Analysis of risk factors for colonic diverticular bleeding: A matched case–control study

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Short title: Risks of colonic diverticular bleeding.

Background and Aims: Diverticular bleeding can occasionally cause massive bleeding that requires urgent colonoscopy (CS) and treatment. The aim of this study is to clarify the significant risk factors for the colonic diverticular hemorrhage. **Methods**: Between January 2009 and December 2012, 26602 patients underwent CS at our institution. One hundred twenty-three patients received an urgent CS because of acute lower gastrointestinal hemorrhage. Seventy-two patients were diagnosed with colonic diverticular hemorrhage. One hundred forty-nine age- and sex- matched controls were selected from the patients with non-bleeding diverticula patients who underwent CS during the same period. The relationship of risk factors with diverticular bleeding was compared between the cases and controls. **Results**: From the results of the univariate and multivariate conditional logistic regression, the usage of non-steroidal anti-inflammatory drugs(OR = 14.70, 95% CI: 3.890-55.800, $P < 0.0001$), as well as the presence of cerebrovascular disease (OR = 8.66, 95% CI: 2.330-32.100, $P = 0.00126$), and hyperuricemia (OR = 15.5, 95% CI: 1.740-138.000, $P = 0.014$) remained statistically significant. **Conclusion**: These factors were significant risks for colonic diverticular hemorrhage. The knowledge obtained from this study may provide some

insight into the diagnostic process for the patients with lower gastrointestinal bleeding.

Introduction

Colonic diverticula are small pouches from the colonic lumen. It typically forms in parallel rows between the taeniae coli because of weakness of the muscle wall at sites of penetration of the vascular supplying the mucosa[1]. Diverticulosis has been labeled a disease of Western civilization because of its striking geographic variability. The disorder is rare in the countryside of Africa and Asia, with the highest prevalence seen in the USA, Europe, and Australia[2].

The prevalence of diverticular diseases increases with age in general[3]. Less than 10% of cases are in adults aged 40 years or more. However, almost one-third of the people aged up to 50 years have diverticulosis, and up to 60% of people older than 80 years have been affected[4]. In Japan, the prevalence of diverticular disease among the aged population also has increased as a result of insufficient dietary fiber intake, as in Western countries[5].

Around 75%–80% of patients with anatomical diverticulosis will remain

asymptomatic throughout their lifetime[1]. However, a few develop complications such as

diverticulitis, abscesses, fistulas, obstruction, and hemorrhage. One of the most frequent

complications is diverticular hemorrhage.

Diverticular hemorrhage is one of the common causes of lower gastrointestinal

bleeding and accounts for 41% of gastrointestinal bleeding[6]. Severe hemorrhage can

arise in 3%–5% of patients with diverticulosis and can frequently cause massive

bleeding that requires urgent colonoscopy (CS).

In pathology, the microangiography of resected specimens from patients with bleeding

diverticula typically shows intimal thickening and medial thinning of the vasa recta as it

runs over the dome of the diverticulum[7]. These changes arise asymmetrically toward the

lumen, leading to a segmental weakening of the artery and eventually rupture. The

factors that initiate these arterial changes are unknown, although inflammation does not

seem to be a contributing factor[1]. This finding is in agreement with the clinical with the

clinical impression that bleeding rarely complicates diverticulitis.

Till date, several reports have analyzed the background factors that might be

associated with diverticular hemorrhage[8]. However, to the best of our knowledge there

have been few reports that have performed analysis in the form of a matched case-control study at a high volume center.

The aim of the present study is to confirm the etiologic factors that cause diverticular hemorrhage by analyzing patients who were cared for at a single center.

Methods

Patients and methods

Between January 2009 and December 2012, 26602 patients underwent a CS at Showa University Northern Yokohama Hospital, Yokohama, Japan. One hundred twenty-three Japanese patients had an urgent CS due to acute lower gastrointestinal hemorrhage. Patients with iatrogenic hemorrhages, caused by endoscopic mucosal resection and endoscopic submucosal dissection, were excluded. Our criterion for performing urgent CS was that the procedure was undertaken within 24 hours of visiting our institution for the diagnosis and treatment of lower gastrointestinal hemorrhage. Of the 123 patients, 72 patients were diagnosed with colonic diverticular hemorrhage on the basis of the following criteria, which was based on the report by Jensen *et al.*[9]: active bleeding from

a diverticulum was observed or blood coagulates were found in the colon with diverticula in the absence of blood in the terminal ileum and any other demonstrable cause of bleeding. When the urgent CS detected an active bleeding point at a diverticulum, endoscopic hemostasis with a hemoclip was performed.

We selected 149 age- and sex-matched controls from the non-bleeding diverticulum patients who underwent CS for other reasons during the same period. These controls were diagnosed with colonic diverticulosis by CS, and they had not experienced bleeding (Fig. 1).

To obtain accurate information, we administrated a questionnaire at the time of CS at our endoscopic unit by medical research staff. The staff double-checked the medical records to avoid possible miscalculations. The information included the presence of cerebrovascular disease (cerebral infarction or hemorrhage), ischemic heart disease, hypertension, hyperlipidemia, diabetes mellitus, chronic renal disease, osteoporosis, and hyperuricemia. These diseases were considered present if the patients had been diagnosed with the condition in past or were taking medicine to treat the condition at the time of investigation. Moreover, information was gathered about medications, including

non-steroidal anti-inflammatory drugs (NSAIDs), antithrombotic agents (antiplatelets,

anticoagulants and low-dose aspirin), body mass index, and lifestyle factors such as

alcohol consumption was gathered. We obtained the information about the type of

NSAIDs, such as coxib- or non-coxib agents and about the frequency of usage, such as

regular or intermittent intake. Subjects who consumed more than 350ml beer considered

to be drinkers, and those who smoked more than 10 cigarettes per day were considered

to be smokers. The relationship of these factors with diverticular bleeding was

compared between cases and controls. The ethics committee of the Showa University

Northern Yokohama Hospital approved this study protocol.

Statistical analysis

To estimate the risk factors for diverticular bleeding, the factors were compared

between cases and controls. The data were evaluated using descriptive statistical

methods (means ± SDs). For the comparison of two factors, the unpaired Student's t-test

was used. A frequency distribution was calculated by the chi-squared test or Fisher's

exact probability test. Univariate and multivariate conditional logistic regression

analyses procedures were used to obtain crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) after controlling simultaneously for potential confounders. Two-sided *P*-values less than 0.05 were regarded as statistically significant. Multicollinearity was assessed by the variance inflation factor. A variance inflation factor was regarded as indicating serious multicollinearity, and values greater than 2.0 may be a cause for concern. All analyses were performed using R version 2.14.0[10].

Results

Table 1 shows the diagnoses of the patients with acute lower gastrointestinal bleeding. Diverticular hemorrhage was the most frequent cause of lower gastrointestinal hemorrhage, and it accounted for 72/123 (58.5 %) of all cases of acute bleeding from the lower intestine. Twenty-six patients were diagnosed with diverticular hemorrhage because of active bleeding from a diverticulum, and 46 patients were diagnosed because of observing blood coagulates in the diverticula in the absence of blood in the terminal ileum and any other demonstrable cause of bleeding.

In the patients with diverticular hemorrhage, 22 (31%) patients had severe anemia that needed red cell transfusions of two units or more. During the preparation for the urgent CS, 59 (82%) patients had been given polyethylene glycol (PEG), 11 (15%) patients had been administrated by a glycerin enema (GE), and 2 (3%) patients were received nothing (no-prep). We detected the 26 bleeding points (26/72; 36%) for these diverticular hemorrhages; in 19(32%) of the 59 PEG cases, 6(55%) of the 11 GE cases, and 1(50%) of the 2 no-prep cases. Table 2 shows the clinical characteristics of the cases and controls. The age range of the patients was 33-93 years (average, 70). The male: female sex ratio of the patients was 51:21. Twenty-four diverticula were located in the left hemicolon and 48 in the right hemicolon in the patients, whereas 77 were located in the left hemicolon, and 72 in the right hemicolon in the controls. The body mass index was 21.3 in the cases and 22.8 in the controls. Drinkers and smokers habits were recognized to be 14 (19.4%) and 10 (13.9%) of the bleeding cases, and 40 (26.8%) and 14 (9.3%) of the controls, respectively.

By using age and sex as matching variables, we conducted a case-control study to analyze the risk factors. In the results of the univariate analysis, the factors of

cerebrovascular disease, hypertension, hyperuricemia, chronic renal disease, and the

usage of antithrombotic agents and NSAIDs were significantly related to an increase in

ORs (Table 3). The variance inflation factors for cerebrovascular   disease,

hypertension, hyperuricemia, chronic renal disease, and the usage of antithrombotic

agents and NSAIDs were 1.6946, 1.0671, 1.5757, 1.0166, 1.0694, and 1.1641,

respectively. Evidence for multicollinearity was absent because the variance inflation

factor for independent variables in all factors was less than 2.0. Using these factors, we

performed multivariate conditional logistic regression with stepwise variable selection.

Finally, the current usage of NSAIDs (OR = 14.70, 95% CI: 3.890-55.800, $P < 0.0001$),

the presence of cerebrovascular disease (OR = 8.66, 95% CI: 2.330-32.100, $P =$

0.00126), and hyperuricemia (OR = 15.5, 95% CI: 1.740-138.000, $P = 0.014$) remained

statistically significant (Table. 4).

 Seventy-two patients were diagnosed with a diverticular bleeding by urgent CS. We

divided diverticular hemorrhage patients into a definite group   (active bleeding from a

diverticulum was observed) and a presumptive group (blood coagulates were found in

the colon), and re-conducted the same case-control study. In the definite group, 26

patients were diagnosed with diverticular hemorrhage with active bleeding, and in the presumptive group, 46 patients with blood coagulate were found in the colon. Table. 5 showed the results of the case- control study for the definite group. NSAIDs (OR = 16.766, 95% CI: 1.5297-183.747, P = 0.021) and hypertension (OR = 3.785, 95% CI: 1.0532-13.6, P = 0.04141) were significantly associated in the multivariate analysis. In the presumptive group, the association of NSAIDs (OR = 19.665, 95% CI: 3.7972-101.843, P = 0.0004), antithrombotic agents (OR = 4.828, 95% CI: 1.603-14.536, P = 0.0051), and hypertension (OR = 2.711, 95% CI: 1.1327-6.489, P = 0.0251) with diverticular hemorrhage was significant in the multivariate analysis (Table 6).

Discussion

This study identified information about colonic diverticular bleeding. Our results indicated that the current usage of NSAIDs, the presence of cerebrovascular disease, and the presence of hyperuricemia were risk factors for bleeding.

The mechanism for diverticular hemorrhage is not completely understood. However,

the bleeding is thought to be a rupture of small arteries, with accumulated endoepithelial

damage[7][11]. Frequently, sclerosis of a vessel might be subject to diverticular bleeding.

Diverticular bleeding has been considered to be a result of a rupture of arteriosclerosis.

The probable sequence of bleeding is first in injury of physically factors arising within

the lumen produce an eccentric damage to the luminal side of the underlying artery. The

artery reacts with eccentric intimal thickening. Following persistent or recurrent damage,

the initial thickening may become concentric but retains accentuation toward the lumen

of the diverticulum. Consequently, progressive segmental weakening of the arterial wall

leads to eccentric rupture and hemorrhage[12]. Arteriosclerosis is commonly accompanies

aging, therefore, colonic diverticula and the bleeding frequently occur among older

patients. In our study, the average age of patients with diverticular bleeding was 70

years. This fact supported the idea that arteriosclerosis is the main cause of bleeding.

However, 16.7%(12/72) of patients were less than 60 years old. Therefore, we

speculated that additional factors might be involved in the vascular frangibility of the

diverticula.

The aim of this study is to clarify the significant risk factors for diverticular

hemorrhage. Because arteriosclerosis is thought to be the main cause of diverticular bleeding, we matched the patients and controls by age and gender, expecting similar arteriosclerosis levels of arteriosclerosis between them. As a result, we found that the current usage of NSAIDs, as well as the presence of cerebrovascular disease, and hyperuricemia may have an additional influence on the complications of diverticula that lead to vascular damage. In addition, the multivariate analysis of the definite group and presumptive group revealed that the current usage of NSAIDs was considered the most significant risk factor. Previous studies have also reported that NSAIDs were a major cause of diverticular hemorrhage[8,13,14]. Most NSAIDs inhibit prostaglandin synthesis. This might impair the microcirculation and inhibit platelet aggregation, such that bleeding might occur in the presence of diverticula[15]. In addition, the benefits of selective COX-2 inhibitors for the protection of the gastrointestinal tract have been generally accepted, confirming the inhibitory effect of prostaglandins in gastrointestinal bleeding. Thus, the usage of NSAIDs may increase the vascular frangibility in patients in whom some level of arteriosclerotic change already exists.

Hyperuricemia was also found to be a risk factor for diverticular hemorrhage in the

present study[16.17]. Research has shown that hyperuricemia directly affects diverticular

bleeding. Increased uric acid levels promote the oxygenation of low-density lipoprotein

cholesterol and facilitate lipid peroxidation, resulting in the increasing the production of

oxygen free radicals. Each of these influences is known to plays an essential role in the

progression of atherosclerosis[16]. Consistent with finding of the present study that

cerebrovascular disease was a significant risk factor in our study, Okamoto T *et al*[18]

reported that cardio- or cerebrovascular disease was a significant risk factor for

diverticular bleeding. These factors, including hyperuricemia, suggest that systemic

metabolic disorders and arteriosclerosis play an important role in diverticular bleeding.

A prospective study to investigate the relationship between diverticular bleeding and

arteriosclerosis will be needed in the future.

 Our study has several limitations. First, a retrospective study includes a potential recall

bias. Second, in general, controls should be enrolled from the same source population or

study base from which the cases were selected, as was done in our study. However, in a

strict sense, not only the similarities in age and sex but also the other factors such as

size, location, and numbers of diverticula should have been equalized between the cases

and controls. Such detailed analysis may be needed in the future to elucidate the risk

factors for diverticular bleeding more precisely.

 In conclusion, this study indicates that the current usages of NSAIDs, as well as the

presence of cerebrovascular disease and hyperuricemia were significant risk factors for

colonic diverticular hemorrhage. The knowledge obtained through this study may give

some insight into the diagnostic process for the patients with acute lower

gastrointestinal bleeding.

Competing interests: None

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Figure legend

Fig 1. Clinical background of the patients enrolled in the present study.