Clinical evaluation of hemorrhagic gastroduodenal ulcer in the elderly: Is *H. pylori* infection a risk factor for hemorrhage?

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Key words

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Abstract

Background: In this study, we aimed to determine the demographic characteristics of elderly patients with gastricduodenal ulcer who had undergone endoscopic hemostasis through a comparison with younger patients.

Subjects and methods: A total of 353 patients with Forrest class I-IIa hemorrhagic gastricduodenal ulcer who underwent endoscopic hemostasis at our hospital between December 2004 and May 2010 were divided into those aged 75 years or more (old-old group; n=71; age ≥75 years) and those who were young, middle-aged, and young-old (younger group; n=282; age <75 years), and their demographic characteristics were compared.

Results: There were significantly more female patients, patients with underlying chronic renal failure, and patients using non-steroidal anti-inflammatory drugs (NSAIDs) in the old-old group than in the younger group. In addition, the prevalence of open-type atrophy in the background gastric mucosa was significantly higher in the old-old group. Although more than half the patients in each group were infected with *H. pylori*, the prevalence was significantly higher in the younger group. Of the patients who underwent endoscopic hemostasis only once, those in the old-old group constituted a significantly higher medical cost than those in the younger group. Comparison of deaths between the two groups revealed that the old-old patients were more likely to develop severe complications associated with hematemesis, such as aspiration pneumonia.

Conclusions: The observed lower prevalence of *H. pylori* infection among the elderly patients compared to the younger patients with hemorrhagic gastroduodenal ulcer suggests that other factors, such as NSAIDs use and chronic renal failure, predispose the elderly to hemorrhagic ulcer.

Introduction

In Japan, where the birth rate is decreasing while the average life expectancy is increasing, the elderly population (≥65 years) is also increasing. Such rapid aging of society is characterized by an increasing number of old-old individuals (≥75 years), which has created a super-aging society since 2007[1)]. Consequently, an increased frequency of emergency endoscopy is performed in elderly patients in emergency rooms. In this study, we divided patients with Forrest[2)] class I-IIa hemorrhagic gastricduodenal ulcer who had undergone endoscopic hemostasis at our hospital into those aged ≥75 years (old-old group) and those <75 years of age (younger group comprised of the young-old, middle-aged, and young) and compared their demographic characteristics.

I. Subjects

The subjects comprised 353 patients (269 males and 84 females; age, 63.0±13.5 years) with Forrest class I-IIa hemorrhagic gastricduodenal ulcer who were admitted to our hospital and underwent endoscopic hemostasis between December 2004 and May 2010. The endoscopist selected appropriate techniques for endoscopic hemostasis from clipping, injection therapy, and electrocoagulation, according to the condition of lesions, and these techniques were used individually or in combination. Patients who had undergone esophageal-gastric surgery, those with esophageal-gastric-duodenal malignancy, and those with metastatic tumor were excluded, and the remaining patients with gastricduodenal ulcer were consecutively examined. For evaluation of DPC cases, to ensure that only patients with hemorrhagic gastroduodenal ulcer were examined, 74 patients who developed hemorrhagic gastroduodenal ulcer during treatment of other medical conditions were excluded and the remaining 279 patients were included in the analysis.

Statistical analysis was performed using the chi-square test, Fisher's exact test, or Mann-Whitney test. Differences were considered significant at $P<0.05$. Written informed consent was obtained from all subjects prior to participation in the study.

II. Methods

The subjects were divided into those aged ≥75 years (old-old group) and those aged <75 years (younger group) and retrospectively compared to determine sex ratio, site of lesion, background gastric mucosa, history of peptic ulcer, presence or absence of diabetes and/or chronic renal failure, use or not of non-steroidal anti-inflammatory drugs (NSAIDs), warfarin, bisphosphonates and/or selective serotonin reuptake inhibitors (SSRI), *Helicobacter pylori* prevalence, and whether or not blood transfusion was performed. Chronic renal failure was defined as serum creatinine levels ≥2.0 mg/dl on repeated blood examinations. *H. pylori* infection was diagnosed when a positive result was obtained for either, or both, serum *H. pylori* IgG antibody testing (reference range <10.0 U/ml) and the urea breath test (UBT). In addition, as the Diagnosis Procedure Combination (DPC) medical payment system has been used by our institution since May 2003, the number of hospital days and cost of hospitalization were also compared between the groups.

III. Results

1) Age and sex (Table 1)

Of the 353 patients included in this study, 71 were classified into the old-old group (≥75 years) and 282 into the younger group (<75 years). The mean age was 81.3±4.9 (range, 75–95) years for the old-old group and 58.4±10.8 (range, 23–74) years for the younger group. The old-old group consisted of 45 males (63.4%) and 26 females (36.6%) while the younger group consisted of 224 males (79.4%) and 58 females (20.6%); the percentage of female subjects was significantly higher in the old-old group ($P<0.01$).

2) Site of lesion and background gastric mucosa (Table 1)

In the old-old group, 57 (80.3%) patients had gastric ulcer and 14 (19.7%) had duodenal ulcer, compared to 224 (79.4%) with gastric ulcer and 58 (20.6%) with duodenal ulcer in the younger

group. There was no significant difference in the distribution of gastricduodenal ulcer between the groups (P=0.874). For gastric ulcer patients in both groups, the stomach was divided into 3 areas: the upper third of the stomach (U), the middle third of the stomach, (M), and the lower third of the stomach (L). In the old-old group, gastric ulcer was found in area U in 21 (36.8%) patients, area M in 30 (52.6%) patients, and area L in 6 (10.5%) patients. In the younger group, the lesion was found in area U in 63 (28.1%) patients, area M in 136 (60.7%) patients, and area L in 25 (11.2%) patients. The distribution of the ulcer lesion sites was similar in both groups (P=0.433).

The examination was then performed for 224 patients with gastric ulcer without duodenal ulcer. When endoscopic images of background gastric mucosa were examined according to the Kimura/Takemoto classification criteria[3)], in the old-old group 21 (36.8%) patients were classified as closed-type, 34 (59.6%) as open-type, 0 (0%) as non-atrophic type, and 2 (3.5%) as unknown type. In the younger group, 114 (50.9%) patients were classified as closed-type, 81 (36.2%) as open-type, 18 (8.0%) as non-atrophic type, and 11 (4.9%) as unknown type. The percentage of patients classified as open-type was significantly higher in the old-old group (P<0.01).

3) History of peptic ulcer (Table 2)

A total of 107 patients had a previous history of peptic ulcer, including 17 (23.9%) patients in the old-old group and 90 (31.9%) in the younger group, with no significant difference between the groups (P=0.191).

4) Presence or absence of diabetes (Table 2)

A total of 56 patients had underlying diabetes, including 10 (14.1%) in the old-old group and 46 (16.3%) in the younger group, with no significant difference between the groups (P=0.646).

5) Presence or absence of chronic renal failure (Table 2)

A total of 35 patients had underlying chronic renal failure, including 12 (16.9%) in the old-old group and 23 (8.2%) in the younger group, with a significantly higher percentage of patients with underlying chronic renal failure in the former group ($P<0.05$). There were 21 (5.9%) patients on hemodialysis therapy, which accounted for 61.8% of all patients with underlying chronic renal failure. These patients consisted of 3 (4.2%) in the old-old group and 18 (6.4%) in the younger group, with no significant difference between the groups ($P=0.492$).

6) Use of NSAIDs (Table 2)

A total of 105 patients were using NSAIDs (of whom 16 were also using PPI or H2RA), including 32 (45.1%) in the old-old group and 73 (25.9%) in the younger group; a significantly higher percentage of patients in the former group ($P<0.01$) were using NSAIDs.

7) Use of warfarin (Table 2)

A total of 17 patients were using warfarin (of whom 4 were also using PPI or H2RA), including 4 (5.6%) in the old-old group and 13 (4.6%) in the younger group, with no significant difference between the groups ($P=0.719$).

8) Use of bisphosphonate and SSRIs (Table 2)

A total of 8 patients were using bisphosphonate, including 2 (2.8%) in the old-old group and 6 (2.1%) in the younger group, with no significant difference between the groups ($P=0.727$). Similarly, 7 patients were being treated with SSRIs, including 1 (1.4%) in the old-old group and 6 (2.1%) in the younger group, with no significant difference between them ($P=0.698$).

9) *H. pylori* prevalence (Table 2)

H. pylori prevalence was evaluated for 260 (73.7%) patients, including 38 of 71 (53.5%) in the old-old group and 222 of 282 (78.7%) in the younger group. Of them, 22 (57.9%) patients in the old-old group and 179 (80.6%) in the younger group were diagnosed as positive. Although more than half of the patients in each group were found to be infected with *H. pylori*, the prevalence was significantly higher in the younger group ($P<0.01$).

10) Blood transfusion (Table 2)

As many as 207 (58.6%) patients had received blood transfusions. They consisted of 51 (71.8%) patients in the old-old group and 157 (55.3%) patients in the younger group, with a significantly higher percentage of patients receiving blood transfusion in the former group ($P<0.05$).

11) Deaths (Table 3)

The number of deaths during hospitalization was 8 (11.3%) in the old-old group and 7 (2.5%) in the younger group; a significantly higher percentage of patients died during hospital stay in the old-old group ($P<0.01$). The breakdown of the causes of death was as follows: hemorrhagic shock in 1 patient, aspiration pneumonia in 6 patients, and prostatic cancer in 1 patient in the old-old group; and liver cirrhosis in 2 patients and hemorrhagic shock, sepsis, dilated cardiomyopathy, interstitial pneumonia, and chronic heart failure in 1 patient each in the younger group.

12) Number of hospital days/cost (Table 4)

The DPC medical payment system was applied to 279 (79.0%) patients, including 44 in the old-old group and 235 in the younger group. The number of hospital days was 13.2±6.6 days for the old-old group and 12.0±8.9 days for the younger group, with significantly more hospital days for the old-old group ($P<0.05$). The mean DPC was 45,087±23,377 points in the old-old group and 41,057±29,065 points in the younger group, indicating a tendency for medical costs to be slightly higher, but not

significantly so, in the old-old group (P=0.058). Forty-one patients in the old-old group and 205 patients in the younger group required endoscopic hemostasis only once. Within this subset of patients, the number of hospital days was significantly higher at 13.5±6.7 days for the old-old group than for the younger group at 11.3±8.3 days (P<0.01). The mean DPC was 46,059±23,764 points in the old-old group and 38,946±27,915 points in the younger group, indicating a significantly higher medical cost in the old-old group (P<0.01).

IV. Discussion

Age-related changes experienced by the elderly include changes in cardiopulmonary and hepatorenal functions as well as decreases in muscle strength, visual acuity, hearing, and cognitive function. Brain, heart, and kidney diseases associated with underlying conditions such as arteriosclerosis tend to be prevalent, and multiple oral medications including antithrombotics for treatment and prevention purposes are often used. Due to the decrease in physical function, mental responsiveness and the use of multiple oral medications, peptic ulcer in the elderly is characterized by atypical symptoms and lack of subjective symptoms, and sometimes results in fatal consequences[4,5].

In terms of sex ratio, the proportion of female patients was higher in the old-old group than in the younger group, which is consistent with previous reports[6,7] and may be related to the fact that women are less frequently affected than men by atrophic changes of the gastric mucosa. Another explanation may be a relatively higher number of women in the old-old group due to their longer life expectancy compared with men.

The elderly tend to develop gastric ulcer in the oral side of the upper body of the stomach (i.e., high gastric ulcer), which has been considered to occur due to advances in age-related atrophic changes of the gastric mucosa and shifting of the border of the fundic and pyloric gland areas to the upper part of stomach[8]. In the present study, a significantly higher proportion of gastric ulcer patients were classified as open-type in terms of background gastric mucosa, probably due to age-related atrophic change. However, no significant difference was observed in the distribution of the lesion site

between the two age groups.

More patients experienced underlying chronic renal failure in the old-old group than in the younger group. Patients with chronic renal failure are strongly predisposed to age-related arteriosclerosis and are therefore likely to have arteriosclerosis of the arterioles in the kidney and other organs, making them prone to ulcerous lesions due to a decrease in local mucosal blood flow. The percentage of patients receiving dialysis was similar between the two groups. Patients on hemodialysis therapy tend to develop gastrointestinal hemorrhage due to uremia, an increased tendency to bleed, and a decreased ability to repair tissue as well as tend to use anticoagulation drugs during hemodialysis. Moreover, they tend to exhibit a poor calcium balance and thus are strongly predisposed to developing arteriosclerosis from arterial calcification, which causes a decrease in local mucosal blood flow, damage to mucosal microcirculation (i.e., arterioles and capillaries), and subsequent ulcerous lesions in the stomach and duodenum[9].

Several studies have identified the use of NSAIDs and the presence of *H. pylori* infection as causes of gastricduodenal ulcer[10–12]. Many of the elderly have chronic joint disease and/or cardiovascular disease and thus continuously use NSAIDs and low-dose aspirin for the treatment of arthralgia and the secondary prevention of cerebrovascular disorder and ischemic heart disease[13]. In the present study, the percentage of patients using oral NSAIDs was significantly higher in the old-old group than in the younger group. The elderly carry an increased risk, approximately several tens of times higher than that of younger people, for NSAID-related ulcer[14]. In addition, the concomitant use of NSAIDs and low-dose aspirin has been shown to increase the risk of gastrointestinal hemorrhage[15]. The 2007 Gastric Ulcer Treatment Guideline recommends the use of proton pump inhibitors (PPIs), prostaglandin preparations, and high-dose H2-receptor antagonists as evidence-based medications for the prevention of NSAID-related ulcer[16]. A number of studies have demonstrated that the use of acid secretion inhibitors, such as PPI, decreases the risks for NSAID- and low-dose aspirin-related upper gastrointestinal mucosal membrane disorder and gastrointestinal hemorrhage[17–21]. Such observations suggest that the concomitant use of PPIs is preferable in elderly patients with underlying conditions who need to take oral NSAIDs. No significant difference was found in the

frequency of use of warfarin, bisphosphonates, or SSRIs between the old-old and younger groups. The use of bisphosphonates in particular has been associated with erosion and ulcer formation mainly in the gastric corpus mucosa[22,23] and shown to increase the incidence of gastric ulcer when administered in a synergistic manner with NSAID[24]. Careful monitoring is thus required for the elderly, many of whom have orthopedic diseases. The prevalence of *H. pylori*, although uncertain due to a small sample size in the old-old group, tended to be lower in the old-old group than in the younger group. This may be explained as follows. As gastric atrophy advances, the prevalence of *H. Pylori* decreases due to changes in the gastric environment caused by an increase in gastric pH. In particular, *H. pylori* was hardly present in the area affected by intestinal metaplasia[25,26]. Intestinal metaplasia often accompanies advanced gastric atrophy and causes the mucus to undergo compositional changes, which makes it difficult for *H. pylori* to survive[27]. The prevalence of *H. pylori* infection among patients with gastroduodenal ulcer usually increases with advancing age. However, when limited to hemorrhagic gastroduodenal ulcer, although *H. pylori* infection is the major cause of ulcer in the younger group, in the older group, other factors such as NSAIDs use and chronic renal failure also contribute to the development of lesions.

The proportion of deaths from ongoing aspiration pneumonia was significantly higher in the old-old group. The direct cause of death in many cases of the younger group was the worsening of the underlying disease. Age-related respiratory changes observed in the elderly include a decrease in swallowing and/or cough reflex, a tendency to develop emphysema, decreases in vital capacity, forced expiratory volume (FEV) 1.0 and %FEV 1.0, decreased pulmonary diffusing capacity, and decreased arterial oxygen pressure[28]. Therefore, elderly patients appear to carry a higher risk for aspiration during endoscopic hemostasis compared to younger ones. Moreover, even after completion of the hemostatic procedure, elderly patients are more likely to develop worsening of aspiration pneumonia because they have decreased basal physical and immune functions[29]. When performing endoscopic hemostasis in elderly patients, the operator should monitor the patient's respiratory condition not only during endoscopy but also after completion of hemostasis.

The DPC medical payment system was introduced in technologically advanced hospitals across

Japan in April 2003. Our hospital has used the system since May 2003. The overall medical treatment fee is calculated as the overall assessment fee plus the pay-by-service fee. The score for overall assessment is calculated as the score per day multiplied by the medical institution coefficient multiplied by the number of days in hospital; the score for the pay-by-service fee is taken as the score for endoscopic treatment. The cost of hospitalization is influenced by the number of hospital days, a component of the overall assessment, and the fee for endoscopic treatment corresponding to the pay-by-service fee. The occurrence of complications may thus lead to an increased cost of hospitalization due to a prolonged stay. A comparison of the number of hospital days and cost between the old-old and younger groups revealed a significantly higher number of hospital days in the old-old group when the number of hemostatic procedures was not taken into account. Similarly, a significantly higher number of hospital days and higher costs for hospitalization in the old-old group were seen when limited to patients who received a hemostatic procedure only once. As mentioned in relation to the cause of death, the elderly tend to develop complications due to decreased physical and immune function. Thus, shortening the operation time for endoscopic treatment and subsequently performing careful monitoring are required steps for reducing medical resource utilization.

Conclusion

Fatal complications associated with hematemesis can occur in the elderly. The observed lower prevalence of *H. pylori* infection among elderly patients compared to younger patients with hemorrhagic gastroduodenal ulcer suggests that other factors, such as NSAIDs use and chronic renal failure, predispose the elderly to hemorrhagic ulcer. Prophylactic use of anti-ulcer drugs is important for the elderly using NSAIDs and for those with a history of chronic renal failure. In addition, severe complications may occur gradually during and immediately after endoscopic hemostasis in the elderly. Careful monitoring should thus be performed after completion of the hemostatic procedure.

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Legends

Table 1: Backgrounds of the subjects. Percentage of female subjects was significantly higher in the old-old group ($P<0.01$), and the percentage of patients classified as open-type was significantly higher in the old-old group ($P<0.01$).

Table 2: Backgrounds of subjects. In the old-old group, there were significantly more patients with underlying chronic renal failure ($P<0.05$) and a using NSAIDs ($P<0.01$). *H. pylori* prevalence was significantly higher in the younger group ($P<0.01$). Significantly more patients received a blood transfusion in the old-old group ($P<0.05$).

Table 3: Cases of patient deaths. More patients in the old-old group died during hospital stay ($P<0.01$).

Table 4: Hospital days/cost. The old-old group had significantly more hospital days ($P<0.05$). Among patients who required endoscopic hemostasis only once, the number of hospital days and medical cost were significantly higher in the old-old group (both $P<0.01$).

Table 1:Backgrounds of the subjects

Chi-square test

		Old-old group (n=71)	Younger group (n=282)	
・Age		81.3±4.9 years	58.1±11.5 years	
・Sex	Male	45 (63.4%)	224 (79.4%)	$P<0.01$
	Female	26 (36.6%)	58 (20.6%)	
・Site of lesion	Stomach	57 (80.3%)	224 (79.4%)	$N.S.$
	Duodenum	14 (19.7%)	58(20.6%)	
		Old-old group (n=57)	Younger group (n=224)	
・Background gastric mucosa				
	Close-type	21 (36.8%)	114 (50.9%)	$P<0.01$
	Open-type	34 (59.6%)	81 (36.2%)	
	Non-atrophic	0 (0.0%)	18(8.0%)	
	Unknown	2 (3.5%)	11 (4.9%)	

Table 2:Backgrounds of the subjects

Chi-square test & Fisher's exact test

	Old-old group (n=71)	Younger group (n=282)	
・History of peptic ulcer	17 (23.9%)	90 (31.9%)	*N.S.*
・Diabetes	10 (14.1%)	46 (16.3%)	*N.S.*
・Chronic renal failure	12 (16.9%)	23 (8.2%)	$P<0.05$
・NSAIDs	32 (45.1%)	73 (25.9%)	$P<0.01$
・Warfarin	4 (5.6%)	13 (4.6%)	*N.S.*
・Bisphosphonate	2 (2.8%)	6 (2.1%)	*N.S.*
・SSRI	1 (1.4%)	6 (2.1%)	*N.S.*
・Blood transfusion	51 (71.8%)	156 (55.3%)	$P<0.05$
	Old-old group (n=38)	Younger group (n=222)	
・*H. pylori*	22 (57.9%)	177(78.7%)	$P<0.01$

Table 3:The causes of patients death

Fisher's exact test

	Old-old group (n=71)	Younger group (n=282)	
・Deaths			
・Total	8 (11.3%)	7 (2.5%)	$P<0.01$
・Multiple organ failure from bleeding	1 (1.4%)	1 (0.4%)	$N.S.$
・Aspiration pneumonia	6 (8.5%)	0 (0.0%)	$P<0.05$
・Liver cirrhosis	0 (0.0%)	2 (0.7%)	$N.S.$
・Sepsis	0 (0.0%)	1 (0.4%)	$N.S.$
・Interstitial pneumonia	0 (0.0%)	1 (0.4%)	$N.S.$
・Dilated cardiomyopathy	0 (0.0%)	1 (0.4%)	$N.S.$
・Prostate cancer	1 (1.4%)	0 (0.0%)	$N.S.$
・Acute exacerbation of chronic heart failure	0 (0.0%)	1 (0.4%)	$N.S.$

Table 4:Hospital days/cost(DPC)

Mann-Whitney's U test

Patients who required no treatment for other conditions	Number of hospital days	Old-old group (n=44) 13.2±6.6	Younger group (n=235) 12.0±8.9	$p<0.05$
	NHI point	45087±23377	41057±29065	$p=0.058$
Patients who required no treatment for other conditions and received a hemostatic procedure only once	Number of hospital days	Old-old group (n=41) 13.5±6.7	Younger group (n=205) 11.3±8.3	$p<0.01$
	NHI point	46059±23764	38946±27915	$p<0.01$