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Case study

Association between gastrointestinal bleeding and 3-year mortality in patients with acute, first-ever ischemic stroke

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ABSTRACT

The influence of gastrointestinal bleeding on clinical presentation and outcomes of patients with acute ischemic stroke remains controversial. We investigate the effect of gastrointestinal bleeding on the outcomes of patients with acute, first-ever ischemic stroke. We enrolled 934 patients with acute, first-ever ischemic stroke and followed up them for 3 years. Patients were divided into 2 groups according to the presence or absence of gastrointestinal bleeding during acute stroke stage. Clinical presentation, stroke risk factors, laboratory data, co-morbidities, and outcomes were recorded. Seventy-six (8.1%) patients had gastrointestinal bleeding at admission. The prevalence of old age, atrial fibrillation, and previous transient ischemic attack was higher in patients with gastrointestinal bleeding ($P < 0.001$, $P = 0.038$, and $P = 0.018$, respectively). Total anterior circulation syndrome occurred more frequently among patients with gastrointestinal bleeding ($P < 0.001$). The mean length of acute ward stay, initial impaired consciousness, and stroke in evolution were higher in patients with gastrointestinal bleeding ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). The occurrence of pneumonia and dependent functional outcome were higher in patients with gastrointestinal bleeding ($P < 0.001$ and $P < 0.001$, respectively). A multivariate Cox regression analysis revealed that gastrointestinal bleeding is a significant risk factor for 3-year all-cause mortality (hazard ratio = 2.76; 95% confidence interval = 1.61–4.72; $P < 0.001$). In conclusion, gastrointestinal bleeding is associated with increased risk of 3-year mortality in patients with acute, first-ever ischemic stroke. Prophylactic therapies for gastrointestinal bleeding might improve ischemic stroke outcome.

1. Introduction

Gastrointestinal (GI) bleeding is a well-known complication in acute stroke patients, and it may interfere with the treatment for ischemic stroke, such as antiplatelet or anticoagulant therapies. The incidence of GI bleeding during the acute phase of stroke is about 0.1–8.0%, depending on the stroke subtype [1–5].

The clinical relevance of GI bleeding on stroke outcome remains controversial. A previous study suggested that GI bleeding after stroke is rarely severe and may not contribute significantly to mortality; however, the number of patients enrolled in this study was relatively small [5]. Recently, Rumalla et al. suggested that GI bleeding following acute ischemic stroke may be associated with a poor functional outcome and in-hospital mortality [6]. Another study reported that GI bleeding after acute ischemic stroke is associated with an increased risk of death and severe dependence; however, the follow-up time in this study was only 6 months [3]. The long-term outcomes of GI bleeding are poorly understood, despite it being the most frequent cause of gastroenterology admission to acute medicine ward. Recently, Crooks et al. have reported that patients who have had a previous nonvariceal upper GI bleeding have higher long-term all-cause mortality rates [7]. To our knowledge, no previous studies have investigated the influence of GI bleeding during the acute stroke stage on the long-term stroke outcome and mortality.

The aim of this study is to investigate: (1) the association between GI bleeding in acute stroke stage and clinical presentations, or acute complications, in patients with acute, first-ever stroke and (2) the association between GI bleeding in the acute stroke stage and clinical outcomes, including the functional outcomes and 3-year mortality.

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2. Materials and methods

This clinical study followed the Declaration of Helsinki and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital (CGMH), Taipei, Taiwan.

2.1. Study patients

All patients enrolled in this study were recruited from the Stroke Unit of the Department of Neurology at CGMH from January 1, 2001, to December 31, 2003. Only patients with first-ever ischemic stroke were enrolled. The clinical diagnosis of acute ischemic stroke was performed according to the World Health Organization criteria. The diagnosis was further confirmed by brain computed tomography or magnetic resonance imaging (MRI) scan [8]. Patients with symptoms lasting less than 24 h and without evidence of acute cerebral infarction in the MRI were diagnosed with transient ischemic attack (TIA) and were excluded.

Co-morbidities were determined after an in-depth review of the medical records. Hypertension was defined as known hypertension diagnosed by a clinician, or systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg on two different occasions. Diabetes mellitus (DM) was diagnosed in patients with previously treated DM or in patients with fasting plasma glucose levels $\geq$126 mg/dl, a 2-h value in the oral glucose tolerance test or a random plasma glucose concentration $\geq$200 mg/dl, in the presence of symptoms. Hyperlipidemia was defined as a fasting blood cholesterol level $\geq$200 mg/dl and/or a triglyceride level $\geq$200 mg/dl. Atrial fibrillation (AF) was diagnosed if it was present on a standard 12-lead electrocardiogram. Coronary artery disease (CAD) was diagnosed if there were past incidences of acute myocardial infarction or angina pectoris. Congestive heart failure (CHF) was present if the patient was previously diagnosed by a cardiologist or confirmed by cardiac echo.

2.2. Definition of gastrointestinal bleeding in acute stroke stage

A GI hemorrhage event was defined according to Davenport et al. as any episode of fresh blood or coffee ground material in nasogastric aspirate, hematemesis, melena or bloody stool [9]. The cause and origin of the bleeding were investigated using endoscopy in most of the patients if they could tolerate the procedure. Patients were divided into 2 groups according to the presence or absence of GI bleeding during the acute stroke.

2.3. Definition and clinical subtypes of ischemic stroke

Clinical subtypes of ischemic stroke were rated according to the Oxfordshire Community Stroke Project classification. The following subtypes were adopted: Partial Anterior Circulation Syndrome (PACS), Total Anterior Circulation Syndrome (TACS), Posterior Circulation Syndrome (POCS), and Lacunar Syndrome (LACS) [10]. The clinical course of acute stroke stage, mean length of acute-ward stay, mortality rates during and following acute ward stay, and frequency of medical complications were monitored. The definition "stroke in evolution" refers to a neurologic deficit that progresses within 7 days after the stroke onset [11]. Functional outcomes upon discharge were assessed according to the modified Rankin Scale (mRS) [12]. The "functionally dependent" condition was defined as having an mRS score of 3, 4 or 5.

2.4. Follow-up

Patients were followed up for 3 years after the initial assessment. Follow-up consisted of clinical examinations performed 1 and 3 months after the first stroke and then every 3 months. Clinical examinations during follow-up included history taking, physical and neurological examinations, and mRS score assessment. New major medical problems (e.g., death, recurrent cerebral infarction, cerebral hemorrhage, epilepsy, cancer, cardiovascular diseases, head injury, etc.) were recorded during follow-up. The end point was death during 3-year follow up. Every death occurring during the follow-up was reviewed.

2.5. Statistical analysis

Continuous variables such as age and laboratory measurement values were expressed as median and interquartile range because the values were not normally distributed, and mean length of stay in the acute ward was expressed as mean ± SD. Categorical variables were expressed as a number, or percentage, for each item. The 2 patient groups were compared using chi-square, Mann-Whitney U or Student *t* test. The independent associations between the variables and the probability of having GI bleeding were analyzed using logistic regression. All variables with a $P < 0.1$ in the univariate logistic regression entered a stepwise, backward multivariate logistic regression. The Cox proportional hazards model was used to determine the significance of each variable in predicting the 3-year all-cause mortality. A univariate Cox model, assessing all previously identified variables, was used to measure hazard ratio (HR) for mortality. A backward, stepwise multivariate Cox regression model was also used to identify the risk factors for the 3-year mortality. All statistical analyses were performed with IBM SPSS statistics 19 for Windows.

3. Results

3.1. Patient characteristics

A total of 934 patients were enrolled in the study. The median age was 70 (62–78) years. At baseline, 76 (8.1%) patients had GI bleeding at admission. Age was significantly higher in the group with GI bleeding. Prevalence of AF and previous TIA were significantly higher among patients with GI bleeding. Upon clinical presentation of stroke, TACS occurred more frequently in the group with GI bleeding, whereas LACS occurred more frequently in the group without GI bleeding. Additionally, hemoglobin and estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) were significantly lower, whereas WBC was higher, in the group with GI bleeding. Among patients with GI bleeding, 37 patients used aspirin, 32 patients use clopidogrel, 2 patients used warfarin, 5 patients did not use antiplatelet or anticoagulant (Table 1).

3.2. Determinants of GI bleeding in patients with acute, first-ever ischemic stroke

After adjusting for the potential risk factors ($P < 0.1$ in univariate logistic regression) in a backward, stepwise multivariate logistic regression, only anemia, TIA and initial impaired consciousness were positively associated with patients having GI bleeding during acute stroke (Table 2).

3.3. Clinical course in patients with an acute stage of first-ever ischemic stroke

The mean length of acute ward stay, initial impaired consciousness, and stroke in evolution were significantly higher in the group with GI bleeding. The occurrence of pneumonia and urinary tract infection (UTI) were significantly higher in patients with GI bleeding. Furthermore, the dependent functional status (mRS score $\geq$3)