Retrospective Cohort Study

Gastroduodenal ulcer bleeding in elderly patients on low dose aspirin therapy

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AIM
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METHODS
A total of 1105 patients with hemorrhagic gastroduodenal ulcer treated in our hospital between January 2000 and March 2016 were grouped by age and drugs used, and these groups were compared in several factors. These groups were compared in terms of length of hospital stay, presence/absence of hemoglobin (Hb) decrease, presence/absence of blood transfusion, Forrest I, percentage of Helicobacter pylori infection, presence/absence of underlying disease, and percentage of severe cases.

Abstract

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RESULTS
The percentage of blood transfusion (62.6% vs 47.7%, P < 0.001), Hb decrease (53.8% vs 40.8%, P < 0.001), and the length of hospital stay (23.5 d vs 16.7 d, P < 0.001) were significantly greater in those on drug therapy. The percentage of blood transfusion (65.3% vs 47.8%, P < 0.001), Hb decrease (54.2% vs 42.1%, P < 0.001), and length of hospital stay (23.5 d vs 17.5 d, P < 0.001) were significantly greater in the elderly. In comparison with the LDA monotherapy group, the percentage of severe cases was significantly higher in the LDA combination therapy group when elderly patients were concerned (16.1% vs 34.0%, P = 0.030). Meanwhile, among those on LDA monotherapy, there was no significant difference between elderly and non-elderly (16.1% vs 16.0%, P = 0.985).

CONCLUSION
A combination of LDA with antithrombotic drugs or non-steroidal anti-inflammatory drugs (NSAIDs) contributes to aggravation. And advanced age is not an aggravating factor when LDA monotherapy is used.

Key words: Hemorrhagic gastroduodenal ulcer; Low-dose aspirin; Antithrombotic drugs; Elderly patients; Proton pump inhibitor

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Core tip: A total of 1105 patients with hemorrhagic gastroduodenal ulcer were grouped by age and drugs used, and these groups were compared in several factors. Among the elderly (over 70 years), the rate of severe conditions was significantly higher in patients receiving low-dose aspirin (LDA) combination therapy than in those receiving LDA monotherapy. Meanwhile, in the LDA monotherapy group, no significant difference in the rate of severe conditions was observed between elderly and non-elderly patients. This result suggests LDA combination therapy contributes to the aggravation, and advanced age is not an aggravating factor when LDA monotherapy is used.

Fukushi K, Tominaga K, Nagashima K, Kanamori A, Izawa N, Kanazawa M, Sasai T, Hiraishi H. Hemorrhagic gastroduodenal ulcer in the elderly patients on low dose aspirin therapy. World J Gastroenterol 2018; 24(34): 3908-3918 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i34/3908.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i34.3908

INTRODUCTION
Japan’s population is aging rapidly. According to the White Paper on Aging Society 2016, Cabinet office, Government of Japan, people 65 years of age or older accounted for 27.3% of the total population as of October 1, 2016. Under a situation where cerebrovascular disorder and ischemic heart disease have been increasing, clinical evidence of the usefulness of low-dose aspirin (LDA) as a means of secondary prevention of such diseases has often been reported and the frequency of its use has increased[1-3]. However, Pearson et al[4] reported that the use of LDA caused an approximately 20% decrease in cardiovascular events in comparison with the control group, but its use was associated with a 2.7-fold higher risk of gastrointestinal hemorrhage. Serious adverse responses to LDA include gastrointestinal mucosal disorder and gastrointestinal hemorrhage; therefore, there is a concern for an increase and aggravation of these conditions[5-9]. Based on the Special Report of Vital Statistics in Japan issued by the Ministry of Health, Labour and Welfare, data in 1996, when the number of patients with gastric ulcer was the greatest after 1990, and the latest available data in 2014 were compared in regard to the number of patients with gastroduodenal ulcer and the number of deaths from gastroduodenal ulcer. The number of patients and the number of deaths in 1996 were 1124000 and 4514, respectively, whereas the corresponding numbers were 311000 (28% of the number in October 1996) and 2770 (61% of the number in 1996) in October in 2014. Although the number of patients with ulcer was decreased to less than one third, there was no marked decrease in the number of deaths from ulcer. This indicates that the clinical picture of ulcer became more severe, presumably reflecting an increase in the incidence of ulcer due to the increased use of antithrombotic drugs including LDA in the aging society, whereas the rate of infection with Helicobacter pylori (H. pylori) has decreased, and the rate of H. pylori eradication has increased, in the younger generation in recent years[10]. In particular, combined use of LDA and non-steroidal anti-inflammatory drugs (NSAIDs) and advanced age serve as risk factors for the occurrence of LDA-induced ulcer and also increase the risk of hemorrhage and aggravation[11-14]. According to a sub-analysis by Nikolsky et al[15], who investigated the presence/absence and prognosis of gastrointestinal hemorrhage within 30 d of hospitalization due to acute coronary syndrome, the overall mortality at 1 year was significantly higher in patients who had gastrointestinal hemorrhage within 30 d of hospitalization than in those who did not. In this study, we paid attention to patients who were on oral LDA therapy, a clinically important issue, among elderly patients with hemorrhagic gastroduodenal ulcer due to oral antithrombotic therapy to elucidate the clinical characteristics of this condition and analyzed patients with hemorrhagic gastroduodenal ulcer treated in our hospital in relation to age and medication.

MATERIALS AND METHODS
Patients
This study included 1105 patients who had hematemesis, melena, or acute anemia symptoms due to hemorrhagic gastroduodenal ulcer [801 (72.5%) cases of gastric ulcer and 304 (27.5%) cases of duodenal ulcer] and who underwent emergency endoscopic hemostasis because
upper gastrointestinal hemorrhage was suspected in Dokkyo Medical University Hospital between January 2000 and March 2016. These 1105 patients comprised inpatients, outpatients at the emergency department, and emergency transport patients.

**Patient management**

The rules of our response to hemorrhagic gastric and duodenal ulcers are as follows: (1) hemostasis is rapidly and continuously performed by a gastroenterologist; (2) the hemostasis procedure uses clipping or argon plasma coagulation at the operator’s discretion, and a local injection of hypertonic saline epinephrine (HSE) and thrombin spray are employed if necessary without restriction to a single technique; (3) blood transfusion is indicated for patients with hemoglobin (Hb) ≤ 70 g/L or patients in shock; (4) intravenous administration of a proton pump inhibitors (PPIs) is given promptly after endoscopic hemostasis, and it is switched to oral administration after initiation of oral feeding; (5) oral feeding is begun with thin rice gruel if blood test shows no progression of anemia and if no bleeding is found by second-look endoscopy performed within 0–5 d; and (6) when the patient is on antithrombin drug or anticoagulation drug therapy, discontinuation of the drug therapy is considered in consultation with a doctor of the specialty concerned after evaluating the risk of thrombosis, embolism, and bleeding.

**Definition**

Patients aged 70 years or older were defined as elderly, and those aged younger than 70 years were defined as non-elderly. A significant decrease in the Hb level was defined as a decrease of at least 20 g/L in comparison with the Hb level in the previous blood examination or as an Hb level of 70 g/L or lower in the absence of available data in the previous blood examination. As for *H. pylori* infection, it was possible that the urea breath test would provide a false-negative result because of the PPIs administered. Therefore, *H. pylori*-IgG antibody was measured in all subjects, and antibody titers of 10 U/mL or more were defined as positive. Multiple ulcer was defined by the presence of two or more ulcer lesions. Rebleeding was defined by the endoscopic evidence and additional treatment of hemorrhage within 72 h after the implementation of the initial endoscopic hemostasis. Hemorrhage found after more than 72 h was defined as recurrence. Severe cases were defined as cases with at least two of the following three items: (1) an Hb decrease of 20 g/L or more or blood transfusion; (2) hospital stay of at least 30 d; and (3) rebleeding, surgery, interventional radiology (IVR), or death. The rules of our response to hemorrhagic gastric and duodenal ulcer were 801 (72.5%) and 304 (27.5%), respectively. Table 1 shows the characteristics of the patients with gastroduodenal ulcer examined in this study. These patients were classified into those with oral drug therapy (medicated group) and those without oral drug therapy (non-medicated group). The medicated group comprised 474 (42.9%) patients, whereas the non-medicated group comprised 631 (57.1%) patients. To investigate factors for aggravation of the condition in elderly patients, the elderly group was further divided into those with and without severe conditions for comparison.

**Statistical analysis**

For statistical analysis, χ² test, t test, and Mann-Whitney U test were used. Logistic regression analysis was also performed using hospital stay of 20 d or more as a dependent variable. SPSS version (IBM SPSS Statistics 21; IBM Japan, Ltd.) was used for statistical analysis processing. This study was approved by the life ethics committee of our institution.

**RESULTS**

**Patient characteristics in each group**

The numbers (percentages) of patients with gastric ulcer and duodenal ulcer were 801 (72.5%) and 304 (27.5%), respectively. Table 1 shows the characteristics of the patients with gastroduodenal ulcer examined in this study. These patients were classified into those with oral drug therapy (medicated group) and those without oral drug therapy (non-medicated group). The medicated group comprised 474 (42.9%) patients, whereas the non-medicated group comprised 631 (57.1%) patients. These patients were also divided into elderly and non-elderly patients. There were 436 (39.5%) and 669 (60.5%) elderly and non-elderly patients, respectively. Table 2 shows the patient characteristics of each group.

**Comparison between the medicated group and non-medicated group**

Types of oral medication included 474 patients (113 cases of LDA monotherapy and 157 cases of NSAIDs
monotherapy and 113 cases of clopidogrel monotherapy and 10 cases of cilostazol monotherapy and 40 cases of warfarin monotherapy and 4 cases of DOACs monotherapy, and 118 cases of combination therapy). When the medicated and non-medicated groups were compared, the percentage of patients with blood transfusion (62.6% vs 47.7%; \( P < 0.001 \)) and the percentage of patients with 

Table 1 Baseline characteristics \( n (%) \)

| Items                              | All cases \( n = 1105 \) |
|------------------------------------|---------------------------|
| Mean age (yr)                      | 64.37                     |
| Sex                                |                           |
| Male                               | 823 (74.5)                |
| Female                             | 282 (25.5)                |
| Mean length of hospital stay (d)   |                           |
| After endoscopic treatment         | 19.8                      |
| Overall                            | 22.1                      |
| Hb (mg/L)                          | 87.4                      |
| Hb decrease                        | 509 (46.1)                |
| Blood transfusion                  | 594 (53.8)                |
| H. pylori positive                 | 857 (77.6)                |
| Endoscopic findings                |                           |
| Ulcer                              |                           |
| Single                             | 279 (68.7)                |
| Multiple                           | 346 (31.3)                |
| Forrest classification             |                           |
| I a                                | 88 (8.0)                  |
| I b                                | 171 (15.5)                |
| II a                               | 525 (47.5)                |
| II b                               | 142 (12.8)                |
| III                                | 179 (16.2)                |
| Rebleeding                         | 82 (7.4)                  |
| Recurrence                         | 60 (5.4)                  |
| Surgery/IVR/death                  | 32 (2.9)                  |
| Prophylactic anti-ulcer medication |                           |
| None                               | 749 (67.8)                |
| PPI                                | 88 (8.0)                  |
| H2RA                               | 117 (10.6)                |
| MP                                 | 152 (13.6)                |
| Comorbidty                         |                           |
| Cardiac disease                    | 254 (22.9)                |
| Cerebrovascular disorder           | 180 (16.3)                |
| Renal failure                      | 125 (11.5)                |
| DM                                 | 198 (17.9)                |
| Orthopedic disorder               | 162 (14.7)                |
| History of ulcer                   | 317 (28.7)                |

Hb: Hemoglobin; H. pylori: Helicobacter pylori; IVR: Interventional radiology; PPI: Proton pump inhibitor; H2RA: Histamine-2 receptor antagonists; MP: Mucosal protectant; DM: Diabetes mellitus.

Comparison between elderly and non-elderly patients
The results of the comparison between elderly and non-elderly patients are shown in Figure 1B. The percentage of patients with blood transfusion (65.3% vs 47.8%; \( P < 0.001 \)), percentage of patients with Hb decrease (54.2% vs 42.1%; \( P < 0.001 \)), and percentage of patients with rebleeding, surgery, IVR, or death (11.7% vs 6.6%; \( P = 0.033 \)) were significantly higher among elderly patients. The length of hospital stay after the implementation of endoscopic treatment (23.3 d vs 17.5 d; \( P < 0.001 \)) and the overall length of hospital stay (26.9 d vs 19.0 d; \( P < 0.001 \)) were significantly longer among elderly patients.

Comparison between patients on LDA monotherapy and those on LDA combination therapy
Patients in the medicated group were divided into those with LDA monotherapy or LDA combination therapy and elderly or non-elderly patients, and the percentage of severe cases and the length of hospital stay were examined. Patients in the medicated group were divided into groups A (elderly receiving LDA monotherapy), B (elderly receiving LDA combination therapy), C (non-elderly receiving LDA monotherapy), and D (non-elderly receiving LDA combination therapy). Elderly patients, a population that may have clinical issues, were investigated by comparing groups A and B. In addition, the age-related tendency in the LDA monotherapy group was examined by comparing groups A and C (Table 3). The results are shown in Figures 2 and 3. A comparison between groups A and B revealed that the length of hospital stay tended to be longer in group B than in group A (group A 20.0 d vs group B 25.5 d; \( P = 0.194 \)). Rebleeding, surgery, IVR, and death were more frequent in group B than in group A (group A 3.2% vs group B 14.6%; \( P = 0.038 \)). In comparison with group A, the percentage of severe cases was significantly higher in group B (group A 16.1% vs group B 34.0%; \( P = 0.030 \)). A comparison of groups A and C showed no significant difference in the length of hospital stay or the percentage of severe cases between the two groups.

Risk factor for aggravation in elderly patients
In the elderly group, severe cases defined by rebleeding or fatal outcome were compared with non-severe cases ending in discharge in remission to determine risk factors for aggravation (Table 4). There was a significant intergroup difference in regard to Hb decrease (70.0% vs 52.1%; \( P = 0.017 \)), blood transfusion (88.0% vs 62.4%; \( P < 0.001 \)), Forrest I (45.1% vs 22.9%; \( P = 0.001 \)), HSE use (9.6% vs 21.6%; \( P = 0.010 \)), and diabetes mellitus (29.4% vs 16.9%; \( P = 0.030 \)). Multivariate logistic regression analysis revealed blood transfusion [odds ratio (95%CI): 3.59 (1.42-9.06); \( P = 0.007 \)], Forrest I [odds ratio (95%CI): 2.40 (1.07-5.45); \( P = 0.047 \)], and diabetes mellitus [odds ratio (95%CI): 2.02 (1.00-4.06); \( P = 0.049 \)] as independent risk factors.

DISCUSSION
Aspirin exerts an anti-inflammatory action by inhibiting the activity of COX-1 and COX-2 as well as an antplatelet action by inhibiting intraplatelet COX-1 and suppressing the production of thromboxane A2, a promoter of plate-
let aggregation. It is known that aspirin inhibits gastric mucosal protection through COX inhibition. In addition, aspirin takes a lipid-soluble nonionic form under the intragastric acidic condition and accumulates in the cell to cause injury directly, with increased drug permeability. Case-control studies conducted in Europe and North America showed that gastrointestinal mucosal disorder would increase the risk of upper gastrointestinal final hemorrhage about 2- to 4-fold\textsuperscript{[16-17]}. Sakamoto \textit{et al}\textsuperscript{[18]} reported based on the results of a case-control study in Japanese people that the odds ratio of upper gastrointestinal hemorrhage due to LDA was 8.2 (95\%CI: 3.3-20.7). In addition, studies that examined the prognosis in relation to the presence or absence of the increasingly prevalent gastrointestinal hemorrhage after acute coronary syndrome or acute stroke found

\begin{table}
\centering
\caption{Characteristics of the medicated vs non-medicated groups and the elderly vs non-elderly groups.} 
\begin{tabular}{lccc}
\hline
& Medicated group & Non-medicated group & \textit{P} value \\
& \((n = 474)\) & \((n = 631)\) & \\
\hline
Mean age (yr) & 69.7 & 60.4 & < 0.001 \\
Sex (male:female) & 352:122 & 491:140 & < 0.001 \\
Hb (mg/L) & 82.6 & 91.1 & < 0.001 \\
\textit{H. pylori} infection (positive:negative) & 73.5\% (324:117) & 89.3\% (533:64) & < 0.001 \\
Single ulcer & 61.4\% (291:183) & 74.2\% (468:163) & < 0.001 \\
Forrest I & 25.7\% (122:352) & 21.7\% (137:494) & 0.118 \\
Anti-ulcer medication & 52.1\% (247:227) & 17.3\% (109:522) & < 0.001 \\
Underlying disease & & & \\
Cardiac disease & 43.0\% (204:270) & 7.9\% (50:581) & < 0.001 \\
Cerebrovascular disorder & 25.9\% (123:351) & 4.0\% (25:606) & < 0.001 \\
Renal disorder & 16.5\% (78:596) & 7.4\% (47:584) & < 0.001 \\
Respiratory disease & 13.5\% (64:410) & 8.1\% (51:50) & 0.003 \\
Orthopedic disorder & 28.9\% (137:337) & 4.0\% (25:606) & < 0.001 \\
History of ulcer & 21.9\% (104:370) & 28.7\% (181:450) & < 0.001 \\
Hypertension & 41.4\% (196:278) & 25.9\% (158:473) & < 0.001 \\
DM & 21.7\% (103:371) & 15.1\% (95:536) & 0.004 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Characteristics of low dose aspirin therapy.} 
\begin{tabular}{lcccc}
\hline
& Elderly patients & Non-elderly patients & \textit{P} (A vs B) & \textit{P} (A vs C) \\
& \((n = 63)\) & \((n = 49)\) & & & \\
\hline
Mean age (yr) & 80.0 & 56.3 & 60.7 & 0.989 & < 0.001 \\
Sex (male:female) & 43:20:00 & 34:14:00 & 45:04:00 & 44:06:00 & 0.770 & 0.003 \\
Mean length of hospital stay (d) & 21.2\% (62:27) & 21.2\% (62:27) & 21.2\% (62:27) & 0.194 & 0.332 \\
Overall & 20.1 & 28.4 & 23.0 & 27.3 & 0.120 & 0.685 \\
Hb (mg/L) & 84.0 & 84.0 & 89.0 & 86.0 & 0.948 & 0.307 \\
Hb decrease (present:absent) & 43.5\% (27:35) & 53.2\% (25:22) & 49.0\% (24:25) & 67.4\% (31:15) & 0.702 & 0.569 \\
Blood transfusion (present:absent) & 61.3\% (38:24) & 66.0\% (31:16) & 38.8\% (19:30) & 58.7\% (27:19) & 0.690 & 0.018 \\
\textit{H. pylori} infection (positive:negative) & 77.4\% (48:14) & 68.3\% (28:13) & 80.8\% (39:88) & 68.8\% (33:15) & 0.303 & 0.664 \\
Forrest I (1:II; III) & 23.8\% (15:48) & 27.1\% (13:35) & 16.3\% (8:41) & 20.0\% (10:40) & 0.694 & 0.331 \\
Ulcus (multisingle) & 42.9\% (27:36) & 39.6\% (19:29) & 22.4\% (11:38) & 46.0\% (23:27) & 0.846 & 0.024 \\
Rebleeding (present:absent) & 3.2\% (6:21) & 16.4\% (7:41) & 4.1\% (2:47) & 8.0\% (4:6) & 0.060 & 1.000 \\
Rebleeding/surgery/IVR/death (present:absent) & 3.2\% (6:21) & 14.6\% (7:41) & 4.1\% (2:47) & 8.0\% (4:6) & 0.038 & 1.000 \\
Recurrence (present:absent) & 0\% (0:63) & 4.2\% (2:46) & 8.2\% (4:45) & 4.0\% (2:48) & 0.185 & 0.034 \\
DM & 17.5\% (11:51) & 25.0\% (12:36) & 36.7\% (18:31) & 36.0\% (18:32) & 0.332 & 0.021 \\
Cardiac disease & 52.4\% (33:30) & 66.7\% (32:16) & 46.9\% (23:26) & 78.0\% (39:91) & 0.130 & 0.568 \\
Cerebrovascular disorder & 38.1\% (24:39) & 39.6\% (19:29) & 22.4\% (11:38) & 34.0\% (17:33) & 0.873 & 0.076 \\
Orthopedic disorder & 12.7\% (8:55) & 25.0\% (12:36) & 6.1\% (4:46) & 20.0\% (10:40) & 0.095 & 0.342 \\
Respiratory disease & 17.5\% (11:52) & 14.6\% (7:41) & 4.1\% (2:47) & 4.0\% (2:48) & 0.684 & 0.028 \\
Renal disease & 12.7\% (8:55) & 22.9\% (11:37) & 18.4\% (9:40) & 24.0\% (12:38) & 0.157 & 0.407 \\
History of peptic ulcer & 19.0\% (12:51) & 12.5\% (6:42) & 28.6\% (14:35) & 20.0\% (10:40) & 0.354 & 0.236 \\
Hypertension & 49.2\% (31:32) & 52.1\% (25:23) & 36.7\% (18:31) & 42.0\% (21:29) & 0.764 & 0.187 \\
Preceding anti-ulcer medication (present:absent) & 38.1\% (24:39) & 79.2\% (38:10) & 44.9\% (22:27) & 58.0\% (29:21) & < 0.001 & 0.468 \\
Preceding PPI medication & 11.1\% (7:56) & 22.9\% (11:37) & 12.2\% (6:43) & 16.0\% (8:42) & 0.095 & 0.853 \\
\hline
\end{tabular}
\end{table}

Hb: Hemoglobin; \textit{H. pylori}: Helicobacter pylori; DM: Diabetes mellitus.
that the occurrence of gastrointestinal hemorrhage after acute coronary syndrome or acute stroke would increase the overall mortality at 1 year\(^{15,19}\). This should not only alert endoscopists but also alert cardiologists and neurologists. Antiplatelet drugs other than LDA are also associated with the risk of gastrointestinal hemorrhage because they inhibit thrombogenesis, but they cause less injury to the mucosa. Clopidogrel is known to increase the risk of hemorrhage by 1.7-2.8 times; case-control studies with more than 10,000 cases showed that its risk of inducing hemorrhage is not statistically significant\(^{16,17,20,21}\). Because reports on antiplatelet drugs other than LDA are limited, accumulation of data and additional investigations in the future are awaited. The anticoagulant warfarin significantly increases the risk of upper gastrointestinal hemorrhage by about two to four times\(^{16,20-22}\). In recent years, the use of DOACs as a new treatment of venous thromboembolism and atrial fibrillation has increased. In a cohort study, Shimomura et al\(^{23}\) performed a long-term follow-up of 508 patients on oral anticoagulant therapy in whom peptic ulcer and hemorrhage were denied and calculated the incidence rate of gastrointestinal hemorrhage. As a result, acute gastrointestinal hemorrhage occurred in 8.3% of the patients during an average observation period of 31 mo, and the cumulative incidence rates of gastrointestinal hemorrhage at 5 and 10 years were reported to be 13% and 19%, respectively, which were clinically relevant. There was no significant difference in the hemorrhage risk between warfarin and DOACs\(^{24,25}\). Our present study included only four patients on DOACs therapy, and therefore DOACs were not analyzed. Because the use of DOACs is expected to increase in the future, additional investigations would be necessary.

Hallas et al\(^{16}\) reported that the risk of hemorrhage was increased 1.8-fold by LDA monotherapy, and the risk was further increased by the combined use of LDA with other drugs, e.g., 7.4-fold by combination with clopidogrel and 5.3-fold by combination with warfarin. Several studies have demonstrated bleeding risk in patients treated with a combination of LDA plus antithrombotic drugs\(^{16,23}\). The present study showed that the condition was significantly more severe in elderly patients aged 70 years or older on LDA combination therapy than in those on LDA monotherapy. Although a comparison among different drugs was not made, this study indicated that the combined use of drugs would increase the risk of hemorrhage, requiring due caution. In addition, when LDA monotherapy was used, there was no significant difference in the severity of the condition between elderly and non-elderly patients. Although oral LDA therapy poses a risk of ulceration as mentioned previously, the results of this study suggest that LDA monotherapy does not contribute to aggravation of hemorrhage in elderly patients in comparison with non-elderly patients.

Increases in the incidence of rebleeding and mortality in relation to the underlying disease and age have been reported. Rockall et al\(^{28}\) have reported that the fatality rate due to upper gastrointestinal hemorrhage was 14% (584/4412) and that the rate increased with the

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Table 4  Comparison between the severe and non-severe groups in the elderly group

| Elderly group (n = 436) | Severe cases (n = 51) | Non-severe cases (n = 385) | Univariate analysis | Multivariate analysis |
|------------------------|----------------------|---------------------------|--------------------|----------------------|
|                        | Mean age (yr)        | 79.0                      | 78.8               | 0.846                |
|                        | Sex (male:female)    | 64.7% (33:18)             | 61.8% (238:147)    | 0.689                |
|                        | Mean length of hospital stay (d) |                |                    |                      |
| After endoscopic treatment | 21.9                | 23.5                      | 0.699               |
| Overall                | 25.9                | 27.0                      | 0.823               |
| Hb (mg/L)              | 76.3                | 81.4                      | 0.113               |
| Hb decrease (present: absent) | 70.0% (35:15)     | 52.1% (198:382)           | 0.017              |
| Blood transfusion (present: absent) | 88.0% (44:6)     | 62.4% (237:143)           | < 0.001            |
| H. pylori infection (positive:negative) | 69.8% (30:13)   | 78.9% (281:75)            | 0.171               |
| Forrest ( I : II, III) | 45.1% (23:28)       | 22.9% (88:297)            | 0.001              |
| Ulcer (multiple:single) | 31.4% (16:35)       | 41.3% (159:220)           | 0.174               |
| HSE use                | 21.6% (11:40)       | 9.6% (37:348)             | 0.010              |
| DM                     | 29.4% (15:50)       | 16.9% (65:320)            | 0.030              |
| Cardiac disease        | 29.4% (15:50)       | 34.5% (133:252)           | 0.467               |
| Cerebrovascular disorder | 27.5% (14:37)      | 21.6% (83:392)            | 0.342               |
| Orthopedic disorder    | 23.5% (12:39)       | 21.3% (82:303)            | 0.716               |
| Respiratory disease    | 21.6% (11:40)       | 14.0% (54:331)            | 0.155               |
| Renal disease          | 5.9% (3:48)         | 14.0% (54:331)            | 0.105               |
| History of peptic ulcer | 23.5% (12:39)      | 17.7% (68:317)            | 0.309               |
| Hypertension           | 41.2% (21:50)       | 45.7% (176:209)           | 0.541               |
| Preceding anti-ulcer medication | 52.9% (27:24)  | 39.7% (153:232)           | 0.072               |
| Preceding PPI medication | 11.8% (6:45)       | 11.7% (45:340)            | 0.987               |

Hb: Hemoglobin; H. pylori: Helicobacter pylori; IVR: Interventional radiology; HSE: Hypertonic saline epinephrine; DM: Diabetes mellitus; PPI: Proton pump inhibitor.
presence of comorbidities such as heart failure, ischemic heart disease, and renal failure. It has also been reported that the mortality within 30 d is proportional to the prevalence of serious comorbidities[29]. In addition, some researchers reported that the Glasgow Blatchford score was the most effective predictive factor for treatment intervention and death[30,31]. Travis et al[32] investigated the risk factors for rebleeding after endoscopy and reported that non-use of PPIs, hepatic cirrhosis, heparin, and the use of epinephrine were independent factors. In this study, the condition was more likely to be more severe in elderly patients and medicated patients, indicating that aggressive treatment intervention would be necessary in such patients. In addition, when elderly patients aged 70 years or older were concerned, Hb decrease, implementation of blood transfusion, Forrest I, HSE, and a history of diabetes mellitus were found to be risk factors for a severe clinical course (rebleeding, surgery, IVR or other treatment intervention, or death). When multivariate analysis was performed, Hb decrease, implementation of blood transfusion, and a history of diabetes mellitus were identified as independent factors. In these patients, endoscopically and clinically more appropriate management including an adequate endoscopic hemostatic procedure and an aggressive second-look procedure is required.

As for management after hemostasis, both the rebleeding risk due to continued oral antithrombotic medication and the risk of developing thromboembolism due to discontinuation of antithrombotic therapy should be considered. Thus, the method of such management is a clinically relevant issue. Discontinuation of antithrombotic drugs was previously reported to be associated with a significantly higher incidence of thromboembolic events and related deaths[5,16,33-35]. The risk of recurrence of underlying disease associated

Figure 1 Comparison between 2 groups. A: Medicated and non-medicated groups; B: Elderly and non-elderly groups. Hb: Hemoglobin; IVR: Interventional radiology.
with discontinuation of LDA has also been reported to be significantly higher than the risk of recurrence of hemorrhagic gastric ulcer associated with continuation of LDA therapy. Nagata et al. have reported that a history of thromboembolism, comorbidity score, discontinuation of LDA, discontinuation of antiplatelet drugs other than aspirin, and discontinuation of anticoagulant drugs were identified as risk factors for thromboembolism and that discontinuation of LDA and anticoagulant drugs resulted in a higher risk of thromboembolism. Therefore, when treating patients, it is necessary to consider the propriety of discontinuation of medication and avoid prolonged withdrawal, in consultation with specialists such as a cardiologist or a neurologist. Elderly patients are at a high risk of rebleeding and are more likely to discontinue antithrombotic medication. In such cases, a second-look procedure should be performed aggressively, and antithrombotic medication should be resumed as soon as possible. It is also necessary to ensure that antithrombotic medication is resumed on discharge.

With regard to LDA-induced peptic ulcer, several randomized controlled trials demonstrated the secondary preventive effect of PPIs, and in Japan, an additional indication for the use of PPIs to prevent recurrence of LDA-induced ulcer was approved for the first time in
In a randomized controlled trial that included patients aged 60 years or older who had no endoscopic evidence of ulcer, esomeprazole 20 mg proved to be effective for prevention of peptic ulcer (primary prevention)\(^{[41]}\). As mentioned previously, the incidence rates of severe ulcer and drug-induced ulcer are increasing, and administration of more appropriate acid-blocking drugs including PPIs has become important. Japanese guidelines recommend the use of PPIs\(^{[42]}\). However, as demonstrated in the present study, the actual frequency of the use of PPIs is currently low, and therefore further spread of this type of drugs is necessary.

Our present study had several limitations. This was a single-center retrospective study that provided restrictive analysis. Endoscopic skills varied among different endoscopists. The definition of severe ulcer was not based on any well-known scoring system but used unique factors produced from evaluable items. The age difference between elderly and non-elderly subjects was small 54.9 years vs 78.5 years. Addition of data and another verification with participation of multiple centers are desirable.

In conclusion, when patients on LDA combination therapy and LDA monotherapy were compared, the percentage of severe cases was high in those on LDA combination therapy among elderly patients, indicating that combined use of LDA with antithrombotic drugs or NSAIDs contributes to the aggravation of hemorrhagic gastroduodenal ulcer. In the LDA monotherapy group, there was no significant difference in the percentage of severe cases between elderly and non-elderly patients, indicating that age is not a risk factor for aggravation of the condition when LDA monotherapy is used.

ARTICLE HIGHLIGHTS

**Research background**

As the Japanese population ages, the prevalence of cerebrovascular disorders and ischemic heart diseases have been increasing. Under these circumstances, low-dose aspirin (LDA) has increasingly been used for secondary prevention of such conditions in recent years. Severe adverse reactions to LDA include hemorrhagic gastroduodenal ulcer. In the future, the incidences of LDA-induced peptic ulcer and ulcer hemorrhage are expected to rise in the elderly.

**Research motivation**

As previously reported, the concomitant use of LDA and other antithrombotic drugs increases the risk of ulcer hemorrhage. However, no report of any study that LDA-induced ulcer hemorrhage in elderly patients who expected to become severe. Uncidation of the current status of this condition would thus be useful.

**Research objectives**

Of patients with hemorrhagic gastroduodenal ulcer caused by oral administration of antithrombotic drugs, those receiving oral LDA, which is likely to be particularly problematic, were targeted. By comparing elderly and non-elderly patients, this study aimed to identify clinical features of the ulcer and factors contributing to its progression to severe conditions. These issues are particularly important in countries that have become aged societies, like Japan, or are aging at a rapid rate.

**Research methods**

This study included 1105 patients with hemorrhagic gastroduodenal ulcer, who were divided according age (the elderly group consisting of those 70 years of age or older and the non-elderly group consisting of those less than 70 years of age) and orally administered drugs (the LDA monotherapy group and the LDA combination therapy group). We retrospectively compared and analyzed the length of hospital stay, presence or absence of decreased hemoglobin (Hb) level, use of blood transfusion, rate of severe conditions, etc.

**Research results**

When elderly patients were compared between the LDA monotherapy and LDA combination therapy groups, the rate of severe conditions was higher in the LDA combination therapy group. Concomitant use of LDA with antithrombotic drugs or nonsteroidal anti-inflammatory drugs was found to contribute to the progression of severe hemorrhagic gastroduodenal ulcer to severe conditions. Moreover, among the LDA monotherapy group, no significant difference in the rate of severe conditions was observed between elderly and non-elderly patients. Oral administration of LDA alone was not found to be a risk factor for progression to severe conditions in elderly patients.

**Research conclusions**

This study showed that LDA combination therapy contributes to progression to severe conditions, such as markedly decreased Hb levels, increased frequency of blood transfusion, and prolonged hospital stay, in elderly patients. Meanwhile, in cases receiving LDA monotherapy, advanced age is not a risk factor for progression to severe conditions. Based on these findings, when LDA combination therapy is administered to elderly patients, efforts should be made toward adequate prevention of hemorrhage. In cases with ulcer hemorrhage, while treatment is given, appropriate antithrombotic therapy is required to prevent the occurrence of vascular events. Furthermore, apparently, if LDA monotherapy is administered, even elderly patients may be at a risk of progression to severe conditions similar to that in non-elderly patients.

**Research perspectives**

The limitations of this study include the single-center retrospective design. In addition, because the analysis in the LDA combination therapy group was not stratified according to the types of antithrombotic drugs used in combination with LDA, the effects of different combinations of drugs on the risk of hemorrhage should be examined in future studies. Although the use of proton pump inhibitors (PPIs) is preferable for prevention of hemorrhage as described in the guidelines, further accumulation of additional data and studies on effects, adverse events, etc. are needed to use PPIs appropriately. Furthermore, evidence must be accumulated for the prophylactic effect of novel therapeutic drugs, such as vonoprazan, for ulcers in elderly patients.

ACKNOWLEDGMENTS

The authors appreciate the great support with the statistical analyses provided by Yasuo Haruyama, Department of Public Health, Dokkyo Medical University. The authors also would like to thank all participants and staff members investigators who participated in this study: Yasunaga Suzuki, Yoshihito Watanabe, Kazunari Kanke, Takeshi Onuma, Yukio Otsuka, Katsuori Morita, Takahiro Mitsuhashi, Michiko Matsuoka, Ayako Aoki, Jun Ishikawa, Etsuko Yonekura, Koji Sudo, Youichi Fujii, Yutaka Okamoto, Daiisuke Arai, Masaya Terauchi, Hayato Takagi, Kenji Yoshida, Takero Koike, Kenichiro Mukawa, Mina Hoshino, Takaumio Hoshino, Rieko Fujii, Genyo Hitomi, Naoto Yoshitake, Yasuuki Saiikaku, Mitsunori Maeda, Makoto Matsumaru, Kohiti Tsutslu, Takeshi Sugaya, Masakazu Nakano, Chieko Tsuchida, Yoshimitsu Yamamoto, Kyoko Yamamoto, Misako Nukumi, Hiroko Sakurai, Naoya Inaba, Takashi Akima, Hitoshi Kin, Yoshihito Kaneko, Atsushi Hoshino, Hidehito Jinnai, Toshihito Komatsubara, Shinji Muraoka, Fumiaki Takahashi, Tsunehiro Suzuki, Mari Iwaseki, Kazuhiro

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P- Reviewer: Caboelo JF, Rodrigo L, Tarnawski AS
S- Editor: Gong ZM
E- Editor: Yin SY
