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Prediction of Ventilator-Associated Pneumonia in Patients Undergoing Stress Ulcer Prophylaxis: A Longitudinal Descriptive Study in Iran

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Abstract

Background: The purpose of this study was to investigate and predict ventilator-associated pneumonia (VAP) in the two groups of patients who received either proton pump inhibitors (Pantoprazole) or histamine H2 antagonist (Ranitidine).

Methods: Patients in ICU received Pantoprazole or Ranitidine as stress-related mucosal injury and GI bleeding prophylaxis. The incidence rate of VAP and GI bleeding was estimated in each group during ICU stay. Chi-Square and Multivariate Logistic Regression Test were used for data analysis. P.value less than 0.05 was considered significant. Data analysis was performed through SPSS version 19.0.

Results: The incidence rate of VAP in the Ranitidine and Pantoprazole groups was 44.7% and 37.3% respectively (p=0.3). According to the multivariable logistic regression analysis, length of mechanical ventilation ≥ 4 days was a predictive factor for VAP only in the Pantoprazole group (OR: 1.8, 95% CI: 1.56-1.90, p=0.006). No relationship between GI bleeding incidence and stress ulcer prophylaxis was found (p=0.4). Kaplan-Meier curve showed no significant difference between the two groups of Ranitidine and Pantoprazole (p=0.4) in survival time according to the length of ICU stay.

Conclusion: According to the results, there was no difference between the two groups in terms of VAP, GI bleeding and stress ulcer. Due to the lower cost of Ranitidine, it may be a more appropriate choice for GI bleeding prophylaxis in ICU patients.

Introduction

Patients admitted to the ICU are at risk of GI bleeding and nosocomial infections such as ventilator-associated pneumonia (VAP), UTI, and catheter-related bloodstream infections, which can increase the mortality rate (1, 2). Stress-related mucosal injury prophylactic agents like proton-pump inhibitor (PPI) and histamine (H2) receptor blockers can reduce the GI stress ulcer and consequently GI bleeding up to 25% (3). Some studies have reported that the incidence of VAP increases by 30% following pharmacological stress ulcer prophylaxis (4-5). The chance of growing and replanting of gram-negative bacteria in the upper GI tract increases following the reduction in gastric acid with acid-reducing drugs. Moreover, the incidence of

VAP increases due to the frequent micro-aspiration in ICU patients (6-7). Some studies have shown that Pantoprazole in comparison to Ranitidine decreases the risk of GI bleeding more efficiently. However, in other studies, Ranitidine has been suggested because of its low cost and lower incidence of VAP (8, 9). Recent observational researches have reported a strong association between the use of proton pump inhibitors and the prevalence of VAP and Clostridium difficile infection (10, 11). In a survey in Iran (12), VAP incidence in the two groups receiving Ranitidine and Pantoprazole, was 10% and 30% respectively (P=0.006). Now, there is no consensus to determine the best GI bleeding prophylaxis drug regimen. The purpose of this study was the investigation and prediction of VAP and GI bleeding in stress-related mucosal injury (Ranitidine and Pantoprazole) prophylaxis.

Material and Methods

This longitudinal descriptive study performed on patients admitted to the general ICU of Loghman Hakim Hospital, Tehran, Iran during March 23, 2017- March 23, 2018. Patients' characteristics (demographic information, chief complaint, cause of admission, primary diagnosis, past medical history, drug history, duration of mechanical ventilation, length of ICU and hospital stay as well as, their outcome including mortality or discharge) were collected in the questionnaire prepared by the researchers. Informed consent was obtained from the patients' next of kin and the study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.RETECH.REC.1397.260). We used the STROBE Statement Checklist in writing this observational study (13).

All patients admitted in ICU received GI stress ulcer prophylaxis (proton pump inhibitor or H2 receptor blockers) according to the physician. In whole, 143 patients fulfilled the inclusion criteria. Inclusion criteria were age over 18 years, ability to tolerate the nasogastric/orogastric (NG/OG) tube feeding and APACHE II score less than 25 at ICU admission. Exclusion criteria were: needing re-intubation or mechanical ventilation less than 48 hours, having chronic obstructive pulmonary disease (COPD), thrombocytopenia, increased international normalized ratio (INR)>1.5 times than normal upper limit, taking corticosteroid, pregnancy, and upper GI bleeding at admission. Clinically significant GI bleeding was defined as an episode of overt bleeding (hematemesis, bloody gastric aspirate, melena, or hematochezia)(Figure 1).

Seventy six patients received 50 mg Ranitidine intravenously every 8 hours, whereas 67 other patients received pantoprazole 40 mg daily during NPO time. The majority of patients received enteral nutrition during the study period. All patients with GI stress ulcer prophylaxis were followed for VAP incidence after 48 hours of mechanical ventilation and GI bleeding duration of ICU stay. For VAP determination, Clinical Pulmonary Infection Score (CPIS) was assessed every day. The CPIS score is based on sensible elements (temperature (°C), white blood cell count, tracheal secretions, oxygenation, PaO2/FiO2 mm Hg, chest radiography, culture of the tracheal aspirated specimen), and the likelihood of VAP seems to be somewhat higher when this score is ≥6. According to the current institutional ICU guideline, the patients' sputum culture samples were obtained and sent when they had CPIS >3. A sample of tracheal tube secretion was collected by Bronchoalveolar lavage (14). Next, for microbial culture and antibi gram assay, blood and tracheal aspiration

samples were sent to the laboratory of the Iran Institute Pasteur for more validity of culture results. We used PCR (polymerase chain reaction), the most sensitive of the existing rapid methods, to detect microbial pathogens in clinical specimens (15). Finally, the difference between VAP and GI stress ulcer prophylaxis and factors predicting VAP during the ICU stay were assessed.

Statistical Analysis

Data are presented as numbers and proportions for categorical variables and mean (standard deviation) for continuous variables. For the evaluation of the relationship between patient characteristics and incidence of VAP, Fisher exact or chi-square (χ^2) test for categorical data, also independent Student *t*-test and for parametric continuous variables and Mann-Whitney *U* test for nonparametric continuous variables, were used. To find an equation for the best prediction of the probability of VAP incidence, multivariable logistic regression was used. Forward likelihood ratio was selected as the predictor variables for the final model (16-17). Kaplan Meier Curves for evaluation of survival according to the length of ICU stay in the two groups of Ranitidine and Pantoprazole were plotted (18). Two-sided *P*.value less than 0.05 was considered statistically significant. All analyses were conducted through SPSS version 19.0.

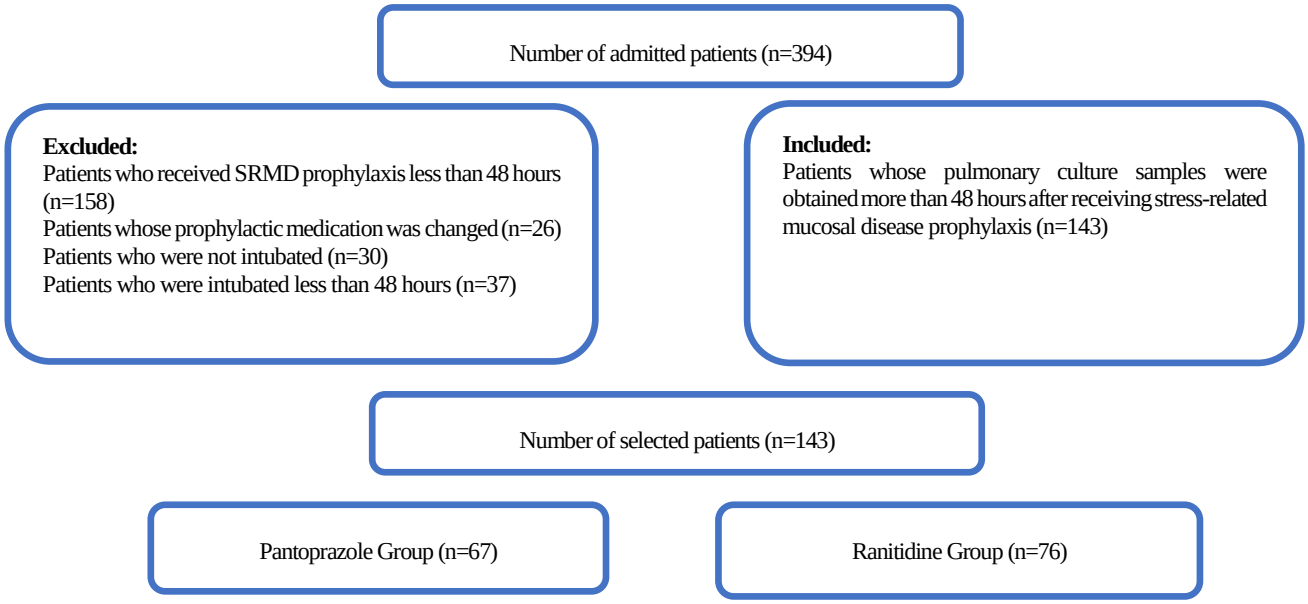

Figure 1. Flowchart of selected patients

Results

In this study, the incidence rate of VAP in the Ranitidine and Pantoprazole group was 44.7% and 37.3% respectively. In the ranitidine group, 55 (72.4%) and in the pantoprazole group, 46 (68.7%) were male (p=0.3). The mean (standard deviation) age in the Ranitidine group was 53.36 (19.79) and in the Pantoprazole group was 55.55 (20.38) years. The incidence rate of GI bleeding in the Ranitidine group was 46.2% while, it was 53.8% in the Pantoprazole group (Table1). As it is seen in table 2, VAP incidence showed significant difference based on APACHE II score (p=0.01), predicted mortality rate (p=0.02), length

of MV (p<0.001), length of ICU stay and hospital stay (p <0.001), GI bleeding (p=0.02), and undergoing tracheostomy (p=0.001). Also, GI bleeding incidence was significant based on the length of mechanical ventilation (MV), ICU stay and hospital stay, and undergoing tracheostomy (Table 3), whereas no relationship between GI bleeding and GI stress ulcer prophylaxis was found (p=0.4).

In forwarding stepwise (Likelihood Ratio) multiple logistic regression analysis, duration of MV (≥ 4 days), only in Pantoprazole group (OR: 1.8, 95% CI: 1.56-1.90, p=0.006), was found as the predictor factor for increase of VAP. Finally, according to Kaplan-Meier curve (Figure 2), there was no difference in the median of survival time between the two groups of Ranitidine and Pantoprazole recipients according to a length of ICU stay (p=0.4).

Table 1. Basic characteristics of the studied patients under GI stress ulcer prophylaxis in ICU

Variables	Ranitidine Number (%) 76 (53.1)	Pantoprazole Number (%) 67 (46.9)
Sex		
Male	55 (72.4)	46 (68.7)
Female	21(27.6)	21 (31.3)
Age		
Mean (SD)	53.36 (19.79)	55.55 (20.38)
Primary ICU diagnostic group		
Number (%)		
Neurosurgery	26 (34.2)	24 (35.8)
Neurology	16 (21.1)	12 (17.9)
Surgery	4 (5.3)	3 (4.5)
Respiratory	6 (7.9)	8 (11.9)
Cardiovascular	3 (3.9)	1 (1.5)
GI	1 (1.3)	1 (1.5)
Metabolic	1 (1.3)	0 (0)
Trauma	12 (15.8)	8 (11.9)
Sepsis	1 (1.3)	2 (3)
Cancer	3 (3.9)	4 (6)
Autoimmune disorder	3 (3.9)	4 (6)
APACHE II		
Mean (SD)	21.92 (6.93)	21.05 (6.93)
Predicted Mortality Rate		
Mean (SD)	43.48 (20.56)	41.46 (25.04)
VAP incidence	34 (44.7)	25 (37.3)
Number (%)		
GI bleeding incidence	12 (46.2)	14 (53.8)
Number (%)		
Length of Mechanical Ventilation (day)	15.04 (18.97)	12.78 (21.37)
Mean (SD)		
Length of ICU stay (day)		
Mean (SD)	14.32 (14.29)	13.99 (20.40)
Length of hospital stay (day)		
Mean (SD)	21.78 (20.68)	22.57 (23.82)
Outcome		
Number (%)	32 (49.2)	33 (50.8)
Alive		

Table 2. The relationship between the occurrence of VAP and studied variables based on the univariate analysis

Variable	VAP occurrence		p.value
	Yes No (%) 59 (41.3)	No No (%) 84 (58.7)	
Sex			
Male	42 (41.6)	59 (58.4)	0.2
Female	17 (40.5)	25 (59.5)	
Age			
Mean (SD)	51.92 (19.45)	56.12 (20.36)	0.2
APACHE II			
Mean (SD)	23.43 (7.06)	20.17 (8.06)	0.01*
Predicted Mortality Rate			
Mean (SD)	47.65 (21.08)	38.94 (22.7)	0.02*
Length of Mechanical Ventilation (days)			
Mean (SD)	23.53 (26.74)	7.27 (8.97)	<0.001*
Length of ICU stay (days)			
Mean (SD)	21.63 (23.10)	8.92 (8.60)	<0.001*
Length of hospital stay (days)	31.71	15.43	<0.001*
Mean (SD)	(28.72)	(12.28)	
GI stress ulcer prophylaxis agent			
Ranitidine	34 (44.7)	42 (55.3)	0.3
Pantoprazole	25 (27.3)	42 (62.7)	
Corticosteroids receiving			
Yes	0 (0)	3 (100)	0.1
No	59 (42.1)	81 (57.9)	
GI bleeding			
Yes	16 (61.5)	10 (38.5)	0.02*
No	43 (36.8)	74 (63.2)	
Tracheostomy			
Yes	22 (66.7)	11 (33.3)	0.001*
No	37 (33.6)	73 (66.4)	
Outcome			
Alive	26 (40)	39 (60)	0.7
Death	33 (42.3)	45 (57.7)	

*: statistically significant

Table 3. The relationship between GI bleeding and studied variables based on Univariable analysis

Variables	GI bleeding		p.value
	Yes	No	
GI stress ulcer prophylaxis agents Number (%)			
Ranitidine	12(46.2)	84(54.7)	0.4
Pantoprazole	14(53.8)	53(45.3)	
Length of MV (day) Number (%)	29.38(36.73)	10.56(11.76)	0.01*
Length of ICU stay (day) Number (%)	25.62(30.82)	11.62(11.29)	0.03*
Length of hospital stay (day) Number (%)	38.27(39.84)	18.56(13.65)	0.01*
APACHE II Mean(SD)	23.38(7.21)	20.65(7.70)	0.005*
Tracheostomy			
Yes	11 (42.3)	22(18.8)	0.01*
No	15 (57.7)	95(81.2)	

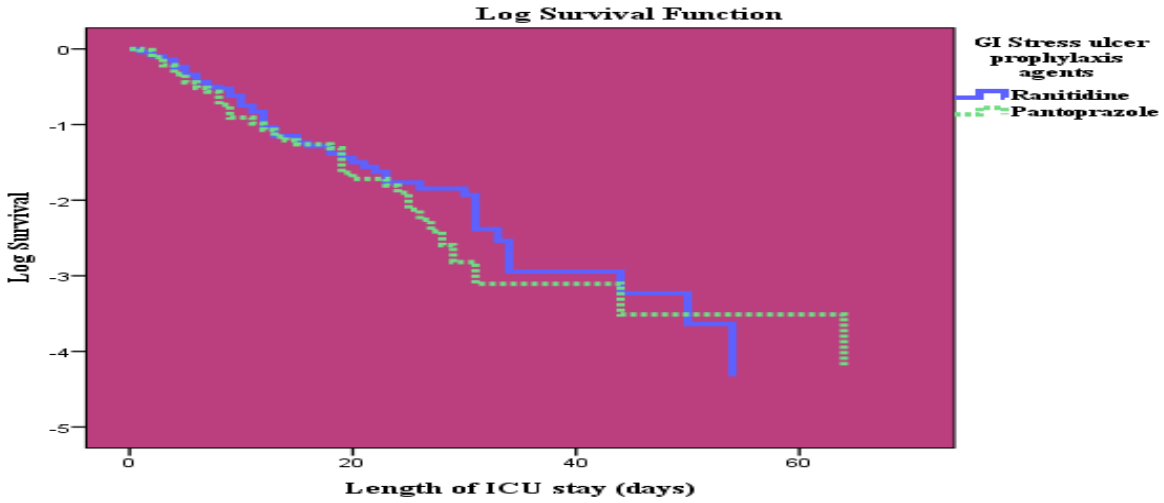

Figure 2. Comparison of survival according to the length of ICU stay between the two groups Kaplan Meier curve, p=0.4)

Discussion

ICU admission plays a significant and vital role in treating and improving patients' outcomes (19). VAP and GI bleeding are complications of critically ill patients in the ICU; therefore, the prevention of these complications is essential. Stress ulcer prophylaxis is recommended in high-risk patients (20), but the best choice for preventing GI stress ulcer and GI bleeding is not clearly defined. Some studies have reported that prophylactic Pantoprazole decreases the risk of developing GI bleeding more than Ranitidine (2, 12,21) but, VAP has been less likely in GI prophylaxis with Ranitidine than Pantoprazole (8, 12, 22-24).

Although in this study the incidence rate of VAP in the Ranitidine and Pantoprazole group was 44.7% and 37.3% respectively, the difference was not statistically significant (p=0.3) which was the same as results of other researches (25, 26). In Alhazzani W. study in 2017, VAP developed in

20.4% of critically ill patients received pantoprazole and 14.3% of patients in the placebo group (27). One crucial point is the incidence rate of GI bleeding reported approximately 1% in ICU patients totally (28), while this rate was 18.2 % in the current survey. Notably, we enrolled only mechanically ventilated critically ill patients that had a higher risk of stress ulceration and GI bleeding. In this survey, we observed a significant difference between the risk of GI bleeding and variables of length of MV, length of ICU and hospital stay, APACHE II, and tracheostomy. Similar to other studies (6, 21, 26) we did not find a significant relationship between the type of GI stress ulcer prophylaxis and the outcome of patients, but one previous study has reported high mortality and a worse prognosis in ranitidine group (3). According to Hammond, *et al*., stress ulcer prophylaxis with H2RA therapy may increase survival and avoid complications compared with PPI therapy (8). Risk factors for VAP such as stress ulcer prophylaxis, duration of MV ≥ 5d, supine head position, chronic renal failure, chronic lung failure, surgery, trauma, burns, steroid therapy reported in other studies and impaired consciousness, tracheostomy, reintubation, emergency intubation, and a nasogastric tube was found to be independent risk factors for VAP (29). This study was a descriptive longitudinal survey and no randomization was performed, so patients received stress ulcer prophylaxis according to the physician's opinion. Based on our finding the best way to prevent GI bleeding is to try to reduce the length of MV, length of ICU, and hospital stay, and time of intubation. According to other studies, if patients fail to be admitted to ICU at the exact time, the risk of death increases five times and the length of hospitalization is doubled (19).

Conclusion

In the present study, the incidence of VAP was higher in the Ranitidine group; however, the difference was not significant. Therefore, due to the lower price of Ranitidine, it may be recommended as effective prophylaxis against GI stress ulcer.

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