

## Effect of Gastric Acid Suppressant Prophylaxis on Incidence of Gastrointestinal Bleeding in Pediatric Intensive Care Unit

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### Abstract

**Background:** Critically ill children admitted to pediatric intensive care unit (PICU) are at increased risk of gastrointestinal bleeding due to stress related mucosal injury. Reducing gastric acid by acid suppressant medication is the accepted prophylaxis treatment, but there is not any definitive guideline for using prophylaxis in PICU patients. The present study aimed to assess the effect of Proton Pump Inhibitor (PPI) and H2 Blocker (H2B) prophylaxis on gastrointestinal bleeding in admitted patients of PICU, Mashhad- Iran.

**Materials and Methods:** In this study, 100 patients admitted in PICU divided into two equal groups on the first day of admission. They received ranitidine or pantoprazole as prophylaxis of stress ulcer. Those patients who had history of gastrointestinal bleeding or coagulation disorder were excluded. 100 PICU patients who had not received prophylaxis during last 6 months retrospectively evaluated as control of the study. Data were collected as demographic characteristics, admission reason, definitive diagnosis, receiving corticosteroid and mechanical ventilation in each patient. Gastrointestinal bleeding (hematemesis, coffee ground aspirate, and melena) and clinically significant gastrointestinal bleeding were daily monitored. Data analyzed through descriptive statistical tests, Chi-square, logistic regression, t-test and using SPSS-16 software.

**Results:** Among 204 patients (control group=105 and case group=99), incidence of gastrointestinal bleeding (GB) was 13.2% in which 6.9% of cases presented with clinically significant gastrointestinal bleeding (CSGB). Loss of consciousness and respiratory distress were the main reason of admission. There was no significant differences between the incidence of (GB) and (CSGB) in experimental and control groups ( $P>0.05$ ) as well as ranitidine and pantoprazole prophylaxis ( $P>0.05$ ). Significant risk factors of (GB) were mechanical ventilation and loss of consciousness and corticosteroid therapy.

**Conclusion:** There is ambiguity about probable benefits of gastrointestinal bleeding prophylaxis in critically ill children. We proposed that prophylaxis should prescribe in patients with two or more risk factors of gastrointestinal bleeding.

**Key Words:** Children, Gastrointestinal bleeding prophylaxis, Pantoprazole, Ranitidine.

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## 1- INTRODUCTION

Stress ulcers and bleeding in upper gastrointestinal tract (stomach and duodenum) is a well-known complication of critical conditions. Based on the reported studies the prevalence of upper GI bleeding due to stress ulceration among pediatric patients of intensive care unit (ICU) estimated between 10% to even more than 50% (1). The estimated risk of major bleeding varies from 1.6 to 5.3% (2-7). Pathogenesis researches indicated that stress can increase the acid secretion in GI and it plays a major role in stress ulceration among children or adults (7). However this mechanism in neonates is uncertain (8). Also, impaired mucosal which induced by shock, sepsis or trauma protection is concerned as another factor for GI bleeding (9, 10). On the other hand, some factors such as mechanical ventilation and coagulopathies can increase the rate of GI bleeding. There are evidences that support the effect of prophylaxis in reduction of this complication (11-17).

But, the optimal pharmacological agent is unknown and there are various options and controversies in selection of medications. Prophylactic agents include: H2 blockers (such as cimetidine, ranitidine, famotidine and etc.), proton pump inhibitors (such as omeprazole, pantoprazole and etc.), sucralfate, antacids and prostanoids (18-26). The conducted studies indicated that the effect of prophylactic medications in prevention from GI bleeding in PICU patients have been associated with controversies. It means that prophylaxis has significant or non-significant effects and the outcomes depend on the presence of risk factors or demographic variables or type of medication (3-5, 27-34).

Regarding to the importance of this issue and controversies about different agents in addition to the lack of such studies in our country (Iran), the present study aimed to assess the effect of gastric acid suppressant

prophylaxis (through ranitidine or pantoprazole) on incidence of gastrointestinal bleeding in PICU, Mashhad- Iran.

## 2- MATERIALS AND METHODS

### 2-1. Study Design and Population

In this clinical trial (Medical dissertation with ID code of 4515), the patients (age: 1 month to 14 years old) of PICUs of Imam Reza and Qaem hospitals (referral hospitals) of Mashhad (the second big city of Iran), during November 2015 to March 2016 were entered. The sample size calculated as 100 participants for each group of experimental and control based on the formula and the same conducted studies (1, 31, 32, 35). So, finally 204 patients entered to this study (105 patients concerned as control group while 99 patients were in experimental group).

### 2-2. Methods

The number of 99 patients as experimental group divided into two groups randomly on the first day of admission. They received ranitidine 2.5 mg/kg twice a day) or pantoprazole (1 mg/kg twice a day) as prophylaxis of stress ulcer. 105 PICU patients who had not received prophylaxis during last 6 months, retrospectively evaluated as control of the study. The consent form for participation, demographic data and initial tests and vital signs were recorded by the standby nurse then nasogastric tube placed for each patient by standby physician. In each shift, blood discharges, coffee-ground or melena were assessed and recorded in medical records. After each gastrointestinal bleeding, vital sign were recorded and decreasing in systolic pressure more than 20 mm Hg, increasing heart rate more than 20 and need to transfusion as signs of significant bleeding were recorded. Also, dose and times of receiving corticosteroids, intubation and ventilator regulations or nosocomial pneumonia were recorded.

Control group included all patients admitted in PICU during May to October 2015 and they had not received prophylaxis for stress ulcer. The mentioned forms such as demographic data, nurse reports and vital signs, discharges of nasogastric tube and the other conditions were recorded same as experimental group retrospectively.

### 2-3. Measuring tools

Data were collected as demographic characteristics, admission reason, definitive diagnosis, vital signs, primary level of hemoglobin, receiving prophylaxis or not, receiving corticosteroid and mechanical ventilation in each patient. Gastrointestinal bleeding (hematemesis, coffee ground aspirate, and melena) and clinically significant gastrointestinal bleeding were daily monitored.

### 2-4. Inclusion criteria

Inclusion criteria included age of 1 month to 14 years old.

### 2-5. Exclusion criteria

Exclusion criteria included: coagulation problems, liver disease, historical of gastrointestinal tract, history of GI bleeding and peptic ulcer or agents that reduce secretion of gastric acid.

### 2-6. Ethical considerations

This study resulted from MD. Dissertation and it approved by ethical committee of Mashhad University of Medical Sciences. All participants' parents consent for participation in this research and data collected only for research purposes.

### 2-7. Data analyses

Data analyzed through descriptive statistical tests, chi-square, logistic regression, Mann-Whitney u test, t-test and SPSS software.  $P < 0.05$  is concerned as significant level.

## 3- RESULTS

In this study, 204 patients were participated. 105 patients concerned as control group while 99 patients received stress ulcer prophylaxis (pantoprazole: 49 cases, ranitidine: 50 cases).

Among patients who received prophylaxis 46.8% were male and 53.2% were female, while 51.4% and 48.6% of control group were male and female respectively. The results of Mann-Whitney and t-test showed that the mean age and gender were not significantly different in two experimental and control groups ( $P=0.075$  and  $P=0.120$ , respectively). The variables related to each group analyzed through t-test were presented in **Table.1**.

The results of Chi-square showed that among 204 patients, 27 patients (13.2%) had GI bleeding [active bleeding as hematemesis ( $n=9$ ) (34%), coffee ground bleeding ( $n=16$ ) (59%) and melena ( $n=2$ ) (7%)].

There were no significant differences in age and gender between patients with or without GI bleeding ( $P=0.120$  and  $P=0.902$ , respectively). Descriptive tests showed that among all patients 106 cases had history of disease in admission time as follows: history of cardiac disease (53.4%), metabolic disease (20.5%), and epilepsy (13.6%), disease of central nervous system (2.3%), liver disease (2.3%), kidney disease (2.3%), diabetes (3.4%) and pneumonia (2.3%). The results of Chi-square showed that there was no significant difference between types of diseases in bleeding ( $P=0.254$ ). **Table.2** presents the vital signs in patients with or without bleeding using chi-square and logistic regression.

Reasons for hospitalization were as follows: respiratory distress (52.7%), poor feeding (9.5%), diarrhea or nausea and vomiting (9.0%), loss of consciousness (18.4%), fever (4.5%), multiple trauma (0.5%) and severe skin lesions (1.0%). The results showed that there was no

significant difference between different reasons and bleeding ( $P=0.373$ ). The definitive diagnosis was as follows: sepsis (10%), pneumonia (19.5%), metabolic disease (21%), diabetic ketoacidosis (8%), cardiac disease (20%), meningitis (4%), other infectious diseases (2%), intoxication (8%), rheumatologic disease (1.5%) and multiple trauma (0.5%).

Comparison between definitive diagnosis did not indicate any significant difference in bleeding ( $P=0.677$ ). Regarding to prophylaxis, data showed that among patients who received prophylaxis 12 cases (12.0%) had bleeding, while among patients without prophylaxis, 15 cases (14.3%) had bleeding ( $P=0.064$ ). Also, in the prophylaxis group 6 cases (6%) had clinically significant bleeding, while this occurred in 8 cases (7%) of control group ( $P=0.66$ ).

Based on the type of prophylaxis, 7 cases (14%) who received ranitidine and 5 cases (6%) who received pantoprazole had bleeding ( $P=0.56$ ). Also, in the ranitidine group 3 cases (6%) had noticeable clinical bleeding and this occurred in 3 cases (6%) of pantoprazole group ( $P=0.98$ ). The

comparison of the mean days of hospitalization through Mann-Whitney test in patients with or without bleeding was significant ( $P=0.049$ ), but there was no significant difference between patients with or without clinically significant bleeding ( $P=0.421$ ). The ventilation and corticosteroids parameters among patients with or without bleeding were presented in **Table.3**.

The results through Chi-square test related to ventilation showed significant differences in bleeding and clinical bleeding among patients with or without ventilation ( $P<0.001$  and  $P=0.001$ , respectively). Also, there was a significant difference in bleeding and clinically significant bleeding among patients who received or did not receive corticosteroids ( $P=0.001$  and  $P=0.041$ , respectively).

Among 204 PICU patients, 9 cases (4.4%) infected by nosocomial pneumonia as part of medical side effect which all of them had received prophylaxis. The comparison of nosocomial pneumonia between experimental and control group showed that there was significant difference ( $P=0.001$ ).

**Table-1:** The variables related to PICU patients

Variables	Control group	Experimental group		P-value
		Ranitidine	Pantoprazole	
Heart rate (per minute)	132.42±29.14	140.16±31.77	128.59±33.49	0.979
Respiratory rate (per minute)	45.70±19.93	41.10±14.06	41.23±20.02	0.271
Systolic pressure (mm Hg)	93.10±16.65	96.16±20.92	94.63±25.81	0.458
Diastolic pressure (mm Hg)	53.76±14.08	58.16±17.40	58.18±17.64	0.141
Glasgow Consciousness Scale (GCS)	11.83±3.56	11.91±3.79	10.06±4.46	0.108

**Table-2:** The vital signs in patients with or without bleeding

Variables	Bleeding group	Non-bleeding group	P-value
Heart rate (per minute)	132.81±31.69	137.46±24.13	0.478
Respiratory rate (per minute)	43.68±19.20	42.04±14.36	0.631
Systolic pressure (mm Hg)	95.32±21.16	87.19±21.16	0.073
Diastolic pressure (mm Hg)	55.99±16.27	55.95±14.00	0.025
Glasgow Consciousness Scale (GCS)	11.62±3.82	10.15±4.29	0.000

**Table-3:** The ventilation and corticosteroids parameters among patients with or without bleeding

Variables	Bleeding	Clinically significant bleeding	Total
	Number (%)	Number (%)	Number (%)
Without ventilation	7 (5.3)	2 (1.5)	133 (65.2)
Mechanical ventilation	20 (28.2)	12 (16.9)	71 (34.8)
Total	27 (13.2)	14 (6.8)	204 (100.0)
No corticosteroids	11 (7.9)	6 (4.3)	140 (68.6)
Corticosteroids	16 (25.0)	8 (12.5)	64 (31.4)
Total	27 (13.2)	14 (6.8)	204 (100.0)

#### 4- DISCUSSION

The results of the present study indicated that the patients who admitted in PICU are at high risk of GI bleeding. Among 204 patients, the incidence of gastrointestinal bleeding (GB) was 13.2% in which 6.9% of cases presented with clinically significant gastrointestinal bleeding (CSGB). Loss of consciousness and respiratory distress were the main reason of admission. There were no significant differences between the incidence of (GB) and (CSGB) in experimental and control groups as well as ranitidine and pantoprazole prophylaxis. Significant risk factors of (GB) were mechanical ventilation and loss of consciousness and corticosteroid therapy.

This incidence of GB in Nithiwathanapong et al. study (n=170) was reported as 43.2% for bleeding and 5.3% for clinically significant bleeding. As seen, the rate of total bleeding is higher significantly than the present study, but the rate of clinically significant bleeding is lower. The different exclusion criteria and reason for hospitalization in Nithiwathanapong et al. study can explain this difference. In addition, according to the present study, mechanical ventilation concerned as a significant risk factor for GI bleeding and respiratory distress was a major reason for admission (3). The incidence of GB is reported in Sahin et al. study as 15.4% that the severity of bleeding as follows: mild

(66.7%), moderately (23.8%) and clinically significant (4.8%) (28). These rates, are same to the present study.

The highest prevalence of GB according to the definitive diagnosis was reported in cardiac disease, pneumonia and infectious disease respectively according to Gutierrez-Gutierrez study et al. that suggests pneumonia as a risk factor for GI bleeding (36).

In conducted studies such as Deerojanawong et al. study, prophylaxis has been related to controversies. In this study 110 patients who underwent mechanical ventilation for more than 48 hours, received prophylaxis of stress ulcer. 4 patients had clinically significant GB that 3 cases had received prophylaxis. There was not seen any significant relation between prophylaxis and GB according to the present study (1), but in Costarino et al. study which assessed 336,010 patients, the results showed that higher prophylactic regimen was related to lower incidence of bleeding. In this study, 1.32% of patients had GB and 0.11% of them had clinically GB, while only 60% of patients received prophylaxis and patients who received higher prophylactic regimen (with diagnosis of respiratory failure, edema, pneumonia, cardiac diseases) the rate of GB was significantly lower than the group with lower prophylactic regimen (with diagnosis such as diabetic ketoacidosis, bronchiolitis, status epilepsy and etc.),

0.3% versus 1.27% (33). Type of agent for prophylaxis is another controversial issue. Lack of studies especially in pediatric field is clear. Quillet et al. suggested that 93% of pediatric physicians prescribe ranitidine as a first line for GI prophylaxis and other agents such as pantoprazole and omeprazole are the second and third choices (52% and 21% respectively) (30).

Tofil et al. evaluated 48 patients who underwent prophylactic regimen with ranitidine or PPIs (pantoprazole or lansoprazole). The gastric pH was measured 2 hours before and 2 hours after taking medicine. Of 48 patients, 3 cases had GI (6%). One case had clinically significant GI. The results showed that the gastric pH more alkalized through PPI (BID) than PPI (once a day) and ranitidine (35). In the present study there was no significant difference between ranitidine and pantoprazole.

According to the results of the present study and past studies and the potential side effects of prophylaxis such as nosocomial pneumonia, it seems that prophylaxis for GI bleeding in PICU patients is not recommended for all patients and it is rational that patients with two or more risk factors (such as mechanical ventilation, corticosteroids and loss of consciousness) receive this prophylaxis.

The gastric pH and pediatric mortality rate scores were not measured in this study and they will be concerned in future studies.

## 5. CONCLUSION

Based on the results, prophylaxis was not related to significant difference in GI bleeding. So, it is not obvious if critically ill children may benefit from receiving prophylaxis in preventing gastrointestinal bleeding due to stress ulcer and consuming increased risk ventilator associated pneumonia when prophylaxis started. We proposed that prophylaxis should prescribe

in patients with two or more risk factors of gastrointestinal bleeding.

**6- CONFLICT OF INTEREST:** None.

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