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BRIEF ARTICLE

Characteristics of nonvariceal upper gastrointestinal hemorrhage in patients with chronic kidney disease

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Abstract

AIM: To evaluate the clinical characteristics of nonvariceal upper gastrointestinal hemorrhage (NGIH) in patients with chronic kidney disease (CKD).

METHODS: From 2003 to 2010, a total of 72 CKD patients (male *n* = 52, 72.2%; female *n* = 20, 27.8%) who had undergone endoscopic treatments for NGIH were retrospectively identified. Clinical findings, endoscopic features, prognosis, rebleeding risk factors, and mortality-related factors were evaluated. The characteristics of the patients and rebleeding-related data were recorded for the following variables: gender, age, alcohol use and smoking history, past hemorrhage history, endoscopic findings (the cause, location, and size of the hemorrhage and the hemorrhagic state), therapeutic options for endoscopy, endoscopist experience, clinical outcomes, and mortality.

RESULTS: The average size of the hemorrhagic site was 13.7 ± 10.2 mm, and the most common hemorrhagic site in the stomach was the antrum (*n* = 21, 43.8%). The most frequent method of hemostasis was combination therapy (*n* = 32, 44.4%). The incidence of rebleeding was 37.5% (*n* = 27), and 16.7% (*n* = 12) of patients expired due to hemorrhage. In a multivariate analysis of the risk factors for rebleeding, alcoholism (OR = 11.19, *P* = 0.02), the experience of endoscopists (OR = 0.56, *P* = 0.03), and combination endoscopic therapy (OR = 0.06, *P* = 0.01) compared with monotherapy were significantly related to rebleeding after endoscopic therapy. In a risk analysis of mortality after endoscopic therapy, only rebleeding was related to mortality (OR = 7.1, *P* = 0.02).

CONCLUSION: Intensive combined endoscopic treatments by experienced endoscopists are necessary for the treatment of NGIH in patients with CKD, especially when a patient is an alcoholic.

Key words: Chronic kidney diseases; Gastrointestinal hemorrhage; Endoscopy; Peptic ulcer; Alcoholics

Core tip: Patients with chronic kidney disease (CKD) have increased hemorrhagic complications, including nonvariceal upper gastrointestinal hemorrhage (NGIH). These individuals also have a higher risk of rebleeding than patients without renal dysfunction. Initial intensive

combined endoscopic treatments by experienced endoscopists are necessary for the treatment of NGIH in patients with CKD, especially when a patient is an alcoholic. Factors of the consumption of alcohol, endoscopic monotherapy, and endoscopists' lack of experience are associated with rebleeding, which is the most important factor for the prediction of mortality in CKD patients with NGIH.

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INTRODUCTION

The hemostasis rate of nonvariceal upper gastrointestinal hemorrhage (NGIH) is 90%[1]. However, rebleeding develops in approximately 20% of patients, and the mortality rate has been reported as ranging from 6%-25%[1-8]. In patients with chronic kidney disease (CKD), gastrointestinal hemorrhage is a common complication[9], and hemorrhage from the upper gastrointestinal tract from these patients accounts for 7.8%-12.2% of patients with total upper gastrointestinal hemorrhage[10]. Peptic ulcer is the most common cause of upper gastrointestinal hemorrhage in CKD, followed by erosive gastritis, esophagitis, vascular ectasia, and angiodysplasia[9-12]. Several reports have suggested that the prevalence of peptic ulcer in patients with CKD is higher than in the general population[13,14]. Many studies on the outcome of and risk factors for peptic ulcer bleeding in patients with normal renal function have been reported. However, there are few studies on the outcome of acute hemorrhage due to peptic ulcer and the risk factors for rebleeding in patients with CKD[10,12].

Although the pathogenesis of hemorrhage in patients with CKD is not completely understood, three hypotheses have been proposed to explain the mechanism. First, uremic platelet dysfunction is believed to be the most important factor[12,15]. Second, a high rate of platelet dysfunction may be responsible for the increased frequency of rebleeding compared with the frequency in patients without renal dysfunction[9,16,17]. Lastly, previous studies on peptic ulcer and upper gastrointestinal hemorrhage in patients with renal dysfunction have suggested that hemorrhage in these patients is associated with acid secretion and mucosal integrity[11,18-20]. Moreover, hemodialysis, heparin use, abnormal platelet function, and anemia could be related to NGIH in patients with end-stage renal disease (ESRD), although the evidence is limited. Thus, the objective of this study was to evaluate the clinical characteristics of upper gastrointestinal ulcer hemorrhage in CKD patients and to determine the risk factors for rebleeding in patients undergoing endoscopic therapy.

MATERIALS AND METHODS

Patients

Between December 2003 and December 2010, a total of 72 CKD patients (M:F = 52:20, mean age: 63.9 ± 11.1) who had undergone endoscopic therapy for NGIH were retrospectively evaluated. CKD was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines for nephrologists, which describe the presence of either kidney damage or decreased renal function (glomerular filtration rate < 60 mL/min per 1.73 m^2) for more than 3 mo. ESRD was defined as chronic kidney failure (glomerular filtration rate < 15 mL/min per 1.73 m^2) treated by dialysis. Patients who were not treated with endoscopic management and who had mallory-weiss syndrome were excluded. The clinical and endoscopic characteristics of patients with rebleeding were reviewed and compared with the characteristics of patients without rebleeding. Data were recorded for the following variables: gender, age, dialysis use, the method of dialysis, alcohol use and smoking history, past hemorrhage history, endoscopic findings (the cause, location, and size of the hemorrhage and the hemorrhagic state), endoscopic therapy, endoscopist experience, clinical outcomes, and mortality. Written informed consent to treatment was obtained from each patient. The study was performed in accordance with the Helsinki Declaration.

The patients' vital signs were checked every 10 min before endoscopy, every 2 h for the 24 h after endoscopy, and every 6 h after follow-up endoscopy. The hemoglobin level was checked more than once per day, and a blood transfusion was performed if the hemoglobin level decreased to below 9 g/dL. Rebleeding was defined as fresh hematemesis, fresh melena with blood pressure < 100 mmHg, a drop in the hemoglobin level of more than 2 g/dL, or endoscopic confirmation of hemorrhage or pathologic lesions necessitating endoscopic management within 7 d after initial therapy. The hemorrhagic state was classified into five groups based on Forrest's classification: active pumping, active oozing, vessel exposure, red clots, and black clots.

Endoscopic therapy

All of the patients presented to the hospital with NGIH and underwent an endoscopic examination within 24 h. Endoscopic management for peptic ulcer bleeding was performed. Intravenous proton pump inhibitors (PPIs) were prescribed to promote healing of the lesion before and after endoscopic therapy. Levin tube irrigation with more than 3000 cc of normal saline was performed before initial endoscopy. Thirteen experienced gastroenterologists (> 6000 cases of endoscopy) performed therapeutic endoscopic procedures for NGIH during the study period. The therapeutic options used to treat NGIH were

Table 1 Clinical characteristics of chronic kidney disease patients with peptic ulcer hemorrhage

Variables	Number
Gender (Male/female)	52/20
Age (yr)[1]	63.9 ± 11.1
Alcohol (Yes/no)	25/47
Smoking (Yes/no)	29/43
Past hemorrhage History (Yes/no)	11/61
ESRD (Yes/no)	50/22
Dialysis	
Hemodialysis	45
Peritoneal dialysis	5
Symptoms	32/28/2/10
(Hematemesis/Melena/Syncope/Others)	
Initial blood pressure	
Systolic (mmHg)[1]	128.7 ± 40.0
Diastolic (mmHg)[1]	75.9 ± 16.5
Initial heart rates[1]	94.0 ± 24.5
Hb (g/dL)[1]	7.4 ± 2.0
Platelet (10^9/L)[1]	208 ± 156
INR/PTT (second)[1]	1.14 ± 0.35/47.2 ± 55.6

[1]mean ± SD. ESRD: End-stage renal disease; INR: International normalized ratio; Hb: Haemoglobin.

1:10000 epinephrine injection, fibrin glue (Greenplast, Green Cross, Chung won, South Korea) injection, hemoclipping, electrocoagulation, endoscopic band ligation, and argon plasma coagulation. The patients were scheduled for a follow-up endoscopic examination within 24 h. If their general condition was not suitable for endoscopy, the follow-up examination was delayed. At the follow-up examination, oral intake was initiated, and endoscopic biopsy and *Helicobacter pylori* (*H. pylori*) tests were performed. If active bleeding or vessel exposure was observed during the follow-up endoscopic examination, this event was considered as rebleeding, and second endoscopic hemostasis was attempted. If continuous bleeding developed, not controlled by endoscopic hemostasis, operational or interventional radiologic management was performed. During fasting periods, intravenous pantoprazole sodium as a 40 mg bolus was supplied twice per day. After starting oral intake, a standard dose of oral PPIs was administered every morning for 6-8 wk. If the tests for *H. pylori* were positive, eradication medications (PPI + amoxicillin + clarithromycin) were administered for 7 d. Laboratory tests, abdominal ultrasonography, and routine abdominal X-ray were performed after the procedure to evaluate possible complications, including rebleeding or perforation.

Statistical analysis

The χ^2 test and Student's *t* test were used to evaluate baseline characteristics. Categorical variables were analyzed by the χ^2 test, and continuous variables were assessed by the Student's *t* test. Univariate analysis and multivariate logistic regression were used to detect independent risk factors related to rebleeding during follow-up periods and prognosis. A *P* value < 0.05 was considered as significant for all tests. Analyses were performed using SPSS software, version 18.0 (SPSS Inc., Chicago, IL, United States).

Table 2 Endoscopic findings, therapy and prognosis of clinical risk factors patients with peptic ulcer hemorrhage

Variables	Numbers
Size of ulcer (mm)[1]	13.7 ± 10.2
Hemorrhage state	6/38/18/5/5
(Pumping/oozing/vessel/red/black)	
Location 1 (Gastric/Duodenum)	48/24
Location 2 (Antrum/Angle/Body/Cardia)	21/11/15/1
Location 3 (Anterior/Posterior/Lesser/Greater)	11/7/22/8
Endoscopic therapy	27/8/5/32
(Injection/Coagulation/Clip/Combination)	
Amount of epinephrine (cc)[1]	15.6 ± 12.9
Experience of endoscopists (yr)[1]	3.5 ± 2.7
H. pylori infection (Yes/no)	19/33
Rebleeding (Yes/no)	27/45
Hemorrhage related death (Yes/no)	12/60

[1]mean ± SD. *H. pylori*: *Helicobacter pylori*.

RESULTS

Characteristics of patients

During the 4-year study period, 72 CKD patients with peptic ulcer hemorrhage were identified. The clinical characteristics of these patients are summarized in Table 1. The mean age of the patients with CKD was 63.9 ± 11.1. In total, 61 (84.7%) patients were experiencing their first hemorrhagic episode; 8 (11.1%) patients, their second; and 3 (4.2%) patients, their third. In this study, 50 (69.4%) ESRD patients were detected, of whom 45 (90%) patients were undergoing hemodialysis, and 5 (10%) were undergoing peritoneal dialysis. The initial systolic blood pressure of the patients was 128.7 ± 40.0 mmHg, and the diastolic blood pressure was 75.9 ± 16.5 mmHg. The hemoglobin level of the patients was 7.4 ± 2.0 g/dL, and the platelet count was 208 ± 156 (10^9/L).

All of these patients were managed by endoscopy for peptic ulcer hemorrhage. The endoscopic findings and treatments of these patients are shown in Table 2. The mean ulcer size (mm) was 13.7 ± 10.2, and the hemorrhagic location the stomach in 48 (66.7%) cases and the duodenum in 24 (33.3%) cases. The most common hemorrhagic site in the stomach was the antrum (43.8%).

The therapeutic method of endoscopy was injection for 27 (37.5%) patients, coagulation for 8 (11.1%) patients, clipping for 5 (6.9%) patients, and combination therapy for 32 (44.4%) patients. The most common combination was epinephrine and glue injection (n = 11), followed by epinephrine injection and coagulation (n = 10) and epinephrine injection and clipping (n = 10). The mean number of years of experience of the endoscopists was 3.5 ± 2.7 years. The total number of patients with rebleeding was 27 (37.5%), and hemorrhage-related death was observed in 12 patients (16.7%, Table 2).

Univariate analysis of risk factors for rebleeding

The incidence of rebleeding was 37.5% (n = 27), and

Table 3 Univariate analysis for clinical risk factors of rebleeding

Characteristics	Rebleeding (n = 27)	No Rebleeding (n = 45)	P value
Gender (Male/female)	18/9	34/11	NS
Age (yr)[1]	62.9 (11.5)	64.6 (11.0)	NS
Heart rate[1]	95 (17)	93 (29)	NS
CKD (not ESRD)/ESRD	10/17	12/33	NS
Previous hemorrhage history (Yes/no)	4/23	7/38	NS
Blood pressure			
Systolic (mmHg)[1]	128 (32)	129 (45)	NS
Diastolic (mmHg)[1]	76 (16)	76 (17)	NS
Lab			
Hb (g/dL)[1]	7.4 (1.9)	7.5 (2.1)	NS
Platelet (10^9/L)[1]	207 (174)	208 (145)	NS
INR/PTT	1.2/46.7	1.1/48.0	NS
Alcohol (Yes/no)	15/12	10/35	< 0.01
Smoking (Yes/no)	15/12	14/31	< 0.05

[1]mean ± SD. NS: Not significant; CKD: Chronic kidney disease; ESRD: End-stage renal disease; INR: International normalized ratio; Hb: Haemoglobin.

Table 4 Univariate analysis for endoscopic risk factors of rebleeding

Variables	Rebleeding	No rebleeding	P value
Hemorrahge state			NS
Active pumping	1	5	
Active oozing	15	23	
Blood vessel	7	11	
Red or black clot	4	6	
Ulcer size (mm)[1]	14.4 (11.9)	13.2 (9.1)	NS
Location (antrum and angle *vs* body)	11/7	21/9	NS
H. pylori infection (Yes/no)	7/20	17/28	NS
Therapy			NS
Injection	11	16	
APC or electrocoagulation	4	4	
Clip	2	3	
Combination	10	22	
Amount epinephrine[1]	16.9 (15.3)	14.7 (11.3)	NS
Endoscopists' experience[1]	2.8 (1.9)	4.0 (3.0)	< 0.05
Endoscopists' status			< 0.05
Fellowship doctor	20	19	
Faculty doctor	7	26	

[1]mean ± SD. NS: Not significant; *H. pylori*: *Helicobacter pylori*; APC: Argon plasma coagulation

16.7% (n = 12) of patients expired due to bleeding. In the univariate analysis of clinical risk factors for rebleeding, there was no statistically significant difference in gender, age, dialysis method, or previous hemorrhage history between the rebleeding and the no-rebleeding groups (Table 3). Alcohol consumption was noted for 15/27 (55.6%) patients in the rebleeding group and 10/45 (22.2%) patients in the no-rebleeding group (P < 0.01). Additionally, smoking was reported by 15/27 (55.6%) patients in the rebleeding group and 14/45 (31.1%) patients in the no-rebleeding group (P < 0.01). The univariate analysis of endoscopic risk factors for rebleeding is shown in Table 4. Hemorrhagic states, ulcer sizes, and therapeutic methods were not significantly different between the rebleeding and the no-rebleeding groups. However, the number of years of experience of the endoscopists was 2.8 years for the rebleeding group and 4.0 years for the no-rebleeding group, which was a statistically significant difference (P < 0.05). In an analysis according to the endoscopists' status, being a doctor on fellowship was associated with rebleeding compared with being a doctors on the faculty (OR = 2.1, P = 0.02).

Multivariate analysis of risk factors for rebleeding and mortality

In the multivariate analysis of risk factors for rebleeding, the consumption of alcohol, endoscopic monotherapy, and endoscopists' lack of experience were associated with rebleeding development (Table 5). The alcohol-consuming group had an OR of 11.19 (P = 0.02) for rebleeding compared with the non-alcohol-consuming group. Although therapeutic methods were not associated with rebleeding in the univariate analysis, combination endoscopic treatment was associated with less frequent development of rebleeding in the multivariate analysis (OR = 0.06, P = 0.01). The experience of endoscopists was significantly associated with the development of rebleeding in the multivariate analysis (OR = 0.56, P = 0.03). The risk factor associated with prognosis was rebleeding alone (OR = 7.10, P = 0.02, Table 6).

DISCUSSION

Patients with CKD have increased hemorrhagic complications[10]. Additionally, there are a higher rebleeding risk and greater mortality in patients on dialysis than in patients without renal dysfunction[11]. The current study investigated peptic ulcer hemorrhage in CKD patients and found that these individuals are at high risk of rebleeding. In this study, the rebleeding rate in patients with CKD was 37.5%. This result is higher than for the CKD (14%) or normal renal function (12%) group and similar to rebleeding in ESRD patients (38%) in a previous study[12]. Moreover, the result is higher than the rate determined for Korean CKD patients (14.3%) in another study[21]. However, the definition of rebleeding differed. In the present study, rebleeding was confined to episodes within 7 d after endoscopic therapy, whereas there was no clear statement about time in previous studies, in which even rebleeding at 30 d after the first hemorrhage was included[12]. Taking these results together, CKD patients have a higher risk of rebleeding than patients without renal dysfunction, with approximately more than one third of CKD patients experiencing rebleeding.

NGIH is associated with high mortality. The mortality of NGIH complicating acute renal dysfunction is 68.3% and of NGIH complicating severe liver cirrhosis (LC) is 68.4%[22,23]. In the present study, the mortality of CKD patients with NGIH was 16.7%. This result is higher than the 13% value determined in a Taiwanese study and

Table 5 Multivariate analysis for risk factors of rebleeding

Variables	*P* value	OR
Age	NS	
Gender	NS	
Smoking	NS	
Hb (g/dL)	NS	
Platelet (10^9/L)	NS	
INR	NS	
Ulcer size	NS	
Location	NS	
Hemorrhage state	NS	
Amount of epinephrine	NS	
Alcohol (Yes/no[1])	0.02	11.19
Therapy (Combination therapy/monotherap[1])	0.01	0.06
Experiences of endoscopists (yr)	0.03	0.56

[1]Reference category. NS: Not significant; INR: International ormalized ratio; Hb: Haemoglobin B.

Table 6 Multivariate analysis for risk factors of prognosis

Variables	*P* value	OR
Age	NS	1.07
Gender (Male/female[1])	NS	1.87
Hemorrhage state	NS	
Active pumping		0.07
Active oozing		0.00
Blood vessel		0.17
Red clot		0.00
Black clot[1]		0.77
Rebleeding (Yes/no[1])	0.02	7.10

[1]Reference category. NS: Not significant.

the 8.6% value reported in another Korean study[10,21]. In particular, rebleeding was related to the mortality of the CKD patients (OR = 7.1, $P = 0.02$). According to a study that used nationwide inpatient samples from the United States, mechanical ventilation, severe sepsis, disseminated intravascular coagulation, cancer, age (> 65 years), coagulation defects, and venous thromboembolism were predictors of mortality in patients with ESRD and NGIH[24]. However, that study did not include rebleeding in the statistical analysis, although other studies have emphasized the importance of this parameter[12,21,24]. Overall, rebleeding is the most important factor for the prediction of mortality in CKD patients with NGIH, and the prevention of rebleeding should be a goal of clinical practice.

Regarding risk factors for rebleeding, the experience of endoscopists was one of the main factors (OR = 0.56, $P = 0.03$). In a retrospective study in Canada, ESRD itself and ulcer with high-risk stigmata were the factors associated with rebleeding[12]. However, the experience of endoscopists was not analyzed. According a study of risk factors for rebleeding in NGIH patients, regardless of renal function, lower hemoglobin levels, endoscopist inexperience (< 2 years of experience), and comorbidity with CKD or LC were the associated factors[25]. These results indicate that insufficient or inappropriate endoscopic management by inexperienced endoscopists could result in rebleeding in CKD patients with NGIH. Moreover, considering that emergency endoscopic hemostasis procedures are frequently performed at night or on holidays by only one endoscopist, without the help of colleagues, intensive endoscopic treatments are important.

Combined endoscopic management was associated with a reduced risk of rebleeding in this study (*vs* monotherapy, OR = 0.06, $P = 0.01$). Recent studies have suggested that combined endoscopic hemostasis treatments are superior to single treatments[26,27]. In a study of the risk factors for rebleeding in NGIH patients, regardless of renal function, combination therapy (injection + thermal therapy) was associated with lower mortality compared with injection therapy alone[25]. These results are consistent with the findings of our study. Among the endoscopic therapeutic options, injection therapy ($n = 27$, 67.5%) was preferred over thermal ablation ($n = 8$, 20%), such as argon plasma coagulation or electrocoagulation, when used as single method in this study. This preference was due to concerns about tissue injury or loss in thermal therapy, which could result in rebleeding in patients with a hemorrhagic tendency. Another finding of this study was that being an endoscopic doctor on fellowship was associated with rebleeding compared with being a doctor on the faculty (OR = 2.1, $P = 0.02$). Overall, intensive endoscopic treatment by experts using a combined method can result in better outcomes in CKD patients with NGIH.

Another finding of this study was related to alcohol use. In the multivariate analysis of risk factors for rebleeding, alcohol use was demonstrated to be an important risk factor (OR = 11.19, $P = 0.02$). Additionally, the most common hemorrhagic site was the lesser curvature of the antrum of the stomach. *H. pylori* infection was detected in only 33.3% of patients. The exact mechanism underlying the association of alcohol use and *H. pylori* with NGIH in patients with CKD is not understood. However, endoscopists have to pay more attention when a patient is an alcoholic because of rebleeding risk, which is associated with high mortality.

There are several limitations of this study. First, it was retrospective study, and a small number of patients were evaluated. Second, hospital stay and blood transfusion, which were evaluated in other studies[12,28], were not assessed. Further studies are needed to improve outcomes in CKD patients with NGIH.

In conclusion, initial intensive combined endoscopic treatments by experienced endoscopists are necessary for the treatment of NGIH in patients with CKD, especially when a patient is an alcoholic, as rebleeding after endoscopic treatment is a risk factor for mortality.

COMMENTS

Background

Peptic ulcer is the most common cause of upper gastrointestinal hemorrhage in chronic kidney disease (CKD). Additionally, there are a higher rebleeding risk and greater mortality in patients on dialysis than in patients without renal dysfunction. Many studies on the outcome of and risk factors for peptic ulcer

bleeding in patients with normal renal function have been reported. However, there have been few studies on the outcome of acute hemorrhage due to peptic ulcer and on the risk factors for rebleeding in patients with CKD.

Research frontiers

According to a study that used nationwide inpatient samples from the United States, mechanical ventilation, severe sepsis, disseminated intravascular coagulation, cancer, age (> 65 years), coagulation defects, and venous thromboembolism were predictors of mortality in patients with end-stage renal disease and nonvariceal upper gastrointestinal hemorrhage (NGIH).

Innovations and breakthroughs

In the previous study on predictors of mortality in patients with ESRD and NGIH, rebleeding was not determined to be a major predictor of mortality. However, only rebleeding was related to mortality (OR = 7.1, P = 0.02) in the current study. Moreover, alcoholism (OR = 11.19, P = 0.02), the experience of endoscopists (OR = 0.56, P = 0.03), and combination endoscopic therapy (OR = 0.06, P = 0.01) compared with monotherapy were significantly related to rebleeding after endoscopic therapy in this study.

Applications

Initial intensive combined endoscopic treatments by experienced endoscopists are necessary for the treatment of NGIH in patients with CKD, especially when a patient is an alcoholic. These factors are associated with rebleeding, which is the most important factor for the prediction of mortality in CKD patients with NGIH.

Peer review

This is a well done study. It is an important topic. The manuscript is interesting, well done and well written.

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