Gastric Mucosal Damage Evaluated by Transnasal Endoscopy and QOL Assessments in Ischemic Heart Disease Patients Receiving Low-dose Aspirin

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Abstract

Objective Transnasal endoscopy was conducted to examine gastric mucosal damage in Japanese patients with ischemic heart disease who were receiving low-dose aspirin for preventing the onset or recurrence of cardiovascular disease.

Patients and Methods An endoscopist assessed gastric mucosal damage. Furthermore, the MOS 36-Item Short-Form Health Survey (SF-36[®]) and the Gastrointestinal Symptom-Rating Scale (GSRS) were used to assess the outcomes of their quality of life (QOL) and the possible presence of gastric cancer and *H. pylori* infection.

Results Seventy-five patients were studied; and 24 (32.0%) and 16 (21.3%) of them concurrently received antithrombotic drugs other than aspirin and antiulcer drugs, respectively. Regarding gastric mucosal damage, 15 (20.0%) and 8 (10.7%) of the patients were endoscopically diagnosed with ulcer and hemorrhagic gastritis, respectively. Furthermore, 5 patients (6.7%) were found to have esophageal or gastric cancer. The positivity rate of *Helicobacter pylori* (*H. pylori*) was 45.3%. Patients receiving low-dose aspirin showed a decreased QOL. Consequently, no significant differences were found among the groups. Regarding endoscopic findings, no differences were found in the scores of both SF-36[®] and GSRS with respect to the presence or absence of gastric ulcer, hemorrhagic gastritis, and *H. pylori* infection.

Conclusion Transnasal endoscopy was possible to perform during the oral intake of low-dose aspirin without causing any hemorrhagic complications. Many patients with gastric mucosal lesions showed no subjective symptom, and patients receiving aspirin were strongly recommended to undergo regular transnasal endoscopy, regardless of the presence or absence of symptoms.

Key words: low-dose aspirin, transnasal endoscopy, quality of life, outcome, fact-finding study

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Introduction

Due to rapid aging of the population in recent years, malignant neoplasms and arteriosclerotic disorders, e.g., cardiovascular and cerebrovascular disorders, account for the leading causes of death in Japan. Because of this situation, opportunities to administer low-dose aspirin as a secondary preventive measure against the onset or recurrence of ischemic heart disease and cerebral infarction have increased. The pharmacological action of aspirin is in its an-

tithrombotic activity through the inactivation of platelet cyclooxygenase-1 and through the inhibition of platelet thromboxane A₂. The adverse reaction of highest incidence caused by aspirin is gastric mucosal damage. Furthermore, gastric mucosal damage involving marked bleeding and ulcer, duodenal ulcer, and small intestinal ulcer has been reported in association with the use of aspirin (75-325 mg/day). According to the meta-analysis performed by Rodriguez and Hernandez-Diaz (1), the incidence of aspirin-induced peptic ulcer has a relative risk of 2.9 (95% confidence interval: 2.3, 3.9); the ulcer is considered to develop

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regardless of dosage form, consumption, and duration of administration. Moreover, Niv et al (2) conducted endoscopy of the upper gastrointestinal tract in 46 asymptomatic patients who were receiving low-dose aspirin for 3 months or longer and found peptic ulcer and erosion in 47.8% of them. However, there are few fact-finding investigations on the development of gastric mucosal damage provoked by low-dose aspirin in medical practice. In addition, the administration of low-dose aspirin in patients with cerebrovascular or cardiovascular disease lasts for a long time and is highly likely to be performed in elderly patients; therefore, the regimen involves a risk of leading to fatal hemorrhage unlike the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

It is mandatory to conduct endoscopy in order to verify gastric mucosal damage. However, pain that may occur during the procedure is nonnegligible. We have focused attention on transnasal endoscopy from the early stages and have applied the procedure clinically. A recent study reported that there is a smaller number of hemorrhagic complications at the site of endoscope passage because transnasal endoscopy provokes less gag reflex compared to peroral endoscopy, the diameter of the endoscope fiber is small, and the fiber itself is highly flexible. Transnasal endoscopy has been reported to reduce a parameter for myocardial oxygen consumption—double product—compared to conventional peroral endoscopy in patients with cardiovascular disease (3). Therefore, we conducted a fact-finding study of gastric mucosal damage and investigated the health-related QOL parameters in Japanese patients with ischemic heart disease who were receiving low-dose aspirin for a long time.

Methods

Among Japanese outpatients who were treated in the Department of Cardiology at Tokyo Medical University between February and November 2007, 75 who were found by coronary angiography to definitely have coronary artery disease and who were receiving low-dose aspirin for 1 month or more after catheterization were enrolled in the present study. One of the inclusion criteria was as follows: “Endoscopy of the upper gastrointestinal tract should not be performed within the last 1 year at any hospital, including other institutions”. Patients under age 20, female patients who were pregnant or likely pregnant, patients who did not provide written informed consent to enrollment, and patients whom the physician considered ineligible for the present study were excluded. Medical records were used to investigate underlying disease, duration of low-dose aspirin intake, combined use of antiulcer drugs and antithrombotic drugs, and other parameters. The urea breath test was performed to investigate *H. pylori* infection. In the present study, H_2 receptor antagonists and proton pump inhibitors (PPIs) were defined as antiulcer drugs. An endoscopist conducted transnasal endoscopy and made a diagnosis. The endoscopist used the modified Lanza scoring system to individually

score 3 items—reddening, erosive lesion, and petechiae—when scaling gastric ulcer. In parallel with the first survey on QOL, the face-to-face questionnaire was used to ask the patient about the following two points: 1) “Do you know the effects of aspirin”; and 2) “Do you know that receiving aspirin possibly causes gastric mucosal damage?” At about 2 to 8 months after the first survey on QOL, the second face-to-face questionnaire survey was conducted and medical records were used to analyze the relationships of gender, age, underlying disease, drinking, cigarette smoking, duration of low-dose aspirin intake, combined drugs, endoscopic findings, and presence or absence of *H. pylori* infection with QOL. Bacterial eradication with the combination of 3 drugs was conducted in *H. pylori*-positive patients, and changes in QOL before and after bacterial eradication were also analyzed.

The present study was approved by the ethics committee at Tokyo Medical University and by the ethics committee at Kyoritsu College of Pharmacy. Written informed consent was obtained from all subjects. The statistical software SPSS II (Japanese version; Tokyo, Japan) was used to make statistical analyses according to Fisher’s t-test and Wilcoxon rank-sum test. A value of $p < 0.05$ was considered statistically significant. To assess the QOL of the patient, the MOS 36-Item Short-Form Health Survey (SF-36[®]) version 2 in Japanese was used as a comprehensive scale, and the Gastrointestinal Symptom Rating Scale (GSRS) version 1.2 in Japanese was used as a gastrointestinal disease-specific scale.

Results

Fifty patients (66.7%) receiving low-dose aspirin for 3 years or more were predominant among 75 enrolled patients (61 males and 14 females; age: 68.3 ± 8.2 years). The preliminary questionnaire survey revealed that there were 47 patients (62.7%) who knew the effects of aspirin and 14 patients (18.7%) who knew the possible development of gastric mucosal damage due to aspirin intake. The mean dose of aspirin was 100 mg/day. Low-dose aspirin was used concurrently with antithrombotic drugs in 24 patients (32.0%); ticlopidine was most predominant in 9 patients (12.0%), followed by warfarin in 8 patients (10.7%). The mean international normalized ratio (INR) was 1.83 ± 2.15 . Furthermore, cilostazol was used in 3 patients (4.0%), while low-dose aspirin was used concurrently with clopidogrel and with clopidogrel and warfarin in 2 patients (2.7%), respectively. Low-dose aspirin was used concurrently with antiulcer drugs in 16 patients (21.3%) (Table 1), 14 of whom continued to receive prescriptions from their previous physicians; the rationale for the prescriptions was unknown. Two patients, who newly initiated to receive antiulcer drugs at our hospital, desired personally to receive the drugs. Four among these 16 patients replied in the preliminary questionnaire survey that they had known aspirin’s adverse reaction of “gastric mucosal damage”; two of these patients desired to be prescribed with antiulcer drugs. Despite the fact that tran-

Table 1. Patient Characteristics

Characteristic	
Total number of patients	75
Mean age $\pm$ SD, yrs	68.3 $\pm$ 8.2
Gender, M/F	61/14
Duration of low-dose aspirin intake for 3 years or longer, n (%)	50 (66.7)
Number of patients receiving antithrombotic drugs without aspirin, n (%)	24 (32.0)
Number of patients receiving antiulcer drugs, n (%)	16 (21.3)

Table 2. Incidences of Gastric Ulcer and Hemorrhagic Gastritis by the Presence or Absence of *H. pylori* Infection

	Number of patients with <i>H. pylori</i> infection	Incidence, %
Gastric ulcer presence (n=15)	7	46.7
Gastric ulcer absence (n=60)	27	45.0
Hemorrhagic gastritis presence (n=8)	0	0.0
Hemorrhagic gastritis absence (n=67)	34	50.7

nasal endoscopy was conducted under aspirin intake, no adverse events, e.g., bleeding from nasal mucosa caused by the passage of the transnasal endoscope, were observed. There were 15 (20%) and 8 patients (10.7%) who were endoscopically diagnosed with gastric ulcer and hemorrhagic gastritis, respectively. *H. pylori* infection was positive for 34 patients (45.3%). Seven patients (47%) and 27 patients (45%) were positive for *H. pylori* infection in the gastric ulcer group and the gastric ulcer-free group, respectively. Furthermore, there were 0 patient (0%) and 34 patients (51%) who were positive for *H. pylori* infection in the hemorrhagic gastritis group and the hemorrhagic gastritis-free group, respectively (Table 2). Furthermore, 10 patients with ulcer scars (13.3%), 5 patients with esophageal cancer (6.7%), and 5 patients with gastric cancer (6.7%) were discovered (Table 3). Gastric ulcer developed in 3 patients (11.5%) in the antiulcer drug combination group and in 12 patients (24.5%) in the antiulcer drug combination-free group. In addition, hemorrhagic gastritis developed in 3 patients (11.5%) in the antiulcer drug combination group and in 5 patients (10.2%) in the antiulcer drug combination-free group (Table 4). This result suggested that antiulcer drug is enough pressed gastric ulcer (11.5% vs 24.5%) but not enough pressed hemorrhagic gastritis (11.5% vs 10.2%).

Regarding the QOL survey, the SF-36[®] scores from 75 patients receiving low-dose aspirin were compared with 50—the international standard score. Consequently, “physical functioning (PF)” (43.6 $\pm$ 15.2) and “role physical (RP)” (45.7 $\pm$ 15.3) showed significantly low scores ($p<0.05$), (Fig. 1). The relationships of gender, age, drinking, cigarette smoking, duration of low-dose aspirin intake, and concurrent drugs with QOL were examined. Consequently, 10 patients receiving low-dose aspirin (<1 year) showed significantly

decreased scores of “general health perceptions (GH)”, “vitality (VT)”, and “role emotional (RE)” ($p=0.025$, $p=0.013$, and $p=0.037$, respectively; Wilcoxon rank sum test) compared to 65 patients receiving low-dose aspirin (≥ 1 year). Forty-six patients (61.3%) receiving 6 drugs or more showed significantly decreased scores of PF, RP, “bodily pain (BP)”, and GH ($p=0.004$, $p=0.004$, $p=0.03$, and $p=0.049$, respectively; Wilcoxon rank-sum test) compared to 29 patients (38.7%) receiving less than 6 drugs. Sixteen patients (21.3%) concurrently using antiulcer drugs showed significantly decreased scores of RP and RE, as well as a significantly increased score of “acid regurgitation (AR)” in GSRS ($p=0.029$, $p=0.033$, and $p=0.012$; Wilcoxon rank-sum test) compared to 59 patients (78.6%) not concurrently using antiulcer drugs (Table 4). Regarding endoscopic findings, both SF-36[®] and GSRS revealed no significant differences in the scores according to the presence or absence of ulcer, hemorrhagic gastritis, and *H. pylori* infection. No improvement in QOL was noted before and after the eradication of *H. pylori*.

Discussion

The arteriosclerotic disease-preventive effect of antiplatelet therapy has been demonstrated in many studies. Especially regarding aspirin—the core drug of the therapy, its effects on a broad array of diseases, including acute coronary syndromes to unstable angina pectoris, were demonstrated in Antiplatelet Trialist's Collaboration (ATT) (4). The meta-analysis performed by Biondi-Zoccai (5) reported that the interruption of aspirin increased the risk of cardiovascular disease by several times; the risk increased very high to 89.78-fold, especially after deployment of drug-eluting stents (DESs). The recommendations announced jointly by several academic societies in the United States (6) and the Japanese Circulation Society guideline (7) described that the concurrent use of aspirin with a thienopyridine compound should last at least for 12 months after DES deployment. Usually, aspirin is administered for patient's lifetime. In patients with gastrointestinal hemorrhage and reported that the incidence of gastrointestinal hemorrhage was 5.5-fold higher in aspirin users and was 7.7-fold higher in patients receiving aspirin necessarily (8). These results indicate an nonnegligi-

Table 3. Endoscopic Findings in Patients

Diagnosis	Number of patients	Incidence, %
Gastric ulcer	15	20.0
Ulcer scar	10	13.3
Hemorrhagic gastritis	8	10.7
Gastric cancer	5	6.7
Adenoma	2	2.7
Polyp	16	21.3
Gastroesophageal reflux	12	16.0

Table 4. Incidences of Gastric Ulcer and Hemorrhagic Gastritis by the Presence or Absence of Antiulcer Drugs

Patients receiving antiulcer drugs n = 26 (34.7%)	Number of patients	Incidence, %
Gastric ulcer	3	11.5
Hemorrhagic gastritis	3	11.5
Patients not receiving antiulcer drugs n = 49 (65.3%)		
Gastric ulcer	12	24.5
Hemorrhagic gastritis	5	10.2

ble issue in patients for whom aspirin discontinuation is difficult. In fact, our investigation disclosed 15 patients (20%) who were diagnosed with ulcer by endoscopy and 8 patients (10.7%) who were diagnosed with hemorrhagic gastritis. Endoscopy discovered 5 patients (6.7%) with esophageal or gastric cancer, by far exceeding the probability of accidentally discovering gastric cancer by health check endoscopy. The following facts may be mentioned as causes to explain the reason why such many cases of ulcer, hemorrhagic gastritis, and gastric cancer were discovered: under aspirin administration, endoscopy was conducted in patients who had not undergone the procedure previously for not less than 1 year; and 46% of patients underwent endoscopy for the first time. As shown by the results from a review of the GSR scores, patients found to have gastric ulcer and hemorrhagic gastritis also exhibited a scant number of symptoms; therefore, the scantiness of subjective symptoms in patients with aspirin-induced peptic ulcer was suggested anew. Namely, regular endoscopy is recommended for patients receiving aspirin, regardless of the presence or absence of subjective symptoms. Thirty-four patients (45.3%) were positive for *H. pylori*. In consideration of the mean age of patients (68.2±8.3 years), we had an impression that the positivity rate was low. According to a recent study (9), the *H. pylori* infection rate in patients with non-NSAID-induced ulcer whom we encounter in routine medical practice is ≥90% in contrast to a rate of 50% in patients with NSAID-induced ulcer. NSAID-induced ulcer is considered to develop preferentially in patients without *H. pylori* infection. Furthermore, 0 patient (0%) and 34 patients (51%) were positive for *H. pylori*

in the hemorrhagic gastritis group and the hemorrhagic gastritis-free group, respectively. The present study indicated no correlation in incidences between *H. pylori* infection and gastric ulcer but rather revealed the absence of hemorrhagic gastritis in patients who were positive for *H. pylori*. The complication rates of gastric ulcer did not change with respect to the presence or absence of *H. pylori* infection. However, patients diagnosed with hemorrhagic gastritis had lower rates of *H. pylori* infection than those free of hemorrhagic gastritis. Mizokami et al (10) have similarly reported that aspirin-induced peptic ulcer presents bleeding more frequently than does non-NSAID-induced ulcer and that patients with aspirin-induced peptic ulcer have low *H. pylori* infection rates. In general, patients with *H. pylori* infection present the advancement of atrophic gastritis in association with aging and their gastric acid-secreting ability decreases. Aspirin is suggested to be less likely to induce ulcer in a condition where the gastric acid-secreting ability is decreased. Therefore, it is necessary to examine whether there is any need to administer potent gastric acid secretion inhibitors represented by PPIs. According to our investigation, the presence or absence of *H. pylori* infection was not associated with the incidence of gastric ulcer. Patients diagnosed with hemorrhagic gastritis had a significantly low *H. pylori* infection rate ($p=0.007$) compared to those without hemorrhagic gastritis. We consider it essential to investigate a greater number of patients in the future and to specify drugs that are suitable for suppressing the gastric acid-secreting ability of Japanese patients.

Next, we discuss the results from a survey on the health-

Figure 1. Quality of life of patients receiving low-dose aspirin as assessed with the MOS 36-item short-form health survey (SF-36®).

Table 5. Outcomes of the QOL Assessment by Background Factor

Background factor	Number of patients	Questionnaire	Outcome
Low-dose aspirin intake	75 patients	SF-36	Physical functioning and role physical: Significantly decreased
Duration of low-dose aspirin intake	< 1 year: 10 patients ≥ 1 year: 65 patients	SF-36	Role physical, role emotional, vitality, and general health perceptions: Significantly decreased in the "< 1 year" group
Number of drugs taken	< 6 drugs: 29 patients ≥ 6 drugs: 46 patients	SF-36	Physical functioning, role physical, bodily pain, and general health perceptions: Significantly decreased in the "≥ 6 drugs" group
Combination of antiulcer drugs	Present: 16 patients Absent: 59 patients	SF-36	Role emotional and role physical: Significantly decreased in the "present" group
		GSRS	Acid regurgitation: Significantly increased in the "present" group

1-sample t-test; $p < 0.05$

related QOL parameters by means of the SF-36® and a survey on gastrointestinal tract-related QOL according to the GSRS. Patient-based outcome determination scales using the QOL questionnaires were initiated in 1985. In the field of cardiology, J-RHYTHM in Japan (11) used Atrial Fibrillation Quality of Life Questionnaire (AFQLQ) to assess the QOL of patients with atrial fibrillation. In fact, patients receiving low-dose aspirin showed the decreased scores of the health-related QOL parameters in the SF-36® compared to

the international standard scores (Fig. 1). Underlying disease in patients receiving low-dose aspirin includes cerebrovascular accident and ischemic heart disease. Therefore, the restriction of physical behavior due to the onset of primary disease may be considered one of the causes of the decreases. The relationship between duration of low-dose aspirin intake and QOL was examined.

Consequently, 10 patients with "<1 year" duration showed significant decreases in the GH, VT, and RE scores com-

pared to 65 patients with “ ≥ 1 year” duration (12-14). The QOL scores were significantly decreased in the aspirin usage (<1 year) group than in the aspirin usage (≥ 1 year) group, suggesting that aspirin possibly lowers the QOL of patients especially at the early stage. However, we could not elucidate why aspirin—which is an inexpensive drug assessed to prolong life prognosis—lowers the QOL. Therefore, further studies including multivariate analysis will be required. In the future, it will be necessary to examine the effects of low-dose aspirin intake on the daily life of patients and to assess drugs as maintenance factors for therapeutic application, efficacy, or health condition and as predictive factors for disease.

Sixteen patients (21.3%) who concurrently used antiulcer drugs showed significant decreases ($p < 0.05$) in the RP and RE scores compared to 59 patients who did not. The GSRS, a disease-specific questionnaire for patients with gastrointestinal symptoms that was developed in Europe, uses QOL to quantitatively determine the effects of 5 gastrointestinal symptoms—acid regurgitation, abdominal pain, dyspepsia, diarrhea, and constipation—on daily living based on replies to 15 questions (15). The GSRS revealed the high AR scores only in patients who took antiulcer drugs (Table 5). However, other gastrointestinal tract-related QOL scores showed no decrease. The present study revealed no significant difference between patients receiving and not receiving antiulcer drugs with respect to the incidences of ulcer and hemorrhagic gastritis. Therefore, patients receiving antiulcer drugs were found to present decreased QOL as indicated by the SF-36[®] and GSRS. Therefore, we consider that in the future the elucidation of causes for decreased QOL will contribute to the establishment of appropriate prophylaxis against and therapeutic modalities for aspirin-induced peptic ulcer in patients with cardiovascular disease. In the future, a large-scale prospective study will be necessary to stratify risks of patients to whom antiulcer drugs should be administered and to examine the cost-benefit performance of drug administration.

We successfully and safely conducted transnasal endoscopy without discontinuing aspirin. Furthermore, only 18.6% of the patients receiving aspirin were aware of the possible development of gastric mucosal damage by the drug. In consideration of the fact that many patients with gastric mucosal lesions showed no subjective symptoms, we consider it difficult to find the patients with gastric lesions by symptoms in patients receiving aspirin. Therefore, it is recommended that patients receiving aspirin undergo regular transnasal endoscopy, regardless of the presence or absence of symptoms.

The authors state that they have no Conflict of Interest (COI).

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