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ORIGINAL WORK

Stress-Related Gastrointestinal Bleeding in Patients with Aneurysmal Subarachnoid Hemorrhage: A Multicenter Retrospective Observational Study

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Abstract

Background/Objective: Stress-related mucosal bleeding (SRMB) occurs in approximately 2–4% of critically ill patients. Patients with aneurysmal subarachnoid hemorrhage (aSAH) have a (diffuse) space-occupying lesion, are critically ill, often require mechanical ventilation, and frequently receive anticoagulation or antiplatelet therapy after aneurysm embolization, all of which may be risk factors for SRMB. However, no studies have evaluated SRMB in patients with aSAH. Aims of the study were to determine the incidence of SRMB in aSAH patients, evaluate the effect of acid suppression on SRMB, and identify specific risk factors for SRMB.

Methods: This was a multicenter, retrospective, observational study conducted across 17 centers. Each center reviewed up to 50 of the most recent cases of aSAH. Patients with length of stay (LOS) < 48 h or active GI bleeding on admission were excluded. Variables related to demographics, aSAH severity, gastrointestinal (GI) bleeding, provision of SRMB prophylaxis, adverse events, intensive care unit (ICU), and hospital LOS were collected for the first 21 days of admission or until hospital discharge, whichever came first. Descriptive statistics were used to analyze the data. A multivariate logistic regression modeling was utilized to examine the relationship between specific risk factors and the incidence of clinically important GI bleeding in patients with aSAH.

Results: A total of 627 patients were included. The overall incidence of clinically important GI bleeding was 4.9%. Of the patients with clinically important GI bleeding, 19 (61%) received pharmacologic prophylaxis prior to evidence of GI bleeding, while 12 (39%) were not on pharmacologic prophylaxis at the onset of GI bleeding. Patients who received an acid suppressant agent were less likely to experience GI bleeding than patients who did not receive pharmacologic prophylaxis prior to evidence of bleeding (OR 0.39, 95% CI 0.18–0.83). The multivariate regression analysis identified any instance of elevated intracranial pressure, creatinine clearance < 60 ml/min and the incidence of cerebral vasospasm as specific risk factors associated with GI bleeding. Cerebral vasospasm has not previously been described as a risk for GI bleeding (OR 2.5 95% CI 1.09–5.79).

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Conclusions: Clinically important GI bleeding occurred in 4.9% of patients with aSAH, similar to the general critical care population. Risk factors associated with GI bleeding were prolonged mechanical ventilation (> 48 h), creatinine clearance < 60 ml/min, presence of coagulopathy, elevation of intracranial pressure, and cerebral vasospasm. Further prospective research is needed to confirm this observation within this patient population.

Keywords: Stress ulcer prophylaxis, Acid-suppressive therapy, Subarachnoid hemorrhage, Cerebral vasospasm, Proton pump inhibitors, Histamine-2-receptor antagonists, Gastrointestinal hemorrhage, Neurocritical care

Introduction

Stress-related mucosal bleeding (SRMB) occurs in approximately 2–4% of critically ill patients receiving stress ulcer prophylaxis. Clinically important gastrointestinal (GI) bleeding increases morbidity and mortality [1]. Neurocritical care patients are often thought to be at increased risk of stress-related bleeding due to increases in vagal tone and gastric acid secretion, dating back to observations by Harvey Cushing in the 1930s [2, 3]. The majority of the landmark trials in this area excluded 'brain injury' patients or included a small number of neurocritical care patients (without specifying the diagnosis) [4].

Few clinical trials have evaluated the incidence of clinically important GI bleeding or the efficacy of stress ulcer prophylaxis in neurocritical care patients and none have evaluated this complication in aneurysmal subarachnoid hemorrhage (aSAH) patients [5, 6]. Patients with aSAH may exhibit all of the classic risk factors for clinically important GI bleeding such as hypotension, increased intracranial pressure, prolonged mechanical ventilation and coagulopathy [7–10]. In addition, these patients may also receive antiplatelet or anticoagulant agents as an aspect of their aneurysm treatment [11–13]. One retrospective study of patients with aSAH demonstrated that approximately 4% of aSAH patients exhibited GI bleeding, though the definition of bleeding was not specified [7]. Additionally, patients with aSAH have a risk of cerebral vasospasm which can increase intracranial pressure, necessitate the use of vasopressor agents, and is associated with a systemic inflammatory response, all of which we hypothesize increase the risk of clinically important GI bleeding.

Studies investigating critically ill patients with risk factors for clinically important GI bleeding suggest that bleeding occurs in 1.7–6.8% of patients receiving a histamine-2 receptor antagonist (H2RA) for prophylaxis [4, 6, 14]. Similarly, the incidence of bleeding in those receiving other prophylactic agents is also within this range, with clinically significant bleeding occurring in 4.5% and 3.8% of patients receiving proton pump inhibitors (PPI) and sucralfate, respectively [4, 6]. Smaller clinical investigations evaluating the GI bleeding rate in patients specifically with intracranial hemorrhage suggest a higher incidence, despite the use of acid-suppressing agents (11–27.8%) [5, 15]. The risk of pneumonia (approximately 20% incidence) or other complications such as *Clostridium difficile* diarrhea with acid suppressive agents has been described in other studies [4, 5, 14]. Patients with aSAH may require prolonged mechanical ventilation, which increases the risk of pneumonia in many of these studies [9, 10]. Additionally, most patients with aSAH also exhibit some degree of immune dysfunction further increasing the risk of infection [7, 16].

No human studies to date have specifically included or described the rate of clinically important bleeding in patients with aSAH nor have any studies evaluated the efficacy or safety of acid suppressive therapies in this unique patient population [17, 18]. This study was conducted to evaluate the following related to clinically important GI bleeding in aSAH patients: the overall incidence, the effect of acid suppression on the incidence, and specific risk factors. The primary objective of the study was to determine the incidence of clinically important GI bleeding in patients with aSAH. Secondary objectives included evaluating the effect of prophylaxis of clinically important GI bleeding in patients with aSAH, identifying specific risk factors for clinically important GI bleeding in this patient population, and assessing incidence of adverse effects, specifically diagnosis of *C. difficile* and diagnosis of pneumonia during hospital stay.

Methods

This was a multicenter, retrospective, observational study conducted across 17 academic medical centers in North America. Each center reviewed up to 50 of the most recent cases of aSAH based on the corresponding ICD-9 code (430) or ICD-10 code (160.0–160.9). Study data were collected and managed using REDCap electronic data capture tools at University of Kentucky HealthCare [19]. Patients were included if they were between the ages of 18 and 85 years and admitted for acute, nontraumatic SAH between the dates of January 1, 2013 and June 30, 2017 in reverse chronological order. Patients were excluded if there was evidence of active GI bleeding on admission, if hospital length of stay was less than 48 h, or if significant gaps in documentation related to data collection were present. Each center obtained approval from

their local institutional review board (IRB) and was subject to regulation by the primary governing IRB.

Variables related to demographics, aSAH severity, GI bleeding, provision of SRMB prophylaxis, infection-related adverse events, intensive care unit (ICU), and hospital length of stay were collected for the first 21 days of admission or until hospital discharge, whichever came first. For the purpose of this analysis, all available histamine-2 receptor antagonists were combined into the same category ("H2RAs"). Similarly, all commercially available proton pump inhibitors were combined into the same category ("PPIs"). Clinically important GI bleeding was defined as any instance of the following within 24 h of reported GI bleeding: blood transfusion requirement, hemoglobin reduction of 2 gm/dl or greater, or abrupt systolic blood pressure reduction of ≥ 20 mmHg. Renal dysfunction was defined as an estimated creatinine clearance less than 60 mL/min (by eGFR or Cockcroft-Gault) and coagulopathy was defined as an INR greater than 1.5. Cerebral vasospasm was defined as receiving intra-arterial treatment by calcium channel blockers or other rescue agents, by radiographic evidence (described during digital subtraction angiography), or by a Lindegaard ratio of >3. Intensity of anticoagulation was collected, including administration of anti-platelet agents (aspirin, clopidogrel, ticagrelor, prasugrel), prophylaxis of venous thromboembolism (VTE), and therapeutic anticoagulation. Other data collected included the presence of enteral or oral nutrition, diagnosis of *C. difficile* any time during hospital stay, and diagnosis of pneumonia any time during hospital stay, including pathogen cultured, if applicable. For this study, a practical definition of pneumonia was employed due to the retrospective nature of the study. Patients were categorized as having been treated for pneumonia if: [1] the patient had BAL, PAL, or sputum cultures and the presence of antibiotics, or [2] a review of progress notes stating a pneumonia was suspected for which antibiotics were initiated. If cultures were obtained, centers provided the pathogen cultured during data collection. Missing data were addressed using casewise deletion.

The statistical analysis consisted of descriptive statistics for the population demographics. A two-tailed Students *t* test or Chi Squared analysis was used to compare demographic characteristics, as appropriate for the type of data. In order to have 80% power, assuming a clinically important GI bleeding rate of 4%, it was estimated that a total number of 352 patients in the two cohorts would be required to detect a 1% incidence of clinically important GI bleeding between treatment groups. The incidence of clinically important bleeding, pneumonia, and *C. difficile* diarrhea was evaluated using relevant tests such as Chi Squared or ANOVA. Bivariate analysis was generated using IBM SPSS Statistics (v23, Armonk, NY). A multivariate logistic regression modeling was utilized to examine the relationship between specific risk factors and the incidence of clinically important GI bleeding in patients with aSAH. The full model included the main effects (age, gender, need for mechanical ventilation, study site, and numerous other variables) and two-way interactions between Hunt-Hess score and vasospasm, vasospasm and age, and creatinine clearance and age. An additional analysis of patients from each cohort (with and without GI bleeding) was also performed by matching patients 1:1 based on Hunt and Hess score, discharge outcome, age (within 10 years), and presence of the following risk factors: mechanical ventilation, vasospasm, no stress ulcer prophylaxis, ICP >20, and renal impairment (CrCl <60 mL/min). Level of significance was set at a p-value <0.05. The data analysis was generated using SAS software (v9.4, Cary, NC).

Results

A total of 627 patients were included in the study population. All patients were admitted for a spontaneous, nontraumatic aSAH. Two cohorts, those with evidence of clinically important GI bleeding and those with no GI bleeding, were compared to evaluate characteristics associated with bleeding. The overall incidence of clinically important GI bleeding was 4.9%. Several clinical characteristics were significantly different in the demographics of the two cohorts (Table 1). Of note, patients who had evidence of GI bleeding more frequently had a prior history of GI bleeding, more severe presentation of their aSAH (based on Hunt-Hess score), a higher incidence of cerebral vasospasm, and a longer length of stay (Table 1). At least one dose of corticosteroid was administered in 47.8% of patients, but the use was not different between the two cohorts. The majority of patients (72.5%) underwent aneurysm embolization during the study period.

A variety of prophylaxis agents were used across the study population in the majority of patients, with many patients receiving both an H2RA and a PPI during the study period (not usually concomitantly, Table 1). There was no difference in the rate of use of one class of agents over the other. One hundred eighteen (20%) patients with no GI bleeding received no pharmacologic prophylaxis for the duration of the study period. Of the patients with clinically important GI bleeding, 19 (61%) received pharmacologic prophylaxis prior to evidence of GI bleeding, while 12 (39%) were not on pharmacologic prophylaxis at the onset of GI bleeding. Overall, patients who received an acid suppressant agent were less likely to experience GI bleeding than patients who did not receive pharmacologic prophylaxis prior to evidence of bleeding (OR 0.39, 95% confidence interval 0.18–0.83). This suggests the

Table 1 Patient demographics

Characteristic	GI bleed ($n=31$)	No GI bleed ($n=596$)	p-value
Age, years	54.6 (10.4)	56.8 (13.1)	0.363
Female sex	23 (74.2)	379 (63.6)	0.230
History of GI bleed	3 (9.7)	10 (1.7)	0.002
Hunt & Hess Score	3 [1–5]	2 [1–5]	0.038
Fisher Score	4 [1–4]	3 [1–4]	0.038
Aneurysm intervention			0.367
Coil	18 (58.1)	253 (42.4)	
Clip	5 (16.1)	134 (22.5)	
Other	1 (3.2)	43 (7.2)	
None	7 (22.6)	166 (27.9)	
SRMB prophylaxis			
PPI*	23 (74%)**	215 (36%)	< 0.0001
H2RA*	25 (81%)**	339 (57%)	0.009
No agent	6 (19.4%)**	118 (20%)	0.952
Corticosteroid use	12 (38.7)	288 (48.3%)	0.296
Length of stay (days)	20 (5-81)	15 (2-175)	0.004
ICU length of stay (days)	17 (5-44)	12 (0-82)	0.005

GI = gastrointestinal; H2RA = histamine-2 receptor antagonist; ICU = intensive care unit; PPI = proton pump inhibitor; SRMB = Stress related mucosal bleeding

Note Data reported as N (%) or median (interquartile range)

*some patients received a combination of PPI and H2RA during their admission

**number of patients reported with PPI, H2RA, or no prophylaxis prior to GI bleeding episode

potential for a protective effect of pharmacologic prophylaxis for the incidence of clinically important GI bleeding.

Bivariate analyses and multivariate regression analyses were performed to identify factors associated with GI bleeding. Variables identified as significant in the bivariate analysis along with Hunt-Hess score, age, gender, and study site were included in the multivariate analysis. Classic SRMB factors such as prolonged mechanical ventilation, any creatinine clearance < 60 ml/min, and coagulopathy were more prevalent in the GI bleed cohort (Table 2). Elevated intracranial pressure was also more prevalent in the GI bleed cohort ($p=0.001$), which links well with the other classic risk factor for SRMB, traumatic brain injury. The multivariate regression analysis identified any instance of elevated intracranial pressure, creatinine clearance < 60 ml/min and the incidence of cerebral vasospasm as specific risk factors associated with GI bleeding (Table 3). Patients with any incidence of cerebral vasospasm were 2.5 times more likely to experience GI bleeding compared to patients without vasospasm. None of the two-way interactions to evaluate the interplay between potential risk factors such as aSAH severity (Hunt-Hess score) and vasospasm, vasospasm and age, and Hunt-Hess score and intracranial pressure were significant for interaction to the model.

A full accounting of all adverse events of the acid suppressive agents was not evaluated due to the retrospective design of the study. The diagnosis of pneumonia at any point in the stay was noted in 23.4% of patients overall ($n=147$). Of the patients with pneumonia, 46.9%

Table 2 Clinically important GI bleeding Risk Factors

	GI bleed ($n=31$)	No GI bleed ($n=596$)	p-value
Mechanical ventilation	25 (81.6%)	349 (58.6%)	0.015
Coagulopathy (INR > 1.5)	5 (16.1%)	23 (3.9%)	0.001
Any corticosteroids	12 (38.7%)	288 (48.3%)	0.296
Any ICP > 20	17 (54.8%)	170 (28.5%)	0.001
Any ClCr < 60 ml/min	14 (45.2%)	93 (15.6%)	0.0002
Cerebral vasospasm	21 (67.7)	267 (44.8)	0.012

Note Data reported as N (%)

ClCr = creatinine clearance; GI = gastrointestinal; ICP = intracranial pressure

Table 3 Multivariate analysis of factors related to clinically important GI bleeding

Characteristic	Odds ratio	95% Confidence interval	*p*-value	*β*
Any ICP > 20	2.27	1.03-4.97	0.041	0.82
Any ClCr < 60 ml/min	5.05	2.31-11.03	< 0.0001	1.62
Cerebral vasospasm	2.51	1.09-5.79	0.0314	0.92
Intercept				−4.30

ClCr = creatinine clearance; GI = gastrointestinal; ICP = intracranial pressure

(n=69) of the patients received a PPI at any point in their stay compared to 35.2% (n=169) of those who did not receive a PPI (p=0.01). H2RA administration occurred in 69.4% (n=102) at any point in their stay of those with pneumonia compared to 54.6% (n=262) of those who did not (p=0.001). The overall rate of *Clostridium difficile* diarrhea was 2.4% (n=15). Two of the fifteen patients received a PPI early in their admission (one for the entire stay, the other for 6 of the first 7 days of the admission, then no PPI thereafter). The other thirteen patients with *Clostridium difficile* diarrhea received an H2RA early in their admission for variable durations.

Discussion

This study is the first to evaluate the GI bleeding rate in patients with aSAH. The GI bleeding rate (4.9%) is within the range typically reported for the general critical care population on pharmacologic prophylaxis (1.7–6.8%) [4, 6, 14]. Several of the classic risk factors for SRMB such as prolonged mechanical ventilation (>48 h), creatinine clearance < 60 ml/min, presence of coagulopathy, and elevation of intracranial pressure were affirmed as risk factors in the aSAH population [1, 2]. The occurrence of cerebral vasospasm was also significantly associated with clinically important GI bleeding. This is the first time that cerebral vasospasm has been implicated as a risk for GI bleeding. Patients who did not receive pharmacologic prophylaxis were more likely to experience clinically important GI bleeding, a finding that is not surprising given the high rate of GI bleeding in the current cohort. This result supports the notion that aSAH patients are at high risk of clinically important GI bleeding and the potential protective effect of pharmacologic prophylaxis. Conversely, the use of acid suppressive agents was associated with an increased rate of pneumonia.

Patients with aSAH exhibit several characteristics that are unique among neurocritical care patients. First, many of these patients are awake and oriented despite the presence of subarachnoid blood. As such, many patients do not require endotracheal intubation (only 59.6% of the current cohort were intubated at any point aside from temporary intubation for necessary procedures). Second, patients with lower grade aSAH are usually able to eat a regular diet by mouth and do not require enteral or parenteral nutrition. In short, patients in the intensive care unit who are neurologically oriented and conversant, while tolerating a regular diet are not typically the patients clinicians feel are at risk for SRMB. Coinciding with this perceived lack of risk, over 20% of the patients included in this study did not receive primary pharmacologic prophylaxis for clinically important GI bleeding. Reasons for omitting this therapy were not recorded. However, with the advent of standardized order sets in electronic medical records and the ubiquity of mnemonics to remind clinicians to add acid suppressant agents in critically ill patients, it is likely that a conscious decision was made to omit prophylaxis due to the perceived low risk of SRMB in patients with aSAH without 'conventional' risk factors [20].

The presence of cerebral vasospasm appears to be a substantial risk for clinically important GI bleeding in patients with aSAH. The etiology of cerebral vasospasm appears to be multi-factorial and is certainly associated with the presence of blood in the subarachnoid space. The physical irritation of the blood on the meninges, liberation of hemoglobin and iron from acute hemolysis, inflammatory mediators aimed at removing the noxious stimulus, increased oxidative stress, increases in endogenous vasoconstrictors (e.g., endothelin) and scavenging of nitric oxide may all play a role in the development of cerebral vasospasm [21]. It is unknown whether any of these factors may directly increase the risk of clinically important GI bleeding. Several recent studies have suggested a link between systemic inflammation and cerebral vasospasm (one begets the other in both directions) [21]. An increase in systemic inflammation similar to the physiologic response to sepsis could be an important factor in increasing the risk of clinically important GI bleeding in patients with aSAH and cerebral vasospasm. Furthermore, red blood cell transfusions are also associated with cerebral vasospasm, which may create a cyclic problem for patients with aSAH and clinically relevant GI bleeding [22]. Finally, the presence of vasospasm is associated with high sympathetic tone, which may also affect gastric motility, acid secretion, and maintenance of the gastric mucosa [23, 24]. Published studies on this dynamic specifically in subarachnoid hemorrhage are not available, though it has been well-demonstrated that high sympathetic tone or high amounts of exogenous catecholamines can reduce splanchnic perfusion thereby increasing the risk of stress-related mucosal damage [25–27]. The majority of the patients who experienced clinically

important GI bleeding and vasospasm experienced vasospasm before bleeding. However, it was not possible to evaluate causation in these instances nor in the instances where bleeding occurred prior to documentation of vasospasm, as the impact of evolving vasospasm on GI bleeding is not well-described. Future translational work aimed at further clarifying the relationship of these factors is necessary.

This study has several strengths which increase our confidence that these findings are not by chance. First, patients were included from 17 different hospitals in North America, which increases the real-life heterogeneous treatment practices that comes with evaluating patients in so many different facilities. Due to the relative ubiquity of the use of pharmacologic prophylaxis seen in this cohort, it is unlikely that institution-specific variations in care contributed to the development of GI bleeding as might be seen with a single center study. Second, the data collection related to potential risk factors was extensive. aSAH patients often have a prolonged intensive care unit stay due to the risk of vasospasm over the first one to two weeks after ictus, allowing for a wealth of data on most patients to assess risk factors for bleeding. Finally, the classic risk factors for SRMB were confirmed with the current study (mechanical ventilation (>48 h), creatinine clearance <60 ml/min, presence of coagulopathy, and elevation of intracranial pressure), which suggests the cohort is reflective of a critically ill population overall.

Several issues which may limit the interpretation of this data merit acknowledgement. The retrospective design limited the opportunity to account for all of the potential risks for clinically important GI bleeding. For instance, the presence of shock and hypotension is also well-associated with SRMB. We did not collect information on shock or hypotension in the current cohort. Patients with aSAH infrequently present with hypotension, but in a small percent of patients, myocardial stunning may result in shock early in the course of illness [28]. Iatrogenic hypotension related to acute blood pressure changes prior to securing the aneurysm or related to nimodipine use may have also occurred, which was not accounted for. Esophagogastroduodenoscopy was not routinely performed in the patients included in this study, as prospective screening for SRMB is not typical without clinical suspicion. Thus, the true incidence of SRMB (as opposed to clinically important GI bleeding) in this population remains undefined. Some severity scores were not available in the medical record, so these patients were not included when evaluating the effect of aSAH severity on the risk of clinically important GI bleeding. We collected information on enteral nutrition, but were not able to consistently assess the amount of caloric intake nor was the extent of oral diet evaluated due to the nature of the retrospective design and missing documentation. Provision of enteral nutrition may be a protective factor for SRMB, but we were unable to include this in our analysis [29]. Finally, we collected data on the incidence of pneumonia and *C. difficile* diarrhea, but other adverse events associated with acid suppressant agents may have occurred and were not accounted for. Many of these potential sources of bias would be neutralized by conducting a prospective trial evaluating the impact of pharmacologic prophylaxis on GI bleeding in this population. It seems unlikely this will occur given the niche population of aSAH and the sample size required.

Conclusion

Patients with aSAH had an incidence of GI bleeding of 4.9% in this cohort. Risk factors associated with GI bleeding were prolonged mechanical ventilation (>48 h), creatinine clearance <60 ml/min, presence of coagulopathy, elevation of intracranial pressure, and cerebral vasospasm. This is the first study to identify cerebral vasospasm as a risk factor for GI bleeding, increasing the risk by 2.5 fold. Given the high rate of GI bleeding and the potential protective effect of pharmacologic prophylaxis, the results of this study suggest that clinicians should consider aSAH as high-risk for clinically important GI bleeding and evaluate prescription of prophylaxis of SRMB in patients with aSAH, particularly through the vasospasm window. These results warrant further exploration within robust randomized controlled trials.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s12028-020-01137-5) contains supplementary material, which is available to authorized users.

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Author Contributions

DA and AC primarily conceived the study design, but all authors had input on study design and execution. Data analysis was performed primarily by DA, AS, and AMC; all authors had input on data interpretation. DA, AS, and AMC primarily wrote the manuscript, but all authors were able to review and revise ad lib. All authors provided a final review and approval of the manuscript.

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Conflict of interest
No pertinent conflicts of interest were reported.

Ethical Approval
The study was approved via expedited review by the University of Kentucky IRB.

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