Making hematochezia of unknown origin known: A retrospective analysis

Running title: Making hematochezia of unknown origin known

Takanao Tanaka, M.D.[1)], Keiichi Tominaga, M.D., Ph.D. [1)], Akira Yamamiya, M.D., Ph.D.[1)], Takeshi Sugaya, M.D., Ph.D.[1)], Mimari Kanazawa, M.D., Ph.D.[1)], Masayuki Kondo, M.D.[1)], Keiichiro Abe, M.D., Ph.D.[1)], Akira Kanamori, M.D., Ph.D.[1)], Makoto Iijima, M.D., Ph.D.[1)], Kenichi Goda, M.D., Ph.D.[1)], Yasuo Haruyama, M.D., Ph.D.[2)], Atsushi Irisawa, M.D., Ph.D.[1)]

1 Department of Gastroenterology, Dokkyo Medical University, Tochigi, Japan

2 Integrated Research Faculty for Advanced Medical Sciences, Dokkyo Medical University, Tochigi, Japan

Correspondence: Keiichi Tominaga, M.D., Ph.D.

Department of Gastroenterology, Dokkyo Medical University

880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan

Email address: tominaga@dokkyomed.ac.jp

Telephone number: +81-282-87-2147

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Abstract

Background and Aim:

Hematochezia is observed frequently in daily practice. However, natural hemostasis often prevents identification of the bleeding source during observations. This study was conducted to clarify risk factors related to rebleeding in hematochezia patients without an identified cause of bleeding.

Methods:

We analyzed patients who were admitted to Dokkyo Medical University Hospital during April 1, 2009 through March 31, 2015 with the chief complaint of hematochezia. Main outcome measures included the rebleeding rate and the period until rebleeding in hematochezia patients without an identified bleeding source.

Results:

We selected 159 patients for analyses. Rebleeding was observed in 46 (28.9%) of 159 patients. The median period until first rebleeding was 166 days (2–3046 days). Univariate analysis indicated that risk factors for rebleeding were male gender (p=0.029), higher age (p=0.023), antithrombotic medicines (p=0.047), lower hemoglobin on admission (p=0.024), and the presence of diverticula (p=0.002).

Multivariate analysis indicated male gender (p=0.043) and the presence of diverticula (p=0.023) as rebleeding risk factors.

Conclusion:

In patients with hematochezia of unknown origin, risk factors for rebleeding indicated in this study should be given particular attention by physicians.

Key Words:

colonoscopy; diverticula; lower gastrointestinal bleeding; rebleeding

INTRODUCTION

Hematochezia, which is observed frequently in daily practice, has been reported in about 20% of adults. The most frequent cause is colonic diverticular bleeding, followed by intestinal ischemia, anorectal disorders, neoplasia, and other causes. [1-2] However, hematochezia can sometimes result from massive bleeding from the upper gastrointestinal (GI) tract or the small intestine. Previous reports have described upper gastrointestinal bleeding (UGIB) as the cause of bleeding in 6.6–14% of hematochezia patients. Identifying the bleeding source in hematochezia can sometimes be difficult. [3-4]

The source of bleeding in hematochezia is identified using dynamic computed tomography (CT), CT angiography, endoscopy, angiography, bleeding scintigraphy, etc. In the guidelines of many countries, colonoscopy is recommended particularly as the first choice for hematochezia patients because it has a high diagnostic yield and because it is useful for treatment.[5-7] A technical review of the American Gastroenterological Association in 2007, American College of Gastroenterology Clinical guidelines in 2015, European Society of Gastrointestinal Endoscopy clinical guidelines in 2015, and others [8-11] recommend that esophagogastroduodenoscopy (EGD) and colonoscopy be performed first with subsequent repeated examination if the bleeding source is not

identified. All guidelines propose differential diagnosis for intestinal bleeding, i.e., searching in the small intestine, and closely inspecting the small intestine by small-bowel capsule endoscopy (SBCE) when the bleeding source is not yet identified. When the bleeding source remains unidentified, one must consider repeated SBCE, enteroscopy, and so on as necessary. However, under present circumstances, the bleeding source is often unidentifiable at the time of observation because of natural hemostasis, even when endoscopy is performed in an emergency. A recent report has described bleeding etiology as 17% from the upper GI tract and 15% from the lower GI tract, with 68% having unknown etiology. [12]

Many reports have described rebleeding, risk factors of death, and proper follow-up in cases of hematochezia for which the cause had been clarified, although few reports have described analyses of hematochezia cases for which the causes were unknown. This study was conducted to clarify risk factors related to rebleeding in hematochezia patients who had no identified cause of bleeding.

MATERIALS AND METHODS

Study Design

This retrospective observational study conducted at Dokkyo Medical University Hospital was approved by the hospital's ethics committee (approval no. R-20-4J). This study was conducted in accordance with ethical principles of the Declaration of Helsinki and was registered with the University Hospital Medical Network Clinical Trials Registry [UMIN000045955]. We provided patients a means to opt out instead of omitting informed consent, which is a way of guaranteeing opportunities for research subjects to notify and publish research information related to our website.

The primary outcomes of this study were the rebleeding rate and the period until rebleeding (period until the first rebleeding when more than one rebleeding episode occurs) in hematochezia patients with an unidentified bleeding source. Secondary outcomes were set as the total number of rebleeding episodes, the source of bleeding and the identification rate in rebleeding, the bleeding-related death rate, and rebleeding risk factors.

Patients

The study included 159 patients out of 460 patients,16–99 years old, who were admitted to Dokkyo Medical University Hospital during April 1, 2009 through March 31, 2015, with the chief complaint of hematochezia, except those who met the exclusion

criteria. Excluded patients were the following: 1. irrespective of the patient complaint at the initial visit, patients whose presence of hematochezia could not be confirmed by any medical staff member: 2. patients who had received endoscopic treatment within 1 month preceding the visit; 3. patients for whom observation up to the terminal ileum could not be done using colonoscopy; 4. patients for whom the cause of hematochezia was identified during the first colonoscopy; 5. patients who had no follow-up visit after hospital discharge (follow-up period 0 day); and 6. patients who had a past history of hematochezia. Figure 1 presents the flow of patient selection.

Patients for whom the source of bleeding was not identified were defined as having hematochezia of unknown origin. Hematochezia that occurred during the follow-up period after the initial colonoscopy was defined as rebleeding. The follow-up period was set as the date of the final visit, based on our hospital's medical record.

Endoscopic Procedures and Clinical Course

All patients were examined using colonoscopy within 48 hr after the detection of hematochezia. Sodium picosulfate hydrate or sennoside A•B calcium was administered as a preparation on the day before the evaluation date. Intestinal lavage was performed on the evaluation date with 2 L of a solution containing polyethylene glycol. When

lavage was insufficient, a hydrostatic enema was added as appropriate. When the source of bleeding was clear, endoscopic hemostasis was performed using a hemoclip.

Data Collection

The following were referred from medical records to identify factors affecting rebleeding or bleeding-related death: age, sex, blood type, number of rebleeding episodes, colonoscopic findings (presence or absence of diverticula, tumor lesions, vascular lesions and anal diseases), hemoglobin (Hb) on admission, platelet count on admission, history of antithrombotic medication, non-steroidal anti-inflammatory drugs (NSAIDs) or prednisolone during the observation period, comorbidity (cardiovascular disease, liver disease, renal disease, cerebrovascular disease, diabetes, or hyperlipidemia), and death during the observation period. When the source of bleeding was identified or when surgical treatment was performed for hemostasis, observation was discontinued.

Statistical Analysis

Statistical analyses were conducted using chi-square tests for category variables or Mann–Whitney U tests for continuous variables between groups with and without rebleeding. Univariate and multivariate logistic regression analyses were applied to

analyze rebleeding risk factors. Considering the sample size, variables with *p*-values less than 0.2 in the univariate analysis were entered into the multivariate analysis, with the exception of sex and age. All statistical analyses were conducted with software (SPSS Statistics 27.0 Inc.; IBM Corp. Chicago, IL, USA) using an assumed type I error rate of 0.05. A statistician evaluated the statistics calculated for this study.

RESULTS

Patient characteristics

Table 1 presents patient baseline characteristics. The mean observation period after the first bleeding was 1314 days ± 1340 (2–4325 days). The mean age was 69.5 years. The percentage of male patients was 56.0%. For medication, 48.4% of the patients were taking antithrombotic medicines. For close examination of hematochezia, 22.9% and 5.9% of patients respectively received EGD and SBCE.

Analysis of rebleeding

Rebleeding in patients for whom the source of bleeding could not be identified, which was the primary outcome of the present study, was observed in 46 (28.9%) of 159 patients. The cumulative rebleeding rates after half a year, 1 year, 2 years, 5 years,

and 10 years were, respectively, 15.8%, 19.9%, 21.7%, 33.3%, and 39.9%. The median period until the first rebleeding was 166 days (2–3046). The numbers of rebleeding episodes were 1–5 times: 4 (8.7%) of 46 cases had 5 rebleeding episodes. Among patients in whom rebleeding occurred, the source of bleeding was identified in 7 cases (15.2%) (5 cases of diverticular bleeding, 1 case of small intestinal ulcer, and 1 case of rectal cancer). The distribution of durations until the first rebleeding in 46 patients is presented in Table 2.

Investigation of risk factors of rebleeding

Groups with and without rebleeding were compared: the group with rebleeding included older patients and had a higher percentage of men. Moreover, the group with rebleeding had significantly higher rates of antithrombotic medicine usage and diverticula (Table 3). Table 4 presents results of an investigation of rebleeding risk factors. Univariate analysis indicated risk factors of rebleeding: male gender (p=0.029), higher age (p=0.023), antithrombotic medicine usage (p=0.047), lower Hb on admission (p=0.024), and presence of diverticula (p=0.002). Parameters used for univariate analysis with $p< 0.2$ were extracted and were used for multivariate analysis (Table 5). The presence of diverticula (p=0.023) and male gender (p=0.043) were inferred as rebleeding risk factors.

Next, multivariate analyses were performed separately on male and female participants (Tables 6 and 7). The presence of diverticula was a risk factor of rebleeding in male patients (p=0.038) but not in female patients (p=0.275).

Investigation of death

Death occurred in 18 patients (11.3%) during the observation period. The 18 deaths included 4 from pneumonia, 2 from bleeding-related deaths, 3 from unknown causes, 2 each from intestinal obstruction and lung cancer, and 1 each from sepsis, cerebral hemorrhage, primary central nervous system lymphoma, suicide, and senility. The period from the first hematochezia to death was 272 days and 116 days in the two bleeding-related deaths. One of them had no rebleeding. The other experienced two rebleedings before death. Both had liver cirrhosis (Child–Pugh class C).

DISCUSSION

Several reports have described hematochezia or Lower GI Bleeding (LGIB) and analyses of GI tract bleeding of unknown origin. [13-17] Our analysis found that 46 of 156 subject patients had rebleeding, with a rebleeding rate of 28.9%. The median period until the first rebleeding was 166 days (2–3046 days). Similar analyses were performed

by Taghavi et al. of 97 patients, [13] and Aoki et al. of 333 patients, [14] who reported respective rebleeding rates of 10.3% and 12%. In addition, Kouanda et al. [18] conducted a meta-analysis of reports on LGIB in which colonoscopy was performed, including emergency and elective. Based on those results, they reported the rate of bleeding source identification in LGIB as 88.6% in emergency cases, and 85.9% in elective cases, suggesting an unidentifiable bleeding source in approximately 10–15% of the cases. However, at least 75% of LGIB come to natural hemostasis. [19]

Analysis of a long-term follow-up of LGIB revealed the cumulative rebleeding rate over five years as 46%. [20] In our investigation, with a longer observation period (mean observation period of 1314 days ± 1340 (2–4325 days)), the cumulative rebleeding rate over five years was 33.3%, which was comparable to that described in a previous report. In addition, 63% (29 cases) of patients with rebleeding in this investigation had experienced rebleeding within 1 year, indicating that care should be taken to detect and observe rebleeding for at least 1 year. However, because rebleeding occurred in one case 3046 days after the first bleeding, it is noteworthy that rebleeding might still occur even when rebleeding is not observed for a long time.

The maximum number of rebleeding episodes was five, although patients with 1 or 2 rebleeding incidents accounted for 70% (32 cases), suggesting that rebleeding is

not frequent. Causes of bleeding were identified in 7 cases (15.2%) among patients who had experienced rebleeding, 5 of them resulted from diverticular bleeding. Diverticular bleeding is a frequently encountered disease in daily practice. However, the source of bleeding was identified in only about 6–42% of cases. [21] For rebleeding risk analysis, we extracted sex, age, antithrombotic medicines, Hb on admission, and the presence of diverticula by univariate analysis, whereas only male gender and the presence of diverticula were rebleeding risk factors in multivariate analysis.

Antithrombotic medications are a risk factor of GI bleeding, as described in a previous report. [20] Nevertheless, antithrombotic medications were not identified as a risk factor in this study. In addition, male gender was extracted as a risk factor of rebleeding. Kinjyo et al. [22] reported male gender as a risk factor in diverticular bleeding, and inferred the prevalence of arteriosclerosis as a cause. This investigation revealed that risk factors of arteriosclerosis such as hypertension, dyslipidemia, smoking and obesity tended to be more prevalent among male patients (data not shown). Consequently, male gender was inferred as a risk factor.

This study was performed as a single-center retrospective study. It therefore has limitations that include the following: 1) unavailable data presented difficulty in several cases, 2) the years of experience of endoscopists who performed the first colonoscopy

differed considerably, 3) the post-rebleeding follow-up period was not constant, and 4) technical reviews of several gastroenterological societies recommend EGD and SBCE for patients whose colonoscopy does not identify the cause of hematochezia. However, for this study, EGD and SBCE were performed respectively for only 22.9% and 5.9% of the patients. Therefore, it is possible that UGIB or small bowel bleeding patients were included. Nevertheless, a salient benefit of this study is its observation of the long-term outcomes of patients with hematochezia of unknown origin.

When hematochezia patients are encountered with a cause of bleeding that cannot be identified even by colonoscopy, attention must be devoted to rebleeding with the risk factors indicated in the present study.

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Statement of Ethics

The study was approved by the institutional ethics committee at Dokkyo Medical University Hospital (approval no. R-20-4J). This study was conducted in accordance with ethical principles associated with the Declaration of Helsinki and registered at the University Hospital Medical Network Clinical Trials Registry [UMIN000045955]. We provided a means to opt out instead of omitting informed consent, which is a way of guaranteeing opportunities for research subjects to notify and publish research information related to our website.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Takanao Tanaka and Atsushi Irisawa designed this study. Takanao Tanaka and Keiichi Tominaga collected and analyzed the data, and drafted the manuscript. Keiichi Tominaga checked the manuscript and approved the final version. Akira Yamamiya, Takeshi Sugaya, Mimari Kanazawa, Masayuki Kondo, Keiichiro Abe, Akira Kanamori, Makoto Iijima, and Kenichi Goda analyzed the data. Takanao Tanaka and Akira Yamamiya created the figures and tables. Yasuo Haruyama, as an expert in statistics, analyzed the data. All authors have read and agreed to the published version of the manuscript.

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Figure Legend

FIGURE 1. Patient selection flow diagram.