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（博　士）

Low-Dose Aspirin and Non-steroidal Anti-inflammatory Drugs Increase the Risk of Bleeding in Patients with Gastroduodenal Ulcer

Running title: NSAIDs and gastrointestinal bleeding

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Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin (LDA), non-aspirin antiplatelet medications (APs) and anticoagulant medications (ACs) increase the risk of gastrointestinal bleeding.

Aims: To examine whether NSAIDs, LDA, APs, and ACs use is associated with bleeding from gastroduodenal ulcers.

Methods: This was a case-control study of patients with endoscopically verified gastroduodenal ulcer diagnosed at our institution from 2004-2011. Among 1,611 patients, we identified those who required endoscopic hemostasis for bleeding ulcers as cases. Age-, sex-, and *Helicobacter pylori* status-matched patients who did not require therapeutic interventions served as controls. Use of NSAIDs, LDA, APs and ACs within 2 weeks prior to endoscopy was compared between cases and controls, and effects on ulcer bleeding were calculated.

Results: We recruited 341 cases and 668 controls. The site and number of ulcers were not different between groups. Multivariate analyses revealed that LDA and NSAIDs, individually, were associated with the increase in the risk of bleeding (OR, 1.80 and 95% CI, 1.18-2.75 for LDA; 1.35 and 1.01-1.80 for NSAIDs). In addition, a combination of LDA and NSAIDs or LDA and APs contributed more profoundly to the bleeding (OR, 3.59 and 95% CI, 1.19-10.81 for LDA/NSAIDs; OR, 6.70 and 95% CI, 1.83-24.50 for LDA/APs). However, ACs, alone or in combination, were not associated with bleeding ulcers.

Conclusions: Both LDA and NSAIDs are risk factors for upper GI bleeding in patients with gastroduodenal ulcer, while ACs are unrelated to the increased risk. The risk of bleeding with LDA may increase with simultaneous use of APs.

Key Words: gastroduodenal ulcer, gastrointestinal bleeding, non-steroidal anti-inflammatory drugs, low-dose aspirin, antithrombotic medication

Introduction

Helicobacter pylori (*H. pylori*) infection and use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin (LDA) are well-established causes of gastroduodenal ulcer [1]. *H. pylori* and NSAIDs are independent risk factors for upper gastrointestinal (GI) bleeding. In addition, antithrombotic medications, which include non-aspirin antiplatelet medications (APs) and anticoagulants (ACs), are associated with a high incidence of upper GI bleeding [2].

Several case-control studies in the literature have evaluated the contribution of LDA, NSAIDs and antithrombotic medications to the development of bleeding gastroduodenal ulcers [3-5]. In those studies, however, healthy controls or patients admitted for other diseases were selected as controls; thus, the studies failed to evaluate the relationship of the medications with actual bleeding from gastroduodenal ulcers. In addition, because Japan has the highest worldwide prevalence of *H. pylori* infection, and *H. pylori* is an independent risk factor for upper GI bleeding, it is not clear whether LDA, NSAIDs, APs and ACs are actually risk factors for bleeding from gastroduodenal ulcers when compared to non-bleeding ulcers [6,7].

To examine whether the use of LDA, NSAIDs, APs, ACs and any combination of these medications actually contributes to the increase in the risk of bleeding from gastroduodenal ulcers, we undertook a single-center, case-control study of patients with endoscopically verified gastroduodenal ulcers.

Patients and methods

Study population

This was a case-control study based on retrospective data collection. We reviewed the endoscopy database at Matsuyama Red Cross Hospital from 2004-2011, and identified all of the patients with a diagnosis of active gastroduodenal ulcer under esophagogastroduodenoscopy (EGD). We subsequently identified cases and controls

according to the following criteria (Figure). First, we excluded patients who had been receiving treatment with proton pump inhibitors (PPI) or histmine-2 receptor antagonists (H2RA). Among the remaining patients, those who were diagnosed as having a bleeding gastroduodenal ulcer treated with endoscopic hemostasis were regarded as cases. Then, we identified two controls with non-bleeding gastroduodenal ulcers for each case. The controls were matched to each case with regard to age (within a maximal difference of 5 years), sex, and *H. pylori* status, as determined by the procedure described below.

The protocol of this case-control study was approved by Institutional Review Board at Matsuyama Red Cross Hospital.

Exposure definition

Clinical characteristics of the study subjects were investigated on the basis of chart review. The characteristics included age, sex, *H. pylori* infection, medication at the time of endoscopic diagnosis of gastroduodenal ulcers, and endoscopic findings of the ulcers.

The endoscopic characteristics included the site and number of active ulcers. An ulcer was defined as a mucosal defect larger than 5 mm in diameter. Mucosal defects less than 5 mm in size, histologically verified cancer, and cardial mucosal defects presumably related to Mallory-Weiss syndrome were not regarded as gastroduodenal ulcer. *H. pylori* status was determined by the following three procedures: 1) histology of the biopsy specimen, 2) titer of serum IgG antibody to *H. pylori* as measured with an enzyme-linked immunosorbent assay kit using the E plate test (Eiken Kagaku, Tokyo, Japan) and 3) ^{13}C-urea breath test. Subjects were considered to be positive for *H. pylori* infection if they had a positive result on any one of the three tests and to be negative if all three demonstrated negative results. LDA, NSAID, AP, AC and steroid use was checked by reviewing the prescriptions at our hospital and the confirmation sheet for medications at the time of the endoscopy. The

latter was completed and filed by medical staff members for patients who had prescriptions from referring physicians or who were taking commercially available medications. The use of LDA, NSAIDs, APs and ACs was regarded to be positive if the patient had taken the agent within 2 weeks prior to EGD. LDA included both coated and buffered aspirin.

Statistical analysis

Parametric data are expressed as mean ± SD. Nonparametric data are expressed as numbers and percents. Comparisons between any two groups were performed with the Mann-Whitney test or χ^2-test where appropriate. Stepwise multivariate logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals for bleeding ulcers. Probabilities less than 0.05 were considered to be significant. All statistical computations were performed with JMP version 11 (Statistical Discovery Program, USA).

Results

There were 1,611 patients in the database who had a diagnosis of active gastrodoudenal ulcer. After excluding those who did not meet the inclusion and exclusion criteria described above, we enrolled 341 patients as cases and 668 patients as controls. The procedures for endoscopic hemostasis (for cases) were argon plasma coagulation (APC) for 94 cases, injection of alcohol or hypertonic saline-epinephrine solution (HSE) for 28 cases, endo-clip for 14 cases, a combination of HSE and APC for 183 cases, or other combinations for 22 cases. Primary endoscopic hemostasis could be achieved in all of the cases.

Table 1 compares the baseline clinical and endoscopic characteristics between cases and controls. The rate of *H. pylori* positivity was 68.6% in cases and 69.6% in controls. There was no difference in the number or location of the ulcers between groups. The incidence of steroid use did not differ between groups.

NSAIDs taken by the cases and controls included loxoprofen, diclofenac, ibuprofen, meloxicam, etodolac, lornoxicam, ketoprofen, mefenamic acid, celecoxib and others. APs included ticlopidine, clopidogrel, cilostazol, ethyl icosapentate, limaprost alfadex, and others, and ACs included warfarin and heparin sodium. As shown in Table 2, the use of LDA (14.7% vs. 8.1%, p=0.002), NSAIDs (31.4% vs. 25.3%, p=0.04) and APs (10.0% vs. 6.1%, p=0.03) was more frequent in cases than in controls. However, the difference in the use of ACs did not reach statistical significance (8.5% vs. 5.2%, p=0.06).

Results of multivariate analysis for bleeding ulcers are shown in Table 3. A logistic regression analysis revealed that neither APs nor ACs increased the risk of bleeding (OR 1.44 and 95% CI 0.88-2.35 for APs; OR 1.52 and 95% CI 0.90-2.35 for ACs). In contrast, LDA and NSAIDs increased the risk of bleeding (OR 1.80 and 95% CI 1.18-2.75 for LDA; OR 1.35 and 95% CI 1.01-1.80 for NSAIDs).

There were six combinations of LDA, NSAIDs, APs and ACs in the study population. As shown in Table 2, two combinations (LDA plus NSAIDs and LDA plus APs) were more frequently used in cases than in controls. As a consequence, these two combinations increased the risk of bleeding, with an OR of 3.59 for LDA plus NSAIDs and 6.7 for LDA plus APs. Of note, addition of APs to LDA resulted in a 3.7-fold increase in the risk of bleeding. However, a combination of NSAIDs and APs and three combinations including ACs did not significantly increase the risk of bleeding.

To further determine the effect of the medications on ulcer bleeding according *H. pylori* status, we performed a stratified analysis (Table 4). When the subjects were classified into 699 patients (234 cases and 465 controls) positive for *H. pylori* and 310 patients (107 cases and 203 controls) negative for *H. pylori*, multivariate analyses revealed that LDA was marginally but significantly associated with the increase in the risk of ulcer bleeding (OR; 1.83 for the *H. pylori*-positive group and 1.95 for the *H. pylori*-negative group).

Discussion

We showed that LDA and NSAIDs are risk factors for bleeding in patients with gastroduodenal ulcer and that a combination of LDA plus NSAIDs or APs increases the risk of bleeding in patients with gastroduodenal ulcer. Furthermore, ACs did not increase the risk of bleeding, either independently or adjunctively.

It is well established that LDA and NSAIDs increase the risk of upper GI bleeding in the general population. Lanas et al.[4] undertook a prospective case-control study and showed that the use of either LDA or NSAIDs was associated with an increased risk of upper GI bleeding. In that study, the OR of upper GI bleeding for the use of LDA was 3.9, and that for NSAIDs was 5.3. In a Japanese retrospective case-control study by Sakamoto et al.,[5] the OR of upper GI bleeding was 5.5 for LDA and 6.1 for NSAIDs. However, it should be noted that in those case-control studies, the controls were selected from patients who were admitted during the same period or from population registries in the same district [3-5,8-13]. As a consequence, it remains unclear whether LDA and NSAIDs increase the risk of gastroduodenal mucosal lesions, the risk of bleeding from the mucosal lesions, or both. To show to what extent the medications increase the risk of bleeding from the mucosal lesions, we performed the present case-control study. As a consequence, we showed that LDA and NSAIDs are risk factors for bleeding from gastroduodenal ulcers.

In addition to the individual risk incurred by the use of LDA and NSAIDs, combinations of LDA plus NSAIDs and LDA plus APs increased the risk of upper GI bleeding. The increase in the risk of bleeding ulcers with a combination of LDA and NSAIDs seems reasonable, because such a synergistic effect has been confirmed in two large clinical studies [14,15]. In a prospective case-control study, the OR of upper GI bleeding was 3.9 for LDA and 5.3 for NSAIDs, while it increased up to 12.7 for a combination of LDA and NSAIDs [4]. However, the synergistic effect of LDA and

APs on GI bleeding has been shown in only a few population-based case-control studies [2,16]. In a study with 1,443 cases of upper GI bleeding and 57,720 controls, the OR of upper GI bleeding was calculated to be 1.8 for LDA and 1.1 for clopidogrel, whereas it increased to 7.4 for the combination of LDA and clopidogrel [2]. In consideration of the results of our present study, the higher risk of GI bleeding with a combination of LDA and APs does not seem to be a consequence of the more severe gastroduodenal mucosal injury, but rather of an increase in the risk of bleeding from pre-existing mucosal lesions [17]. In contrast, ACs did not increase the risk of bleeding either independently or synergistically with LDA or NSAIDs in our study population, while it has been well established that ACs increase the risk of GI bleeding [2]. Although we are not able to explain the discordance in the effect of APs and ACs on the risk of ulcer bleeding, it can be presumed that platelet functions, such as adhesion, aggregation, and formation of the initial plug, may be pivotal for the prevention of bleeding from gastroduodenal ulcers.

H. pylori infection plays an important role in the pathogenesis of gastroduodenal ulcers. Furthermore, a close association of upper GI bleeding with *H. pylori* infection has been shown in a meta-analysis and a retrospective case-control study [1,5]. *H. pylori* status should be taken into consideration for the interpretation of our results, because the prevalence of *H. pylori* infection is much higher in Japan than in Western countries [6,7,18,19]. In the above-mentioned case-control study of a Japanese population, the OR of upper GI bleeding was 4.9 for NSAIDs in patients with negative *H. pylori* status and 5.4 in patients with positive *H. pylori* status without NSAID use. In contrast, the OR increased up to 10.4 with a combination of NSAID use and positive *H. pylori* status [5]. However, the effect of LDA, NSAIDs, APs and ACs on the OR for upper GI bleeding was not obviously different between our *H. pylori*-positive and -negative subjects, with only a marginal effect of LDA in both groups. It thus seems possible that the effect of the medications on ulcer bleeding is

unrelated to *H. pylori* status.

This study has some limitations. First, its retrospective nature in a single-center protocol seems to have been a source of potential bias. This is especially the case for the uncertainty regarding the severity of underlying diseases, thereby resulting in a provisional overestimation of the role of LDA and APs. To minimize this type of bias, we recruited age- and sex-matched controls. Second, we could not take other potential factors, such as smoking and alcohol use, into consideration. However, we believe that there have not been any data showing that alcohol and smoking have a more significant role than LDA, NSAIDs and APs in the development of bleeding gastroduodenal ulcers. Third, we could not specifically show the risk of each drug classified as an AP or AC, because of the small sample size for each medication.

In conclusion, this study showed that LDA and NSAIDs increase the risk of bleeding in patients with gastroduodenal ulcer. In addition, a combination of LDA and NSAIDs or LDA and APs increases the risk of bleeding in those patients. Thus, it seems to be reasonable to modify therapeutic considerations for patients with gastroduodeneal ulcer according to the use of LDA and NSAIDs. This seems to be the case especially for patients taking LDA, because the risk of bleeding seems to be affected by simultaneous use of APs. This issue needs to be investigated prospectively in a large cohort or in a randomized clinical trial.

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Figure legend

Figure. Selection of cases and controls. Among 1,611 patients with a diagnosis of gastroduodenal ulcer, we first excluded patients who had been receiving treatment with proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA). Among the remaining patients, those who were diagnosed as having a bleeding gastroduodenal ulcer treated with endoscopic hemostasis were regarded as cases. We then identified two controls with non-bleeding gastroduodenal ulcers for each case. Controls were matched to each case with regard to age, sex, and *H. pylori* status. We enrolled 341 cases and 668 controls.

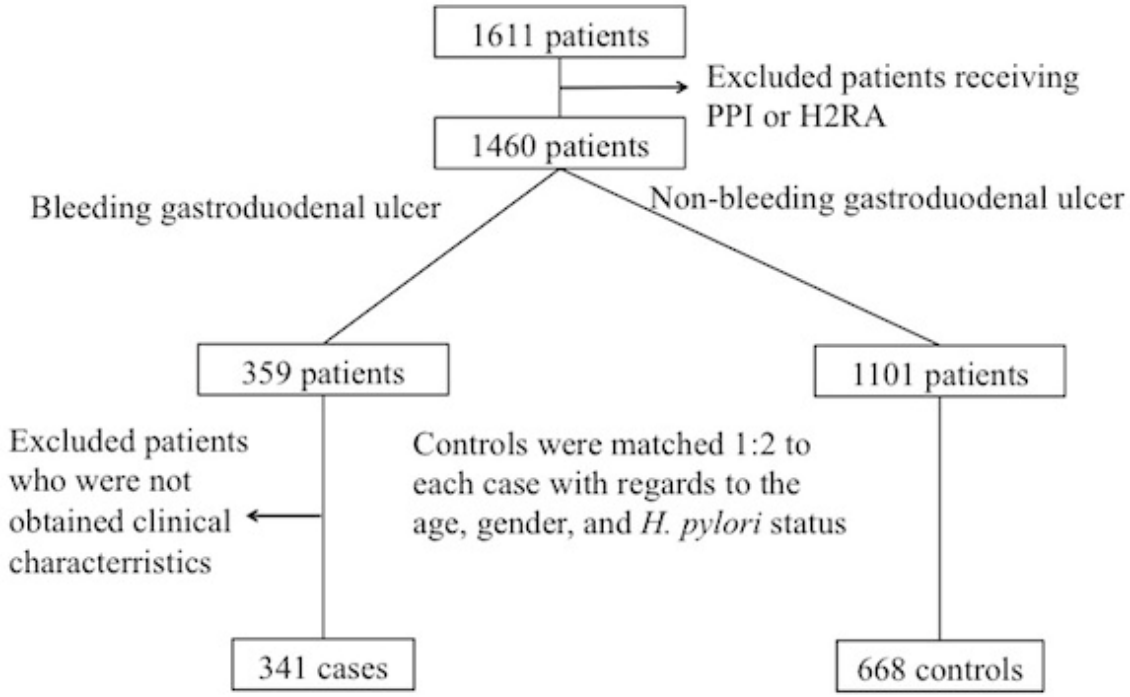

Table 1. Characteristics of cases and controls

Demographics		Cases (N=341)	Controls (N=668)	*p*-value
Age, mean ± SD		65.2 ± 15.3	65.1 ± 15.0	NS
Gender	M (%)	230 (67.4)	446 (66.8)	NS
	F (%)	111 (32.6)	222 (33.2)	
H.pylori infection	+ve (%)	234 (68.6)	465 (69.6)	NS
	-ve (%)	107 (31.4)	203 (30.4)	
Number of active ulcers, mean ± SD		1.7 ± 1.7	1.7 ± 1.9	NS
Site of ulcer	stomach (%)	253 (74.2)	460 (68.9)	NS
	duodenum (%)	88 (25.8)	208 (31.1)	
Steroid user, n (%)		21 (6.2)	42 (6.3)	NS

F=female; M=male; NS=not significant; SD=standard deviation.

Table 2. Results of univariate analysis for the risk of bleeding

Type of medication	Cases (N=341)	Controls (N=668)	*p*-value	Odds ratio (95%CI)
LDA	50 (14.7%)	54 (8.1%)	0.002	1.95 (1.30-2.94)
NSAIDs	107 (31.4%)	169 (25.3%)	0.04	1.35 (1.01-1.80)
APs	34 (10.0%)	41 (6.1%)	0.03	1.69 (1.05-2.72)
ACs	29 (8.5%)	35 (5.2%)	0.06	1.68 (1.01-2.80)
Combinations				
LDA+NSAIDs	9 (2.6%)	5 (0.75%)	0.02	3.59 (1.19-10.81)
LDA+APs	10 (2.9%)	3 (0.45%)	0.002	6.70 (1.83-24.50)
LDA+ACs	5 (1.47%)	6 (0.9%)	0.52	1.64 (0.50-5.42)
NSAIDs+APs	6 (1.76%)	9 (1.35%)	0.59	1.31 (0.46-3.72)
NSAIDs+ACs	8 (2.35%)	7 (1.05%)	0.17	2.27 (0.82-6.31)
Acs+Aps	1 (0.29%)	2 (0.30%)	1	1.00 (0.09-10.84)

CI: confidence interval, LDA: low-dose aspirin, NSAIDs: nonsteroidal anti-inflammatory drugs.

APs: non-aspirin antiplatelet medications, ACs: anticoagulant medications.

Table 3. Results of multivariate analysis for the risk of bleeding

Type of medication	*p*-value	Odds ratio (95%CI)
LDA	0.006	1.80 (1.18-2.75)
NSAIDs	0.04	1.35 (1.01-1.80)
APs	0.14	1.44 (0.88-2.35)
ACs	0.12	1.52 (0.90-2.35)

CI: confidence interval, LDA: low-dose aspirin, NSAIDs: nonsteroidal anti-inflammatory drugs, APs: non-aspirin antiplatelet medications, ACs: anticoagulant medications.

Table 4. Results of multivariate analysis for the risk of bleeding by *H. pylori* status

Type of medication	*H. pylori*-positive				*H. pylori*-negative			
	Cases (N=234)	Controls (N=465)	*p*-value	Odds ratio (95%CI)	Cases (N=107)	Controls (N=203)	*p*-value	Odds ratio (95%CI)
LDA	23 (9.8%)	25 (5.4%)	0.049	1.83 (1.00-3.34)	27 (25.2%)	29 (14.3%)	0.04	1.95 (1.05-3.63)
NSAIDs	50 (21.4%)	80 (17.2%)	0.15	1.34 (0.90-1.99)	57 (53.3%)	89 (43.8%)	0.08	1.54 (0.95-2.52)
APs	18 (7.7%)	22 (4.7%)	0.22	1.51 (0.77-2.91)	16 (15.0%)	19 (9.4%)	0.35	1.43 (0.67-3.01)
ACs	13 (5.6%)	20 (4.3%)	0.57	1.23 (0.58-2.52)	16 (15.0%)	15 (7.4%)	0.08	2.00 (0.93-4.33)

CI: confidence interval, LDA: low-dose aspirin, NSAIDs: nonsteroidal anti-inflammatory drugs,

APs: non-aspirin antiplatelet medications, ACs; anticoagulant medications.