Impact of discontinuing non-steroidal antiinflammatory drugs on long-term recurrence in colonic diverticular bleeding

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METHODS: A cohort of 132 patients hospitalized for CDB examined by colonoscopy was prospectively enrolled. Comorbidities, lifestyle, and medications (NSAIDs, low-dose aspirin, antiplatelet agents, anticoagulants, acetaminophen, and corticosteroids) were assessed. After discharge, patients were requested to visit the hospital on scheduled days during the follow-up period. The Kaplan-Meier method was used to estimate recurrence.

RESULTS: Median follow-up was 15 mo. The probability of recurrence at 1, 6, 12, and 24 mo was 3.1%, 19%, 27%, and 38%, respectively. Of the 41 NSAID users on admission, 26 (63%) discontinued NSAID use at discharge. Many of the patients who could discontinue NSAIDs were intermittent users, and could be switched to alternative therapies, such as acetaminophen or an antiinflammatory analgesic plaster. The probability of recurrence at 12 mo was 9.4% in discontinuing NSAID users compared with 77% in continuing users (P < 0.01, log-rank test). The hazard ratio for recurrence in the discontinuing NSAIDs users was 0.06 after adjusting for age > 70 years, right-sided diverticula, history of hypertension, and hemodialysis. No patients developed cerebrocardiovascular events during follow-up.

Abstract

AIM: To determine the effect of discontinuing non-steroidal antiinflammatory drugs (NSAIDs) on recurrence in long-term follow-up patients with colonic diverticular bleeding (CDB).

METHODS: A cohort of 132 patients hospitalized for CDB examined by colonoscopy was prospectively enrolled. Comorbidities, lifestyle, and medications (NSAIDs, low-dose aspirin, antiplatelet agents, anticoagulants, acetaminophen, and corticosteroids) were assessed. After discharge, patients were requested to visit the hospital on scheduled days during the follow-up period. The Kaplan-Meier method was used to estimate recurrence.

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CONCLUSION: There is a substantial recurrence rate after discharge among patients hospitalized for diverticular bleeding. Discontinuation of NSAIDs is an effective preventive measure against recurrence. This study provides new information on risk reduction strategies for diverticular bleeding.

Key words: Non-steroidal anti-inflammatories; Drug withdrawal; Diverticular hemorrhage; Hemodialysis; Antithrombotic drugs

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Core tip: The probability of recurrence of diverticular bleeding at 1, 12, and 24 mo was 3.1%, 27%, and 38%, respectively. Of the 41 non-steroidal anti-inflammatory drugs (NSAIDs) users on admission, 26 (63%) discontinued NSAID use at discharge. The probability of recurrence at 12 mo was 9.4% in discontinuing NSAID users compared with 77% in continuing users (P < 0.01, log-rank test). The hazard ratio for recurrence in the discontinuing NSAIDs users was 0.06 after adjusting for age > 70 years, right-sided diverticula, history of hypertension, and hemodialysis. No patients developed cerebrovascular events during follow-up. This study provides new information on risk reduction strategies for diverticular bleeding.

INTRODUCTION

Colonic diverticular bleeding (CDB) is the most common cause of acute lower gastrointestinal bleeding (LGIB), representing approximately 40% of cases[1]. A significant proportion of patients with CDB experience severe bleeding and receive emergency treatment with resuscitative measures, possibly because of their advanced age, use of antithrombotic agents, or comorbidities[2-4]. Even though intensive management of CDB is successful during the hospital stay, following discharge, patients are at high risk of recurrent bleeding, which has been reported at a rate of 14%-43%[5-7]. As a result, patients often undergo frequent examinations, rehospitalization, and a consequent decrease in quality of life.

Risk reduction is an important clinical issue because no preventive therapy for recurrence is currently available for LGIB, such as proton-pump inhibitors used for the prevention of upper gastrointestinal bleeding (UGIB)[8]. Withdrawal of aspirin was recently reported to significantly reduce UGIB recurrence[9]. In LGIB, particularly CDB, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is a significant risk factor for recurrence[2,10,11], but the risks and benefits of their discontinuation on CDB have not been examined.

We previously conducted a study on the recurrence risk of CDB[5], but the retrospective investigation included biases that likely led to exposure variables being missed. Furthermore, it was unknown whether antithrombotic agents were continued, and follow-up was not conducted in a systematic manner. The present study builds upon our previous work by focusing on multiple risk factors for CDB, prospective follow-up of newly diagnosed cases, and detailed assessment of medications. The objectives of this study were to identify the risk factors associated with the recurrence of CDB after discharge, and to evaluate the effect of discontinuing NSAIDs on rebleeding risk over long-term follow-up.

MATERIALS AND METHODS

Subjects

Patients admitted to our hospital for overt LGIB between September 2009 and October 2013 and examined at the endoscopy unit of the National Center for Global Health and Medicine (NCGM) were enrolled. Patients from a previous study cohort[12], a newly diagnosed cohort (approval No. 750), and a randomized trial cohort (approval No. 765) were prospectively followed after discharge. Inclusion criteria were: (1) > 18 years old; (2) Japanese nationality; (3) overt LGIB examined within 1 wk of onset; and (4) being managed in hospital. Exclusion criteria were: (1) no informed consent provided; (2) not independent in activities of daily living; (3) not undergoing colonoscopy; (4) LGIB due to causes other than CDB; and (5) barium impaction therapy in the randomized controlled trial (approval No. 765). All inclusion and exclusion criteria were fulfilled before patients were enrolled. The NCGM is a large emergency hospital, with 900 beds, located in metropolitan Tokyo, Japan. All patients provided written informed consent prior to enrollment. The institutional review board at the NCGM approved this study (approval No. 810), and all clinical procedures conformed to Japanese and International ethical guidelines (Declaration of Helsinki).

Exposure variables

Patients were asked about their lifestyle habits, medications, and comorbidities in a face-to-face interview on the pre-colonoscopy day.

Medication: The questionnaire survey form asked about the use of 9 kinds of NSAIDs, 2 kinds of low-
dose aspirin, 10 other antiplatelet agents, 3 anticoagu-
lants, acetaminophen, and oral corticosteroids. The ques-
tionnaire included photographs of all of these oral drugs,
which are approved in Japan. Use of a medication was
defined as oral administration within 1 mo of the inter-
view. During hospitalization, low-dose aspirin, other antiplatelet drugs, and anticoagu-
lants were temporarily stopped or other bridging drugs
given whenever possible after consulting a cerebrocardiovascular specialist. Low-
dose aspirin and other antiplatelet agents were res-
umed after hemostasis before discharge. Also, 
NSAIDs were temporarily stopped on admission and
prescribed during hospitalization only on the advice
of an orthopedist or rheumatology specialist. We
suggested NSAID withdrawal to those who were inter-
mittent users and to those who were suitable for
alternative therapy such as acetaminophen, an
antinflammatory analgesic plaster, antigout drugs,
antirheumatic drugs, or corticosteroids.

**Comorbidities:** Hypertension, diabetes mellitus, dys-
lipidemia, cerebrocardiovascular disease, chronic
liver disease, and chronic kidney disease (CKD) were
assessed. A history of cerebral infarction, cerebral
hemorrhage, myocardial infarction, or angina pectoris
was considered cerebrocardiovascular disease. CKD
was considered present in patients on hemodialysis.
Chronic liver disease included chronic viral hepatitis
and alcoholic liver disease.

**Diagnostic criteria of colonic diverticular bleeding**
An electronic high-resolution video endoscope (mo-
del CFH260; Olympus Optical, Tokyo, Japan) was
used after spontaneous cessation of bleeding. CDB
was defined as either definite or presumptive on
the basis of colonoscopy with multidetector com-
tputed tomography (MDCT). Definitive diagnosis
was based on coloscopic visualization of colonic
diverticula with stigmata of recent hemorrhage
such as active bleeding, adherent clot, or visible
vessel. A presumptive diagnosis was based on
MDCT visualization of the extravasation of contrast
medium in colonic diverticula and colonoscopy
showing (1) a potential bleeding site in an area of
positive MDCT findings; (2) fresh blood localized
to colonic diverticula in the presence of a potential
bleeding source on complete colonoscopy; or (3)
bright red blood in the rectum confirmed by objective
color testing and colonoscopy demonstrating a single
potential bleeding source in the colon, complemented
by negative upper endoscopy, or negative capsule
endoscopy. Patients in whom the bleeding source
was identified received endoscopic treatment such as
clipping or endoscopic ligation.

**Follow-up and rebleeding**
After discharge, all patients were requested to visit
the hospital in the case of bloody stools or on a
scheduled day within the first month and then every
three months during the observation and follow-up
periods. Telephone interviews were conducted with
patients who did not visit the hospital on scheduled
days, and a hospital visit was recommended.
Rebleeding was defined as a significant amount of
fresh bloody or wine-colored stools (> 200 mL)
during the follow-up period and was evaluated by
both anoscopy and MDCT within 12 h of onset.
Clinically suspected rebleeding should prompt fur-
ther colonoscopy when possible, but no routine second-
look colonoscopy was performed when rebleeding
occurred during hospitalization or within 1 mo of
discharge. Colonoscopy was performed to confirm
rebleeding and determine the need for intervention
when frequent or massive bleeding occurred along
with unstable vital signs, systolic blood pressure ≤
90 mmHg or pulse ≥ 110 beats/min, and a non-
response to ≥ 2 units of transfused blood during a
24-h period. We distinguished between rebleeding
and remaining blood from the index bleeding
episode.

**Statistical analysis**
The primary outcome was rebleeding due to CDB.
The secondary outcome was a cerebrocardiovascular
or thrombotic event during the follow-up period.
Patients lost to follow-up or death were censored
at the time of their last visit. The Kaplan-Meier
method was used to estimate the recurrence of
CDB at 1, 6, 12, and 24 mo after discharge. Risk
factors and the effect of NSAID withdrawal on
rebleeding were analyzed using the log-rank test. Cox
proportional hazards regression was used to analyze
the independent risk factors for rebleeding
by considering factors significant (P < 0.1) in the
log-rank test and adjusting for factors such as age > 70
years and hypertension, as previously reported.

A value of P < 0.05 was considered significant.
All statistical analysis was performed using Stata
version 10 software (StataCorp, College Station, TX,
United States).

**RESULTS**

**Participants**
During the study period, 337 patients were admitted
to our hospital for acute LGIB. After exclusion,
132 patients with CDB were enrolled in this study.
Baseline characteristics at discharge are shown in
Table 1. Diverticula were located predominantly in
the bilateral colon in 48%, in the right side in 32%,
and in the left side in 20% of cases. Of these, 17%
(23/132) had colonoscopic evidence of stigmata
of recent hemorrhage diverticula and were treated
by endoscopic procedures during hospitalization,
in which 37 patients (28%) received a mean
transfusion of 8 units of packed red blood cells.

Among the patients using NSAIDs on admission
(n = 41), 26 (63%) discontinued NSAID use. Many patients who could withdraw NSAIDs were intermittent users (n = 23), and could be switched to alternative therapies included acetaminophen (n = 11), an antiinflammatory analgesic plaster (n = 10), narcotic analgesics (n = 2), antigout drugs (n = 3), anti-rheumatic drugs (n = 1), and corticosteroids (n = 1), while the remaining patients (n = 7) took nothing. Some of these 26 patients took more than one of these drugs. No patients were taking NSAIDs for cardiovascular disease. Fifteen patients (11%) on NSAIDs and 13 patients (8.5%) on acetaminophen continued to take them after discharge. No patients on low-dose aspirin, non-aspirin antiplatelet agents, or corticosteroids discontinued use or started taking them during the follow-up period (Table 1).

The most common comorbidities were hypertension (63%), cardiovascular disease (25%), dyslipidemia (22%), diabetes mellitus (20%), hemodialysis (5.3%), chronic liver disease (3.8%), and cerebrovascular disease (1.5%) (Table 1).

Rebleeding outcomes
After discharge, 39 patients (30%) experienced rebleeding with a mean follow-up of 15 ± 13 mo. The
probability of rebleeding was 3.1% at 1 mo, 19% at 6 mo, 27% at 12 mo, and 38% at 24 mo (Figure 1A). No patients required angiographic embolization or surgical resection within the follow-up period.

Log-rank tests revealed NSAID use and hemodialysis as significant risk factors for rebleeding, while the other factors were not found to be significant (Table 2). Patients without right-sided diverticula had a risk of rebleeding, but this did not reach statistical significance (Table 2). The probability of rebleeding was 2.6% (95%CI: 0.86%-8.0%) at 1 mo and 21% (95%CI: 14%-30%) at 12 mo in non-NSAID users, and 7.1% (95%CI: 1.0-41) at 1 mo and 77% (95%CI: 52-94) at 12 mo in NSAID users (Figure 1B). The probability of rebleeding was 2.5% (95%CI: 1.0-7.6) at 1 mo and 24% (95%CI: 17-34) at 12 mo in non-hemodialysis patients, and 14% (95%CI: 2.1%-67%) at 1 mo and 71% (95%CI: 39%-96%) at 12 mo in hemodialysis patients (Figure 1C). Multivariate analysis revealed NSAID use and hemodialysis as independent risk factors for rebleeding (Table 3).

**Discontinuation of NSAIDs and rebleeding**

Of the NSAID users (n = 41), 15 continued and 26 discontinued NSAID use after discharge. During the follow-up period, no patient developed a thrombotic event, such as pulmonary embolism, deep vein thrombosis, or a cerebrocardiovascular event. No patient who discontinued NSAID use on discharge resumed NSAID use during the follow-up period. The probability of rebleeding was 0% at 1 mo and only 9.4% (95%CI: 2.4%-33%) at 12 mo in discontinuing NSAID users compared with 7.1% (95%CI 1.0%-41%) at 1 mo and 77% (95%CI: 52%-94%) at 12 mo in the continuing users (P < 0.01 by the log-rank test; Figure 2). The hazard ratio (HR) for rebleeding in the discontinuing NSAIDs group was 0.06 (95%CI: 0.01%-0.31%) after adjusting for age > 70 years, right-sided diverticula, history of hypertension, and hemodialysis in the Cox proportional hazards model.

**DISCUSSION**

To our knowledge, this is the first report showing that discontinuation of NSAIDs at discharge significantly reduced rebleeding compared with continuous NSAID use. Although, the number of NSAIDs users was small, this finding is useful in the long-term management of CDB. Moreover, no patients developed a worsening condition of underlying disease, thrombotic events, or cerebrocardiovascular events after cessation of

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**Table 2** Risk factors for rebleeding after discharge on univariate analysis (n = 132)

| Factor                      | Non-rebleeding/rebleeding | Hazard ratio (95%CI) | P  |
|-----------------------------|---------------------------|----------------------|----|
| Age > 70 yr                 | 45 (48/25 (64)            | 1.6 (0.83-3.1)       | 0.15 |
| Sex, male                   | 59 (63/28 (72)            | 1.1 (0.57-2.3)       | 0.70 |
| Anatomical distribution of diverticula | 40 (37/6 (21)            | 1.5 (0.79-2.8)       | 0.21 |
| Endoscopic procedure        | 20 (22/3 (7.7)            | 0.43 (0.13-1.4)      | 0.16 |
| Transfusion requirement     | 25 (27/12 (31)            | 1.2 (0.63-2.5)       | 0.53 |
| Current drinker             | 90 (97/36 (92)            | 0.78 (0.24-2.5)      | 0.68 |
| Current smoker              | 26 (28/10 (26)            | 0.80 (0.39-1.7)      | 0.55 |
| NSAID users                 | 4 (4/3/11 (28)            | 5.1 (2.5-10)         | < 0.01 |
| Non-aspirin antplatelet users | 16 (17/11 (28)            | 1.6 (0.78-3.1)       | 0.21 |
| Anticoagulant users         | 7 (7.5/2 (5.1)            | 0.54 (0.13-2.2)      | 0.38 |
| Acetaminophen users         | 10 (11/3 (77)             | 0.72 (0.22-2.3)      | 0.58 |
| Corticosteroid users        | 3 (3/2/1 (5.1)            | 1.4 (0.35-6.0)       | 0.61 |
| Hypertension                | 55 (60/28 (72)            | 1.4 (0.69-2.8)       | 0.35 |
| Diabetes mellitus           | 22 (24/9 (13)             | 0.52 (0.20-1.3)      | 0.16 |
| Dyslipidemia                | 20 (22/9 (23)             | 0.88 (0.42-1.8)      | 0.73 |
| Cardiovascular disease      | 25 (27/6 (21)             | 0.55 (0.25-1.2)      | 0.13 |
| Cerebrovascular disease     | 1 (1/1 (126)              | 1.4 (0.19-10)        | 0.76 |
| Chronic liver disease       | 3 (3/2/1 (5.1)            | 1.4 (0.34-5.9)       | 0.62 |
| Hemodialysis                | 2 (2.2/3 (13)             | 4.0 (1.5-10)         | < 0.01 |

**Table 3** Risk factors for rebleeding after discharge on multivariate analysis (n = 132)

| Factor                      | Hazard ratio (95%CI) | P  |
|-----------------------------|----------------------|----|
| Age > 70 yr                 | 1.2 (0.6-2.3)        | 0.68 |
| Right-sided diverticula     | 0.6 (0.3-1.5)        | 0.29 |
| Continued NSAID use         | 4.6 (2.2-9.4)        | < 0.01 |
| Hypertension                | 1.3 (0.6-2.8)        | 0.43 |
| Hemodialysis                | 3.0 (1.1-7.8)        | 0.03 |

CI: Confidence interval; NSAID: Non-steroidal anti-inflammatory drugs.

Figure 2 Probability of recurrent bleeding in patients with non-steroidal anti-inflammatory drugs on admission (n = 41). The probability of rebleeding was higher in subjects continuing non-steroidal anti-inflammatory drugs (NSAIDs) than in those discontinuing NSAIDs (P < 0.01).
NSAIDs.

In agreement with previous studies, this study showed that patients using NSAIDs had a risk of rebleeding during follow-up (often within the first year) approximately 5-fold greater than those without. A previous large cohort study found that NSAID users had a 1.7-fold higher risk of CDB\(^{10}\), and other case-control studies have reported increased bleeding risks of 4-15-fold\(^{[6,11,15]}\) and re-bleeding risks of 3-6-fold\(^{[5,6]}\). Tsuruoka et al\(^{[16]}\) conducted CDB case-control (patients hospitalized for other diseases during the same period) investigations and showed that only NSAID use was an independent risk factor for bleeding (OR = 9.9) and rebleeding (OR = 5.4). Another report by Wilcox et al\(^{[17]}\) compared 105 patients with LGB and 1895 non-bleeding controls, and found that NSAID users had a 3.4-fold higher risk of CDB. Although a wide range of risk ratios have been reported, likely due to differences in study design or sample size, it is clear that NSAID use is an unequivocal risk factor for CDB.

In contrast to this greater risk of rebleeding, withdrawal of NSAIDs significantly reduced the risk of rebleeding during follow-up compared with continued use (HR = 0.06). In UGB, protonpump inhibitors reduce recurrence\(^{[8]}\), but there is no preventive therapy for LGB. It is thus all the more critical to validate factors associated with risk reduction in LGB. A few studies have examined the risk reduction of GI bleeding associated with drug withdrawal, but not non-aspirin NSAIDs: Witt et al\(^{[18]}\) found that patients with GI bleeding who resumed warfarin use had a higher GI re-bleeding risk and fewer thrombotic events than those who discontinued use. Sung et al\(^{[19]}\) conducted a randomized controlled trial in patients with peptic ulcer bleeding and found that continuous low-dose aspirin increased the risk of re-bleeding, but potentially reduced mortality, while prolonged discontinuation of aspirin led to a lower risk of rebleeding, but higher mortality. One of the reasons we could withdraw NSAIDs in many of our patients (26/41) was that most were not regular users and could be switched to other drugs, such as acetaminophen, an antiinflammatory analgesic plaster, antigout drugs, antirheumatic drugs, or corticosteroids. Furthermore, we could closely monitor these patients and confirm no exacerbation of pain. However, one randomized controlled trial on the treatment of painful knee osteoarthritis found that discontinuation of non-aspirin NSAIDs exacerbated pain and negatively impacted patient quality of life\(^{[19]}\). Thus, the decision to terminate NSAIDs should be carefully considered.

In contrast, the cessation of NSAIDs may cause cardiovascular events. Fischer et al\(^{[10]}\) conducted a large case-control study and suggested that the risk of developing acute myocardial infarction (AMI) is increased for a period of several weeks after discontinuing NSAID use, particularly in patients using NSAIDs on a long-term basis. Their study indicated that the risk of AMI was not increased in patients currently using NSAIDs or in users who stopped using NSAIDs more than 3 mo before. In this study, no patients had a high risk of AMI such as long-term internal users or regular users. Therefore, caution should be exercised in such patients when discontinuing NSAIDs.

Hemodialysis was associated with rebleeding in the present study. Intermittent use of heparin for dialysis treatment and the presence of uremia-induced platelet dysfunction are associated with GI bleeding\(^{[21,22]}\). In addition, patients with chronic kidney disease demonstrate abnormalities in blood coagulation and bleeding predisposition, resulting in consistent anemia in UGB cases\(^{[22,23]}\). Thus, hemodialysis patients with CDB should be carefully managed after discharge.

In this study, we were able to prospectively collect detailed information on comorbidities and medication, and to conduct long-term follow-up of patients hospitalized for CDB. Nonetheless, there are several limitations to this study. First, the number of patients who discontinued NSAIDs was relatively small. Second, no data on hemodynamic instability, hematocrit, and abnormal white blood cell count were collected. Third, the study had a non-randomized controlled design.

In conclusion, discontinuation of NSAIDs is an effective preventive measure against rebleeding in CDB. Patient education about the reduction in the risk of bleeding is important, but medication withdrawal should be considered in view of its risks and benefits, particularly in patients of advanced age or with comorbidities.

ACKNOWLEDGMENTS

We wish to thank Hisae Kawashiro, Clinical Research Coordinator, for assistance with data collection.

COMMENTS

Background

Even though intensive management for diverticular bleeding is successful during the hospital stay, patients are at high risk of recurrent bleeding following discharge. Unlike upper gastrointestinal (GI) bleeding, there are no preventive therapies for lower GI bleeding. Thus, preventing recurrence requires risk factors to be identified.

Research frontiers

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is a significant risk factor for recurrence, but the risks and benefits of their discontinuation on diverticular bleeding have not been examined.

Innovations and breakthroughs

In total, 39 patients (30%) had rebleeding during a median follow-up of 15 mo. Of the 41 NSAID users on admission, 26 (63%) discontinued NSAID use at discharge. Multivariate analysis revealed continued NSAID use (HR = 4.6, \(P < 0.01\)) and hemodialysis (HR = 3.0, \(P < 0.01\)) as independent risk factors for rebleeding. Discontinuation of NSAIDs significantly reduced rebleeding risk continuing NSAID use, particularly in patients using NSAIDs on a long-term basis. Their study indicated that the risk of AMI was not increased in patients currently using NSAIDs or in users who stopped using NSAIDs more than 3 mo before. In this study, no patients had a high risk of AMI such as long-term internal users or regular users. Therefore, caution should be exercised in such patients when discontinuing NSAIDs.
compared with continued use (log-rank test, P < 0.01).

Applications
Discontinuation of NSAIDs is an effective preventive measure against rebleeding in diverticular bleeding. However, medication withdrawal should be considered in view of its risks and benefits, particularly in patients of advanced age or with comorbidities.

Terminology
The precise mechanisms of NSAID-induced diverticular bleeding has been suggested to be due to the inhibition of platelets, cyclooxygenase-1, and prostaglandin synthesis in the lower GI tract. Mucosal injury due to the inhibition of intestinal prostaglandin synthesis might lead to the development of intestinal erosion and ulcers. When mucosal ulceration induced by NSAIDs occurs at the neck or dome of the diverticulum, nutrient-providing arteries rupture into the colonic lumen with the potential to cause sudden bleeding.

Peer review
The manuscript investigates the impact of discontinuing NSAIDs and the long-term recurrence in colonic diverticular bleeding. The authors tried to bring new ideas about preventive measures against colonic diverticular re-bleeding.

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P- Reviewer: Guo YM S- Editor: Qi Y L- Editor: Cant MR E- Editor: Zhang DN
