consider their own skills and the patient characteristics as they select from a wide range of strategic hemostatic approaches, including endoscopic hemostasis techniques used alone or in combination with other methods. This will allow them to perform safer endoscopic procedures and achieve better hemostatic outcomes in the future.

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