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STUDY ON FACTORS AFFECTING THE OCCURRENCE OF UPPER GASTROINTESTINAL BLEEDING IN ELDERLY ACUTE STROKE PATIENTS UNDERGOING REHABILITATION

C.-M. CHEN[1,2,3], H.-C. HSU[1,4], Y.-W. CHUANG[1], C.-H. CHANG[5], C.-H. LIN[1], C.-Z. HONG[6]

1. Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Chiayi, Taiwan; 2. Chang Gung Institute of Technology, Chiayi Campus, Chiayi, Taiwan; 3. College of Medicine, Chang Gung University, Taoyuan, Taiwan; 4. Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan; 5. Department of Nursing, Chang Gung Institute of Technology, Chiayi Campus, Chiayi, Taiwan; 6. Department of Physical Therapy, Hung Kuang University, Taichung County, Taiwan.
All correspondence and requests for reprints should be addressed to: Hung-Chih Hsu, M.D., Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital, Chiayi, No.6, W. Sec., Jiapu Rd., Puzih City, Chiayi County 613, Taiwan (R.O.C.), Tel: +886-5-3621000-2671, E-mail: dr.tonyhsu@gmail.com

Abstract: *Objective:* To investigate factors affecting upper gastrointestinal bleeding (UGIB) in elderly first-time acute stroke patients undergoing rehabilitation. *Participants and setting:* Three hundred and thirty-one elderly first-time acute stroke patients (age ≥65 years) transferred to our rehabilitative ward from July 2002 to June 2009 were included in the study. *Design:* We divided patients into UGIB and non-UGIB groups. Demographic data and possible precipitating factors were analyzed. *Results:* Sixty-eight (20.5%) patients experienced UGIB. The patients with UGIB were of older age (75.4 vs. 72.92 years, P = 0.003), had a longer rehabilitative ward stay (26.32 vs. 21 days, P = 0.002), more frequently had stroke-induced consciousness impairment (60.3 vs. 38%, P = 0.001), had a higher incidence of bilateral brain lesion (7.4 vs. 1.9%, P = 0.034), and more frequently used anticoagulants (17.6 vs. 9.1%, P = 0.044) than patients in the non-UGIB group. In multivariate logistic regression analysis, stroke-induced impaired consciousness (odds ratio: 2.806, 95% CI = 1.588–4.957, P = 0.000) was the most important risk factor for UGIB. *Conclusions:* UGIB may prolong a patient's length of stay in a rehabilitative ward. These identified factors may help clinicians identify risks of UGIB before it develops.

Key words: Upper gastrointestinal bleeding, elderly, stroke, rehabilitation, consciousness.

Introduction

The incidence of upper gastrointestinal bleeding (UGIB) is approximately 47.7/100000 in the general population and is higher among older patients (1). Age is an independent predisposing factor for gastrointestinal bleeding, with the risk increasing significantly after 65 years of age (2).

Cerebral stroke is one of the leading causes of death in Taiwan, and its incidence increases with age in adults (3). UGIB is a common complication in acute hospitalized stroke patients (4, 5) and in those undergoing rehabilitation (6, 7). Some medications, including antiplatelets (8), anticoagulants (8), steroids (9), non-steroid anti-inflammatory drugs (NSAIDs) (10), and calcium channel blockers (11), can increase the risk of UGIB in certain patient groups. On the other hand, ulcer prophylaxis drugs (12) or HMG-CoA reductase inhibitors (statins) (13) can decrease the incidence of UGIB. Stroke patients may need to use these medications to control co-morbidities. Thus far, UGIB in acute stroke patients has been reported in some published articles (4, 14-17). Davenport's study (4) and Wijdick's study (14) enrolled ischemic and hemorrhagic stroke patients, but the risk factors of UGIB were not investigated. Misra's study (15) focused on hemorrhagic stroke patients, while O'Donnell's study (16) and Hsu's study (17) focused on ischemic stroke patients; however, these 3 studies did not contain both hemorrhagic and ischemic stroke patients. Besides, the factors affecting elderly acute stroke patients in the rehabilitative department have not been well studied. The aim of the present study was to survey factors affecting UGIB occurrence in elderly first-time acute stroke patients undergoing rehabilitation and to examine the relationship between UGIB and rehabilitative outcome.

Method

Participants and assessment procedures

Two physicians retrospectively reviewed the medical records of patients in the registry of the rehabilitation department between July 2002 and June 2009. Patients in this study met the following inclusion criteria: [a] ≥65 years of age; [b] confirmed first-time acute stroke based on World Health Organization criteria; [c] motor deficits of the limbs; and [d] receiving rehabilitation. Patients with a definite diagnosis of upper gastrointestinal or esophageal neoplasm were excluded. UGIB was defined as either [a] episodes of bloody nasogastric aspirate or [b] ulcers, erosions or bleeding source proven by esophagogastroduodenoscopy. The Institutional Review Board for Human Studies at our hospital approved the study protocol.

Patients were divided into two groups: UGIB and non-UGIB. Demographic data, including age and gender, were recorded. In addition, we recorded data on stroke-induced impaired consciousness; stroke type and location (including side of involvement); habit of heavy smoking; history of UGIB; hypertension; diabetes mellitus (DM); renal function impairment; congestive heart failure (CHF); liver cirrhosis; and use of anticoagulants, antiplatelets, steroids, NSAIDs, calcium channel blockers, statins, and ulcer prophylaxis.

We also recorded data on mean length of stay in the rehabilitative ward. Mean improvement of the Brunnstrom's

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motor recovery (BMR) stages (18) of the affected limbs was recorded to demonstrate improved rehabilitative outcome. The BMR stages had been used widely (19, 20) to describe the sequential motor recovery of post-stroke patients into 6 stages; the higher the stage, the better the motor recovery. Improvement of the BMR stages was defined as the summation of difference between the BMR stages of the affected limbs (the upper proximal limb, the upper distal limb, and the lower limb) on the first day the patients were transferred to the rehabilitative ward and those on the day that the patients were discharged. If a patient with UGIB received esophagogastroduodenoscopy during hospitalization, the bleeding origin location was also recorded.

Stroke-induced impaired consciousness was defined as a persistent Glasgow Coma Scale score <15 after stroke during the entire course of hospitalization. Stroke locations and sides of involvement were recorded by brain imaging such as computed tomography or magnetic resonance imaging. Habit of heavy smoking was defined as a patient smoking ≥10 cigarettes per day for >6 months before the stroke. History of UGIB was defined as any episode of UGIB prior to the stroke.

Hypertension was defined as hypertension diagnosed by a clinician prior to the stroke or a systemic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg on 2 separate occasions. DM was defined as fasting plasma glucose ≥126 mg/dl or random plasma glucose ≥200 mg/dl. Renal function impairment was defined as serum creatinine >1.5 mg/dl on any occasion. CHF was defined as positive findings in cardiac echo and confirmed by a cardiologist. Liver cirrhosis was defined as positive findings in sonographic study and confirmed by a gastroenterologist.

In patients without UGIB, used medication was defined as any dose of medication used during this hospitalization. In patients with UGIB, used medication was defined as any dose of medication used before the episodes of UGIB during this hospitalization. Topical or transdermal drugs were not included in these definitions. Anticoagulant drugs included warfarin and any molecular weight of heparin administrated either intravenously or subcutaneously. Antiplatelet drugs were divided into aspirin and clopidogrel subcategories for analysis purposes. NSAIDs were also divided into cyclooxygenase-2 (COX-2) inhibitors and conventional NSAIDs (not including COX-2 inhibitors) subcategories for analysis purposes. Ulcer prophylaxis was defined as H2 receptor antagonists or proton pump inhibitors.

Statistical analysis

SPSS 12.0 for Windows was used for analysis. Continuous variables such as age, length of rehabilitative ward stay, and improvements in BMR stages were expressed as means ± standard deviation and analyzed by independent t test. Categorical variables were compared by the Chi-square test. A P value < 0.05 was considered statistically significant. Significant variables identified in univariate analysis were used by Pearson's and Spearman's correlations to analyze the collinearity for identifying the independent variables. Identified independent variables were analyzed by stepwise logistic regression analysis to identify the most important risk factor for UGIB.

Results

Three hundred and thirty-one first-time stroke patients were enrolled in the study. Among the 331 patients, 68 (20.5%) had UGIB and 263 (79.5%) patients did not have UGIB during hospitalization. The frequency of UGIB was 16.7% (19/114) in hemorrhagic stroke patients and 22.6% (49/217) in ischemic stroke patients; the difference did not reach statistical significance (P = 0.252). Table 1 lists the univariate analysis of patient characteristics. The mean age of patients in the UGIB group (75.4 years) was significantly higher (P = 0.003) than that of patients in the non-UGIB group (72.92 years). Impaired consciousness was significantly more frequent in the UGIB group (60.3%) than in the non-UGIB group (38.0%) (P = 0.001). Bilateral brain lesions (7.4% vs. 1.9%, P = 0.034) and use of anticoagulants (17.6% vs. 9.1%, P = 0.044) were more frequently seen in the UGIB group than in the non-UGIB group. The UGIB group had significantly longer rehabilitative ward stay than the non-UGIB group significantly (26.32 vs. 21 days, P = 0.002). Forty-six (67.6%) UGIB patients received esophagogastroduodenoscopy. Among the 46 patients, 17 (37.0%) had bleeding of esophageal origin, 34 (73.9 %) had bleeding of gastric origin, and 14 (30.4%) had bleeding of duodenal origin.

Pearson's and Spearman's correlations were used to analyze collinearity between the significant variables from the univariate analysis. Mean length of the rehabilitative ward stay and bilateral brain lesions were highly correlated with stroke-induced impaired consciousness. Therefore, age, impaired consciousness and anticoagulant use were included in the multivariate logistic regression analysis (Table 2). Age (odds ratio [OR]: 1.066, 95% CI = 1.021–1.114, P = 0.004), anticoagulant use (OR: 2.396, 95% CI =1.092–5.260, P =0.029), and presence of stroke-induced impaired consciousness (OR: 2.806, 95% CI = 1.588–4.957, P = 0.000) were independent factors for UGIB.

Discussion

In our study, the frequency of UGIB in first-time acute stroke inpatients undergoing rehabilitation was 20.5%. In two studies illustrating the complications of acute stroke patients undergoing inpatient rehabilitation, the reported frequency of UGIB was 4.9% by Hung (6) and 8.6% by Doshi (7). These two studies included younger adult patients than did our study. The limit of patient age was ≥18 years in Hung's study and ≥40 years in Doshi's study. The frequency of UGIB in our study is relatively high compared to that in previous studies, and we believe this to be attributable to the patients in our study being ≥65 years of age since elderly patients have a higher risk of

UGIB (1, 2). The previous studies did not focus on older patients. Different study designs may also lead to different results.

Table 1
Characteristics of patients with and without upper gastrointestinal bleeding

	Patients with UGIB (n = 68)	Patients without UGIB (n = 263)	P value
Mean age, years	75.4 ± 6.4	72.92 ± 6.1	0.003
Male	34 (50)	125 (47.5)	0.716
Impaired consciousness	41 (60.3)	100 (38)	0.001
Ischemic stroke	49 (72.1)	168 (63.9)	0.206
Brain lesion			
Left brain	24 (35.3)	109 (41.4)	0.356
Right brain	39 (57.4)	149 (56.7)	0.917
Bilateral brain	5 (7.4)	5 (1.9)	0.034*
Heavy smoking	13 (19.1)	49 (18.6)	0.927
History of UGIB	9 (13.2)	15 (5.7)	0.061*
Hypertension	53 (77.9)	218 (82.9)	0.345
Diabetes mellitus	27 (39.7)	100 (38)	0.799
Renal function impairment	6 (8.8)	19 (7.2)	0.656
Congestive heart failure	3 (4.4)	5 (1.9)	0.213*
Liver cirrhosis	2 (2.9)	2 (0.8)	0.188*
Anticoagulant use	12 (17.6)	24 (9.1)	0.044
Antiplatelet use	49 (72.1)	162 (61.6)	0.11
Aspirin	37 (54.4)	123 (46.8)	0.261
Clopidogrel	12 (17.6)	39 (14.8)	0.566
Steroid use	5 (7.4)	11 (4.2)	0.337*
NSAIDs use	18 (26.5)	66 (25.1)	0.816
Conventional NSAIDs	17 (25)	52 (19.8)	0.344
COX-2 inhibitors	1 (1.5)	14 (5.3)	0.323*
Calcium channel blockers use	35 (51.5)	142 (54)	0.71
Statin use	11 (16.2)	60 (22.8)	0.235
Ulcer prophylaxis use	19 (27.9)	67 (25.5)	0.679
Mean rehabilitative ward stay, days	26.32 ± 10.98	21 ± 12.95	0.002
Mean BMR stages improvement	0.43 ± 1.06	0.6 ± 1.41	0.332
Valid endoscopy results of UGIB	46		
Esophageal origins	17		
Gastric origins	34		
Duodenal origins	14		

Figures in parentheses are percentages. * P values obtained by Fisher's exact test. UGIB, upper gastrointestinal bleeding; ICU, intensive care unit; NSAIDs, non-steroid anti-inflammatory drugs; COX, cyclooxygenase; BMR, Brunnstrom's motor recovery

Table 2
Results of multivariate logistic regression for potential risk factors of upper gastrointestinal bleeding

Dependent variable	Covariate	Odds ratio	95% CI	P value
UGIB	Age	1.066	1.021–1.114	0.004
	Impaired conscious	2.806	1.588–4.957	0.000
	Use of anticoagulant	2.396	1.092–5.260	0.029

Older age was an important risk factor in our study for predicting UGIB occurrence. The UGIB group patients (mean age: 75.4 years) were significantly older than the non-UGIB group patients (mean age: 72.92 years). Our results are similar to those of other studies discussing acute stroke patients (4, 16, 17). The mean age of the UGIB group patients vs. the non-UGIB group patients was 75.82 years vs. 72.05 years in the O'Donnell study (16), 74.7 years vs. 69 years in the Hsu study (17), and 78 years vs. 71 years in the Davenport study (4). These three studies did not separate patients in rehabilitation from others. In these three studies, the age discrepancy between the UGIB and non-UGIB patients reached statistical significance. Unlike our study, no age limit was set as an inclusion criterion. Older age appears to increase the risk of UGIB in acute stroke inpatients undergoing rehabilitation, even their age were ≥65 years.

We found that UGIB group patients had higher rates of impaired consciousness than non-UGIB group patients. Impaired consciousness (OR: 2.806, P = 0.000) is the most important predictor of UGIB in logistic regression analysis. It was not clearly document in previous literature whether impaired consciousness could increase the risk of UGIB. One early study documented that vagal overactivity after a brain lesion could result in hypersecretion of gastric acid and damage to the gastric mucosa (21). Another article claimed that the increased catecholamine concentrations in patients with cerebral infarction or hemorrhage may cause vasoconstriction and ulceration of the gastrointestinal mucosa (22). One recent study suggested that cerebral ischemia may lead to an interruption of the axis between the central nervous and gastrointestinal systems (23), which could cause gastrointestinal hemorrhage or dysmotility. It is likely that patients with impaired consciousness are more susceptible than those with clear consciousness to breaks of the axis between the central nervous and gastrointestinal systems. However, confirmation of this point requires further study.

Previous studies reported that the incidence of UGIB in stroke patients in the acute ward was 0.1%–3%(4, 14). It appears that the incidence of UGIB in the rehabilitative ward is higher than that in the non-rehabilitation ward. It is unclear whether the rehabilitation program itself adds extra stress or another unknown factor increases the incidence of UGIB. Gastrointestinal bleeding after prolonged exercise had been reported and is thought to be related to visceral ischemia (24, 25). Patients in our study received adequate but difficult-to-qualify rehabilitative exercises. However, a prolonged length of rehabilitative ward stay did not mean that patients received prolonged exercise. There is currently no evidence proving that longer length of rehabilitative ward stay or undergoing rehabilitation could lead to UGIB. To explain our results, we interpreted it conversely: occurrence of UGIB may prolong the duration of ward stay in acute stroke patients undergoing rehabilitation.

In our study, UGIB group patients had longer lengths of rehabilitative ward stays than non-UGIB group patients. Saxena et al. illustrated that medical complication is a determinant of increased length of ward stays in post-stroke patients receiving rehabilitation (26). UGIB is one of the listed complications that sometimes require emergent management. We suspected that UGIB might play a certain role in longer rehabilitative ward stays in the patient group. In our study, the mean length of rehabilitative ward stay was highly correlated with the stroke-induced impaired consciousness; however, the

idea that impaired consciousness leads to more complications that prolong patients' ward stays has yet to be proven.

According to the endoscopic results of our study, the stomach was the main site of UGIB. This finding was compatible with another study on 1933 patients with UGIB due to ulcers confirmed by endoscopy (27). In that study, the frequency of gastric ulcers was 1.24 times higher than that of duodenal ulcers and 5.51 times higher than that of esophageal ulcers (27). In our study, gastric origin frequency was nearly 2.43 times more than duodenal origin and 2 times more than esophageal origin. Our results incompletely reflect the bleeding source locations of patients with UGIB since some patients did not receive endoscopy due to poor consciousness or cooperation. To elucidate the locations of bleeding ulcers in this UGIB group, we need to collect more patients and analyze associated factors in the future.

Patients in the UGIB group (13.2%) had higher though insignificant (P = 0.061) rates of UGIB history than did those in the non-UGIB group (5.7%). We originally thought that this was because some patients with a history of UGIB might persistently use ulcer prophylaxis before stroke and might use clopidogrel instead of aspirin for secondary stroke prevention following our National Health Insurance regulation. However, we found that the percentage of ulcer prophylaxis use was similar between the UGIB group (29.7%) and the non-UGIB group (25.5%). Ulcer prophylaxis use in our patients did not appear to provide any protection against UGIB. In our study, any use of these medicines, even short-term or for a different purpose (such as prophylaxis of coronary artery disease), recorded in the medical charts was included in our data collection. Atar surveyed 10288 patients with acute coronary syndrome and found that the gastrointestinal bleeding rate in statin users was significantly lower than in non-statin users (13). In our study, the rate of statin use in the UGIB group (16.2%) was lower than in the non-UGIB group (22.8%) but was not statistically significant. More studies are required to prove that statin use prevents UGIB.

Because of medical needs, ischemic stroke patients might be more likely than hemorrhagic stroke patients to use antiplatelets or anticoagulants. In our study, the percentage of ischemic stroke patients, as well as that of patients using antiplatelets or anticoagulants, was higher in the UGIB group than in the non-UGIB group; however, the differences in percentages of ischemic stroke and in those using antiplatelets did not reach statistical significance. Interestingly, patients in the UGIB group more frequently used anticoagulants than did those in the non-UGIB group (P = 0.044). In Perez-Gomez's study (28) on patients with atrial fibrillation receiving standard anticoagulation, elderly patients (≥75 years) suffered a higher bleeding rate than younger ones (<75 years). In this study, however, UGIB was not analyzed statistically due to limited case numbers. Use of anticoagulants might create a potential risk of bleeding including UGIB in elderly patients. In our study, there were 12 patients with anticoagulants use in the UGIB group and 24 in the non-UGIB group. More data are required in the future before any conclusions can be drawn.

The frequency of use of steroids, NSAIDs, and conventional NSAIDs was higher in the UGIB group (7.4%, 26.5%, and 25%, respectively) than in the non-UGIB group (4.2%, 25.1%, and 19.8%, respectively), but the discrepancy was not statistically significant. Some patients might use intravenous steroids for several days due to brain swelling; others might use short-term NSAIDs for musculoskeletal pain. Regardless of duration, all use was recorded for statistical analysis. In addition, a factor such as combined ulcer prophylaxis use might also influence the results to some degree.

The major limitation of this study was the small number of patients. Another limitation was that the patients in our study were not classified into different groups based on rehabilitation intensity. Despite its limitations, this study demonstrated the situation of UGIB in acute stroke patients undergoing rehabilitation.

In summary, upper gastrointestinal bleeding is a common complication among elderly first-time acute stroke patients undergoing rehabilitation that could be affected by many factors. Older patients and those using anticoagulants tend to have a higher risk of UGIB. Impaired consciousness was the most important risk factor associated with UGIB in this patient group. Although the degree of motor recovery during rehabilitation may not be influenced by UGIB, occurrence of UGIB may prolong the length of the rehabilitative ward stay. These results may help clinicians identify the risks of UGIB before it develops.

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