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• *RAPID COMMUNICATION* •

Prevalence and risk factors of stress-induced gastrointestinal bleeding in critically ill children

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Abstract

AIM: To assess the frequency and the risk factors of stress-induced gastrointestinal (GI) bleeding in children admitted to a pediatric intensive care unit (PICU).

METHODS: The medical records of children aged between 1 month and 15 years admitted to the PICU between January 2002 and December 2002 were reviewed. Demographic data, indications for PICU admission, principle diagnosis, and basic laboratory investigations were recorded. Previously described factors for stress ulcer bleeding (mechanical ventilation, sepsis, acute respiratory distress syndrome, renal insufficiency, coagulopathy, thrombocytopenia, and intracranial pathology) were used as independent variables in a multivariate analysis.

RESULTS: One hundred and seventy of two hundred and five medical records were eligible for review. The most common indication for PICU admission was respiratory failure (48.8%). Twenty-five children received stress ulcer bleeding prophylaxis with ranitidine. The incidence of stress ulcer bleeding was 43.5%, in which 5.3% were clinically significant bleeding. Only mechanical ventilation and thrombocytopenia were significantly associated with stress ulcer bleeding using the univariate analysis. The odds ratio and 95% confidence intervals were 5.13 (1.86-14.12) and 2.26 (1.07-4.74), respectively. However, the logistic regression analysis showed that mechanical ventilation was the only significant risk factor with the odds ratio of 14.1.

CONCLUSION: The incidence of gastrointestinal bleeding was high in critically ill children. Mechanical ventilation was an important risk factor for gastrointestinal bleeding.

Key words: Gastrointestinal; Hemorrhage; Stress; Risk factor; Child

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INTRODUCTION

Stress ulcer bleeding is one of the common complications in critically ill patients admitted to the intensive care unit. Its incidence in adults ranges from 0.17% to 14%, depending on the diagnostic criteria, patient selection, and methods of investigation[1-4]. There have been a few reports of this condition in pediatric populations with the incidence varying from 10% in a pediatric intensive care unit to 53% in a neonatal intensive care unit[5,6]. This study was designed to assess the frequency and the risk factors of stress-induced upper gastrointestinal bleeding in critically ill children admitted to a pediatric intensive care unit.

MATERIALS AND METHODS

Patients

All medical records of children younger than 15 years admitted to the PICU between January 2002 and December 2002 at Chiang Mai University Hospital were retrospectively reviewed. Our hospital is a tertiary care center with a facility of six-bed PICU, taking care of approximately 83% of medical and 17% of surgical pediatric patients. The general indications for admission included respiratory/cardiovascular failure, shock, coma, post-operative care, and patients requiring intensive monitoring. The patients with duration of admission in PICU shorter than 48 h, positive previous history of GI bleeding, recent GI tract surgery, brain death, and epistaxis/oropharyngeal bleeding were excluded. Demographic data, indications for PICU admission, and principle diagnosis as well as basic laboratory investigations including hemoglobin level, platelet count, coagulation studies, blood urea nitrogen (BUN), creatinine (Cr), and liver function tests were recorded. Upper GI bleeding during PICU admission was categorized as overt and clinically significant bleeding. Overt GI bleeding (OB) was diagnosed, if there was evidence of hematemesis, coffee ground gastric content, or melena;

whereas clinically significant bleeding (CSB) was defined as overt GI bleeding associated with major changes in vital signs, namely a decrease in blood pressure greater than 20 mmHg, an increase in heart rate of >20 beats above the baseline value, and a decrease in hemoglobin level of more than 2 g/dL. Based on previous studies in adults, potential risk factors were used. These were the use of mechanical ventilation, sepsis, acute respiratory distress syndrome (ARDS), renal insufficiency, coagulopathy, thrombocytopenia, and intracranial pathology. The diagnostic criteria for these conditions were: sepsis-at least two of the following, body temperature >38 °C or <36 ° C, heart rate >160/min (infant) or >150/min (child) or >90/min (adolescent), WBC >15 000 or <4000/mm^3, and band form >10% or there was a positive blood culture; ARDS - positive alveolar infiltration in both lungs on chest X-ray and PaO_2/FiO_2 <200 without evidence of left-sided heart failure; *renal insufficiency* - Cr >2 mg/dL, or requiring dialysis; *coagulopathy* - prothrombin time (PT) >3s and partial thromboplastin time (PTT) >10 s above the control value; *thrombocytopenia* -'platelet count<100 000/mm^3; *intracranial pathology* - abnormal imaging study, meningitis, or encephalitis. This study protocol was approved by the Research Ethic Committee of Chiang Mai University.

Statistical analysis

All data were assessed by SPSS program. Cross-tabulations were analyzed using the χ^2 test, presented as the odds ratio and 95% confidence interval, in which a $P<0.05$ was considered statistically significant. Multivariate analysis of various independent variables was performed using logistic regression modeling.

RESULTS

Over the 12-month period, 205 of 258 medical records were available for review (53 records were missing). Thirty-five cases were excluded for the following reasons: duration of admission shorter than 48 h (n = 28), incomplete medical records (n = 3), epistaxis (n = 2), brain death (n = 1), and recent gastrointestinal surgery (n = 1). Therefore, a total of 170 charts were eligibly reviewed. There were 89 males (52.4%) with an average age of 3.8 years. The total duration of admission was 7.2 d (2-35 d). The most common indication for PICU admission was respiratory failure (48.8%). The demographic data of children with and without bleeding are shown in Table 1. Twenty-five children received stress ulcer bleeding prophylaxis, in which ranitidine was used in 22 cases with a dosage of 3 mg/kg/d; whereas the other three patients received antacids. In the subgroup of children who received stress ulcer prophylaxis, 14 cases developed upper GI hemorrhage (3 CSB and 11 OB); whereas stress ulcer bleeding occurred in 60 of 145 cases who did not receive the prophylactic treatment (6 CSB and 54 OB). GI bleeding complicated 43.5% of cases admitted to the PICU and 5.3% had clinically significant bleeding. Twenty-two percent of patients with CSB were diagnosed as dengue hemorrhagic fever, compared to none in the patients without bleeding.

Table 1 Demographic data of children with and without stress-induced GI bleeding

Characteristic	Bleeding (n = 74)	No bleeding (n = 96)	P
Age (yr)[1]	3.82 (0.44)	3.84 (0.40)	0.977
Sex, male	41	48	0.484
Duration of admission (d)[1]	8.23 (0.78)	6.41 (0.58)	0.062
Underlying diseases			
Respiratory system	8	15	0.445
Cardiovascular system	9	18	
Neurological system	19	25	
Hemato/oncologic system	11	11	
Infections/HIV	14	9	
Gastrointestinal system	5	6	
Others	8	12	

[1]Presented as mean±SE.

Among the independent variables, only mechanical ventilation and thrombocytopenia were significantly associated with stress ulcer bleeding using the univariate analysis. The odds ratio and 95%CI were 5.13 (1.86-14.12) and 2.26 (1.07-4.74), respectively (Table 2). Using multivariate analysis, only mechanical ventilation was found to be significantly associated with the development of gastrointestinal bleeding in critically ill patients ($P<0.05$). In our study, stress ulcer prophylaxis did not reduce the risk of bleeding. The overall mortality rate was 18.8%. Gastrointestinal bleeding and transfusion requirements were associated with high mortality ($P<0.05$).

DISCUSSION

Stress-induced gastrointestinal lesions, including gastritis, erosions, gastric, and duodenal ulcers, can result in significant upper gastrointestinal hemorrhage, increased morbidity and mortality[2]. The prevalence varies between studies[1-6]. In our series, 5% of the cases developed clinically significant bleeding which is considerably higher than that in previous studies performed in pediatric population[5,7]. This might result from a relatively high prevalence of hemorrhagic fever which commonly causes thrombocytopenia and subsequent gastrointestinal bleeding in our region. As noted in our report, 22% of the cases with CSB were diagnosed as dengue hemorrhagic fever. Additionally, we did not routinely use stress ulcer prophylaxis in all patients, and patients with ranitidine prophylaxis did not receive the recommended dose of 6 mg/kg/d[8]. This may explain the poor beneficial prophylactic effect noted in our study. Apart from clinically significant bleeding, we also found a high prevalence of overt upper gastrointestinal bleeding (38.2%), which is comparable to the retrospective report section from Kuusela *et al.* in neonates[6]. However, this figure could be exceptionally high due to a possibility of inclusion of traumatic nasogastric tube injuries which are very difficult to be documented in such a retrospective design and we did not routinely perform endoscopy in all children to delineate the cause of upper GI bleeding during the study period. Although we believe that the prevalence

Table 2 Risk factors for stress-induced GI bleeding in children (*n* = 170)

Risk factors		*n*	Gastrointestinal bleeding (%)	Odds ratio (95%CI) simple regression	Odds ratio (95%CI) multiple regression
Mechanical ventilation	Yes	139	49.6	5.126 (1.861–14.118)	14.096 (2.205–90.112)
	No	31	16.1	*P* = 0.001	*P* = 0.005
Thrombocytopenia	Yes	37	59.4	2.256 (1.073–4.745)	3.462 (0.843–14.216)
	No	132	39.4	*P* = 0.030	*P* = 0.085
Renal insufficiency	Yes	9	77.8	4.858 (0.978–24.124)	2.763 (0.326–23.426)
	No	160	43.1	*P* = 0.035	*P* = 0.351
Prolonged PT	Yes	34	64.7	2.292 (0.946–5.551)	1.222 (0.289–5.161)
	No	32	44.4	*P* = 0.064	*P* = 0.785
Prolonged PTT	Yes	37	62.2	2.071 (0.876–4.899)	1.198 (2.640–5.446)
	No	52	44.2	*P* = 0.095	*P* = 0.815
ARDS	Yes	96	46.9	2.050 (0.912–4.610)	0.772 (0.171–3.487)
	No	54	38.5	*P* = 0.080	*P* = 0.737
Sepsis	Yes	69	49.3	1.481 (0.799–2.748)	1.234 (0.325–4.691)
	No	101	39.6	*P* = 0.212	*P* = 0.757
Intracranial pathology	Yes	32	46.8	1.181 (0.546–2.556)	1.192 (0.283–5.010)
	No	138	42.8	*P* = 0.672	*P* = 0.811

reported in this study might be over-estimated, it discerns a significant magnitude of the problem that requires careful medical attention. Similar to previous studies in adults and children, the mechanical ventilation was found to be the most significant risk factor for stress-induced gastrointestinal bleeding in our study[1,2,5,6]. Although coagulopathy is also noted as a significant independent risk factor in some studies[1,2,5,7], this was not observed in our series using multivariate analysis. A further prospective study with a larger sample size is needed.

Imbalance between protective and destructive factors has been postulated as a basic pathophysiology of GI bleeding. Increased acid production and decreased gastric blood flow, secondary to hypotension and metabolic acidosis, are composed of major physiologic responses leading to mucosal injuries. Hemorrhagic gastritis affects mainly the gastric body as it is the most vulnerable area for ischemic injury[4]. As a result, prophylactic strategies with H_2RA and cytoprotective agents have been widely prescribed to the critically ill patients admitted to the intensive care unit. Lacroix *et al.*[9] have reported a significant increase in the gastric pH following cimetidine prophylaxis stress ulcer bleeding in children, but no prophylactic benefit was demonstrated in their study. Kuusela *et al.*[10] showed that short-term prophylactic ranitidine treatment could prevent gastric mucosal lesions in newborn infants under stress. Cook *et al.*[11] performed a meta-analysis and showed that H_2RA significantly reduces clinically important bleeding over sucralfate and antacids. However, overgrowth of Gram-negative bacteria following the increase of gastric pH by antisecretory agents can be associated with ventilator-associated pneumonia (VAP)[12,13]. Lopriore *et al.*[14] reported that 8.4% of mechanically ventilated children develop VAP. Among these, more children prophylactically treated with ranitidine tend to be associated with VAP than those in the control group (11.1% *vs* 6.2%), despite no statistical significance. The use of sucralfate, since its introduction, seems logically useful in preventing this complication. Unfortunately, this hypothesis was not supported by the large meta-analysis study[11].

Ben-Menachem *et al.*[15] did a cost-effective analysis on stress ulcer prophylaxis and suggested that the cost of prophylaxis is substantial and may be prohibitive in ICU patients at low risk of developing stress-related hemorrhage. Therefore, several authors have recently suggested that such prophylaxis should be selective and may be indicated only for patients at high risk, particularly in those with mechanical ventilation and coagulopathy[2,7]. However, the cost estimation in PICU on this issue has not been well studied.

In conclusion, the incidence of gastrointestinal bleeding is high in critically ill children. Mechanical ventilation is a significant risk factor for gastrointestinal bleeding.

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