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RESEARCH ARTICLE

The Effectiveness of Ranitidine Compared to Omeprazole in Maintaining Gastric Acidity in Head Injury Patients

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Abstract

Background: Gastric bleeding due to stress-related mucosal damage (SRMD) is a condition that is caused due to erosive gastritis that often occurs in critically ill patients in intensive care. One condition that is known as a risk factor for SRMD is traumatic brain injury. Two common agents used as gastric ulcer prophylaxis are proton pump inhibitor (PPI) and H2 antagonist receptor (H2AR). The goal of this study was to compare the effectiveness of PPI and H2AR administration as prophylaxis of SMRD in patients with TBIs who were treated in the ICU. Patients and Methods: This is a single-blind, randomized, controlled trial with pre and post-test measurements. All subjects were measured for baseline gastric pH before being given gastric ulcer prophylaxis. Gastric pH was measured using a pH-meter. The subjects were divided into two groups: omeprazole group (omeprazole 40 mg every 12 hours) and ranitidine group (received ranitidine 50 mg every 12 hours). The pH levels were measured regularly twice daily for five days. Results: 56 subjects were involved in this study and divided equally into two groups. For each gastric pH measurement, the pH in both groups did not significantly differ. The optimal gastric pH was achieved in 24 hours after the first administration of gastric ulcer prophylaxis. Conclusions: The administration of ranitidine or omeprazole is equally effective in maintaining the acidity of gastric acid in TBI patients in ICU. There was no significant difference in the incidence of gastric bleeding in ranitidine and omeprazole groups.

Keywords: *ICU, Gastric pH, PPI, H2-receptor antagonist.*

Introduction

Gastric bleeding due to stress-related mucosal damage (SRMD) is a condition that is caused due to erosive gastritis that often occurs in critically ill patients in intensive care. The risk of SRMD occurs from 75-100% in the first 24 hours in critically ill patients treated in intensive care [1].Certain conditions that are well-known as risk factors for SRMD include the use of mechanical ventilation for more than 48 hours, coagulopathy, multiple trauma, post brain surgery, shock, respiratory failure, multi-organ failure, and severe burns [2].Severe gastric bleeding can occur as a result of SMRD in 3.5% of patients with mechanical ventilation for 48 hours or more in intensive care unit [1].For prevention, prophylactic administration has been recommended for all critically-ill patients in ICU who are at high risk of developing SMRD.

This prophylaxis strategy is included in the bundle care for critically ill patients with mechanical ventilation and recommended by the Institute for Healthcare Improvement, and later adopted by the National Health Service Modernization in the United Kingdom. The American Society of Health-System Pharmacists (ASHP), the Surviving Sepsis Campaign (SSC), and the International Sepsis Forum also recommend that ulcer prophylaxis to be part of critical patient care in the ICU [2]. Patients with traumatic brain injuries (TBI) are at high risk of developing SMRD. At our hospital, the incidence of head injuries is around 2,000 cases yearly, with 30% of them being moderate-severe injuries [3, 5].ASHP stated that TBI patients with a Glasgow Coma Scale (GCS) of <10 are at high risk of developing gastric ulcers and recommended gastric ulcer

prophylaxis for those populations. Gastric acid hypersecretion that occurs in TBI patients can increase the risk of SRMD which causes gastric ulcers. Prophylactic administration of gastric ulcers is expected to reduce the risk of gastric ulcers in patients with severe head injury. The use of standard prophylactic agents that are widely used is the proton pump inhibitor (PPI) and H2 antagonist receptor (H2AR) groups [6]. The goal of this study was to compare the effectiveness of PPI and H2AR administration as prophylaxis of SMRD in patients with TBIs who were treated in the ICU.

Patients and Methods

This is a single-blind, randomized, controlled trial with pre and post-test measurements. Inclusion criteria include TBI patients with GCS <10 upon examination. Exclusion criteria include known history of allergy and contraindications to the administration of H2ARs or PPIs, ongoing acute gastric and upper airway bleeding, contraindicated for nasogastric/orogastric (NGT/OGT) tubes insertion, burns >30% of total body surface area, major trauma patients with Injury Severity Score >16, coagulopathy, gastric malignancy, and patients with unstable hemodynamics. We used permuted block randomization technique in this study for patient selection.

The study protocol was granted by the institutional review board of Udayana University and Sanglah Hospital. All subjects were measured for baseline gastric pH before being given gastric ulcer prophylaxis. Gastric fluid samples were taken per NGT/OGT and then measured using a pH-meter. We also performed benzidine tests using benzidine sticks (produced by Intec Inc.). The subjects were then received either IV omeprazole 40 mg (every 12 hours) or IV ranitidine 50 mg (every 12 hours) depending on which group they were assigned to. Subjects in both groups also received 15 ml of sucralfate (every 8 hours). Enteral nutrition was started on the second day of treatment in ICU. The pH levels of the subjects are measured regularly twice daily for five days, one hour before the administration of either omeprazole or ranitidine. After three days, benzidine test will be carried out again to determine the presence of gastric bleeding. The target of gastric pH was 3.5 to 5.0. Based on the daily-measured gastric pH, target prophylaxis will be discontinued when the gastric pH rose above 5.0, but the subjects still have the gastric pH tested as scheduled.

We used the Shapiro-Wilk test for normality test in this study. For normally distributed data, we used independent t-test, while Mann-Whitney test was used otherwise. To compare the incidence of bleeding between the two groups, we used the Chi-Square test. All statistical calculations are analyzed with SPSS 24.0 for Windows. A p-value of <0.05 was considered statistically significant.

Results

We randomly assigned 28 subjects to each group for this study. The characteristics of the subjects are presented in Table 1. The mean age of the ranitidine group was 45.70 years and in the omeprazole group was 44 years.

At the first gastric pH measurement after the administration of a gastric ulcer prophylactic agent, there were six patients (21.4%) and seven patients (25%) who showed the desired pH target in ranitidine and omeprazole groups, respectively. This result was no statistically significant. This insignificance was also found in each measurement between the groups. From this study, we can see that both ranitidine and omeprazole administration achieved optimal gastric pH within 24-36 hours after its first respective administration (Table 2).

Table 1: Characteristics of the subjects

Variables	Groups		p
	Ranitidine (n = 28)	Omeprazole (n = 28)	
Age (years), median (min-max)	45.70 (16-86)	44 (18-83)	0.902[a]
GCS, median (min-max)	7 (3-10)	7 (3-10)	0.901[a]
Sex Male, n (%) Female, n (%)	 21 (75.0) 7 (25.0)	 21 (75.0) 7 (25.0)	1.000[b]
Smoking history None, n (%) Yes, n (%)	 23 (82.1) 5 (17.9)	 22 (78.6) 6 (21.4)	0.737 [b]
Alcohol drinker			

None, n (%) Yes, n (%)	28 (100) 0 (0)	28 (100) 0 (0)	1.000 [b]
History of gastritis None, n (%) Yes, n (%)	 28 (100) 0 (0)	 28 (100) 0 (0)	 1.000 [b]

GCS: Glasgow Coma Scale; [a]Mann-Whitney test; [b]Chi-square test

Table 2: Distribution of gastric pH, grouped in the category based on the pH target

Measurements		Groups		p-value[a]
		Ranitidine	Omeprazole	
Baseline	<3.5	28 (100%)	28 (100%)	-
	3.5-5.0	0 (0.0%)	0 (0.0%)	
	>5.0	0 (0.0%)	0 (0.0%)	
Day-1, 1st measurement	<3.5	22 (78.6%)	21 (75.0%)	0.752
	3.5-5.0	6 (21.4%)	7 (25.0%)	
	>5.0	0 (0.0%)	0 (0.0%)	
Day-1, 2nd measurement	<3.5	1 (3.6%)	0 (0.0%)	0.565
	3.5-5.0	24 (85.7%)	24 (85.7%)	
	>5.0	3 (10.7%)	4 (14.3%)	
Day-2, 1st measurement	<3.5	0 (0.0%)	0 (0.0%)	0.061
	3.5-5.0	10 (35.7%)	17 (60.7%)	
	>5.0	18 (64.3%)	11 (39.3%)	
Day-2, 2nd measurement	<3.5	0 (0.0%)	0 (0.0%)	0.342
	3.5-5.0	8 (28.6%)	5 (17.9%)	
	>5.0	20 (71.4%)	23 (82.1%)	
Day-3, 1st measurement	<3.5	0 (0.0%)	0 (0.0%)	0.957
	3.5-5.0	1 (3.6%)	1 (3.6%)	
	>5.0	27 (96.4%)	25 (96.2%)	
Day-3, 2nd measurement	<3.5	0 (0.0%)	0 (0.0%)	0.092
	3.5-5.0	3 (10.7%)	0 (0.0%)	
	>5.0	25 (89.3%)	25 (100%)	
Day-4, 1st measurement	<3.5	0 (0.0%)	0 (0.0%)	0.172
	3.5-5.0	4 (15.4%)	1 (4.0%)	
	>5.0	22 (84.6%)	24 (96.0%)	
Day-4, 2nd measurement	<3.5	0 (0.0%)	0 (0.0%)	0.342
	3.5-5.0	1 (3.8%)	0 (0.0%)	
	>5.0	25 (96.2%)	23 (100%)	
Day-5, 1st measurement	<3.5	0 (0.0%)	0 (0.0%)	0.647
	3.5-5.0	2 (10.0%)	1 (5.9%)	
	>5.0	18 (90.0%)	16 (94.1%)	
Day-5, 2nd measurement	<3.5	0 (0.0%)	0 (0.0%)	-
	3.5-5.0	0 (0.0%)	0 (0.0%)	
	>5.0	6 (100%)	10 (100%)	

[a]Chi-square test

In Table 3, we can see that both ranitidine and omeprazole groups are equally effective in maintaining gastric acidity in ICU patients. There is no significant difference in the mean gastric pH of the two groups at each measurement.

Table 3: Gastric pH measurement results in both groups

Gastric pH measurements	Groups		p
	Ranitidine (n = 28)	Omeprazole (n = 28)	
Baseline	2.07±0.47	2.07±0.57	0.969[a]
Day 1, 1st measurement	2.97±0.77	3.04±0.73	0.700[a]
Day 1, 2nd measurement	4.27±0.52	4.50±0.50	0.054[a]
Day 2, 1st measurement	5.11 (3.88-5.53)	4.98 (4.12-5.45)	0.108[b]
Day 2, 2nd measurement	5.42 (4.48-7.58)	5.34 (4.17-7.52)	0.838[b]
Day 3, 1st measurement	6.06±0.61	6.03±0.67	0.955[a]
Day 3, 2nd measurement	5.85±0.60	6.14±0.48)	0.056[a]
Day 4, 1st measurement	5.88 (3.72-6.28)	6.00 (4.78-7.00)	0.341[b]
Day 4, 2nd measurement	5.85 (4.21-6.24)	5.86 (5.32-6.51)	0.237[b]
Day 5, 1st measurement	5.46±0.54	5.68±0.24	0.401[a]
Day 5, 2nd measurement	5.46±0.28	5.98±0.67	0.095[a]

[a]Independent t-test; [b]Mann-Whitney U test
For normally distributed data, the results are presented in mean ±SD. Otherwise; they are presented in median (min-max)

In this study, we evaluated the occurrence of bleeding in the stomach fluid which was carried out using a benzidine stick test to see the presence of vague bleeding. The results are presented in Table 4. We observed 6 (21.4%) cases who presented the presence of gastric bleeding in the ranitidine group, compared to 5(17.9%) in the omeprazole group (p=0.737). There was no significant

difference between the two groups in case of preventing gastric bleeding.

Table 4: Bleeding occurrence on the third day of measurements

Groups	Bleeding		p
	None	Yes	
Ranitidine	22 (78.6%)	6 (21.4%)	0.737[a]
Omeprazole	23 (82.1%)	5 (17.9%)	

[a]Chi-square test

Discussion

The aim of this study is to compare the effectiveness of ranitidine with omeprazole in maintaining gastric acidity and preventing gastric bleeding in head injuries patients with GCS <10 treated in the ICU. Prophylactic administration of gastric ulcers is routinely given to patients at risk of gastric bleeding. The parameter assessed in this study was the gastric acidity (pH) measurements before the administration of the prophylactic agent until the fifth day of treatment. While the identification of gastric bleeding is carried out at the beginning before prophylactic agent administration and on the third day of treatment. During this study, there were no complications, or side effects emerged from the administration of ranitidine and omeprazole. Head injured with GCS <10 are one of the risk factors for SRMD.

It may cause stomach bleeding, which can worsen the patient's general condition. In this study, both groups showed that all subjects achieved the desired pH target after 24 hours of prophylactic administration. Both agents properly maintained the target pH on subsequent examinations. In TBIs, gastric acid hypersecretion occurs immediately after the onset of head injury, with the peak occurred 3 to 5 days after the injury to the central nervous system [7].Coelho et al. reported that pantoprazole 40 mg (every 24 hours), a PPI agent, maintains stability of gastric pH at >4 better than ranitidine 50 mg (every 8 hours) [8].However, in a meta-analysis study, the pH values of both ranitidine and omeprazole can reach the desired target pH of 3.5 to 5.0, although gastric pH in patients receiving omeprazole was reported more effective in maintaining a more stable and alkaline gastric pH [9].

Keshavarz and Rahimi [10] compared the effects of oral administration of 20 mg of omeprazole every 12 hours to 40 mg of omeprazole every 12 hours. The results showed that omeprazole was more effective in reducing gastric hypersecretion and maintaining a stable gastric pH above 4. From the mechanism of action, the PPIs work centrally in the final process of gastric acid secretion, the proton pump (H^+, K^+) ATPase in the nucleus of the parietal cells. Whereas the H2RAs work on one receptor of the three parietal cell receptors, the histamine receptor. The mechanism of action of these two drugs is used as the basis for omeprazole is still believed to be better given to patients who have a multifactorial risk of developing gastric ulcers compared to ranitidine. The pathophysiological mechanism of SRMD in head injury patients involves almost all receptors of gastric parietal cells and causes acidity in the stomach to produce more and more acid. The basic hormones or neurotransmitters that directly stimulate gastric gland secretion are histamine, acetylcholine, and gastrin. Gastric acid secretion is stimulated by histamine through H2 receptors, acetylcholine through muscarinic M1 receptors and by gastrin through gastrin receptors in the parietal cell membrane.

H2 receptors increase intracellular AMP cycles while muscarinic receptors and gastrin receptors have an effect through increased intracellular free Ca^{2+} levels. Intracellular processes interact with each other so that the activation of one type of receptor will strengthen the response of other receptors to stimuli [11].A clinical study has shown that maintaining a gastric pH at 3.5 to 5.0 can prevent lesions in the gastric mucosa, where the use of H2RAs or PPIs is recommended as prophylaxis of gastric ulcer [8].Furthermore, ASHP states that TBI patients with GCS <10 are at high risk of developing gastric ulcers and are recommended for gastric ulcer prophylaxis. The standard prophylactic agents that are widely used are PPIs and H2RAs [6].

In severe TBIs, the mechanism of gastric ulcer is the presence of hypersecretion from gastric acid as well as the release of inflammatory factors [6, 12].Increasing gastric pH to be too alkaline can increase the risk of bacterial colonization. In several studies, there was an increased risk of

bacterial colonization in the use of these prophylactic ulcer agents, such as the risk of bacterial colonization of Clostridium difficile and an increased incidence of nosocomial pneumonia [13].From this study, we found that gastric pH remained alkaline enough to prevent gastric bleeding in both ranitidine and omeprazole groups. The enteral nutrition started on the second day of treatment may play an important factor in maintaining the condition of the stomach to stay "awake". As mentioned in the literature, the use of enteral nutrition is controversial and is considered capable of being a substitute for prophylactic agents for gastric ulcers. Enteral nutrition is said to reduce the risk of gastric ulcer occurrence, like the prophylactic administration of a gastric ulcer [14].There were no significant differences between the two groups in terms of gastric bleeding on the third day of treatment.

In several previous studies, it was mentioned that omeprazole and ranitidine were said to be effective in preventing gastric bleeding, and omeprazole was said to be more effective in preventing gastric bleeding from bleeding [9].However, based on the two agents being able to reach the target pH that is in accordance with the target, the estimation of the incidence of gastric bleeding can be prevented equally well in the use of these two prophylactic agents for gastric ulcer. In this study, we found that although the gastric pH can be maintained at a sufficiently alkaline value, gastric bleeding still occurs. This shows that the pH value of the stomach which is maintained in a more alkaline condition does not necessarily prevent gastric bleeding in critically ill patients.

The major destructive factors are gastric acid, and protective factors are mucosal blood flow, mucosal layer of bicarbonate, regeneration of gastric mucosal epithelium and prostaglandin levels. Increased synthesis of nitric oxide leads to hyperemia of reperfusion and cell death, increased inflammatory response, and gastric and small intestinal dysfunction. Increased oxygen radical production and reduced ability to cleanse it also causes inflammation, cell death, and further release of damaging cytokines. This facilitates the occurrence of ulcers in the gastric mucosa [15]. An imbalance between the two factors will affect the occurrence of lesions and gastric mucosal damage which can then cause gastric bleeding in patients with critical ill conditions [7]. The condition of mucosal blood flow in the gastric wall is one of the most important factors to prevent gastric bleeding. Significant reduction in gastric mucosal blood flow caused by splanchnic hypoperfusion can occur even in conditions of well-maintained circulatory and hemodynamic systems [16].Nutrition is also said to have a protective effect on the occurrence of gastric ulcers. Providing enteral nutrition supports the stimulation of mucosal immunity, modulating the progression of ischemia in the digestive tract [14, 16].

However, its role in prevention of gastric bleeding is still controversial. In a meta-analysis study, enteral nutrition did not reduce the incidence of gastric bleeding in patients receiving gastric ulcer prophylaxis [17].This study has several limitations. We used simple tools like pH-meter benzidine sticks. An endoscopic evaluation would be a better option to evaluate the gastric mucosa. The examination of gastric pH in this study is in periodic inspection. A continuous pH monitoring using a pH-meter with sensors mounted on the tip of the NGT/OGT will certainly provide better information on the pH and its fluctuations.

Conclusions

The administration of ranitidine or omeprazole is equally effective in maintaining the acidity of gastric acid in TBI patients in ICU. Both agents achieved the desired pH target at 24 hours after its first administration. There was no significant difference in the incidence of gastric bleeding in ranitidine and omeprazole groups.

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