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Upper Gastrointestinal Bleeding in the Absence of Proper pH Control in Patients Admitted to ICU

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Authors' contributions

This work was carried out in collaboration between all authors. Author AZ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FF and BA managed the analyses of the study. Author BA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Stress-related mucosal disease (SRMD) occurs in many critically ill patients in Intensive Care Units (ICU) and may develop within 24 hours of admission. Proton pump inhibitors (PPI) therapy has been documented to produce more potent inhibition of gastric acid secretion than Histamine 2 Receptor Antagonists (H2RAs) and suspension preparations can increase the gastric pH more than intravenous PPIs. The incidence of clinically important gastrointestinal (GI) bleeding, indicated as overt bleeding complicated by hemodynamic instability, low hemoglobin, and/or need for a blood transfusion from stress-related mucosal disease (SRMD) is 3.5% in the ICU patients who are mechanically ventilated for ≥ 48 h. In addition, this type of ulceration is accompanied by increasing the risk of mortality. Moreover, it prolongs the length of stay in the ICU. Although ischemia of the gastric mucosa leads to SRMD, the significant role of gastric acid in the development of mucosal damage and bleeding could not be ignored. Thus, early preventive prophylaxis of the probable GI bleeding, by means of acid-reducing agents, in these patients is rational Studies have shown that patients with gastrointestinal bleeding are admitted for longer periods of time to ICU. The role of gastric acid in the development of SRMD and the need for early

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intervention to prevent the potential occurrence of upper gastrointestinal bleeding have led to the preventive use of gastric acid-reducing agents in patients admitted to ICU. Therefore, this study evaluated the effect of omeprazole oral suspension in increasing gastric pH and compare it with the previous study which has been done in the same center, followed by upper gastrointestinal bleeding that may occur due to lack of proper pH control in patients admitted to ICU.

Methods: Patients were selected to treat with omeprazole suspension 2 mg/ml (40 mg every day) for up to 4 days. Gastric aspirates were sampled before and 1-2.5 hours after the drug administration for the pH measurement using an external pH meter. To evaluate the results more accurately, the results were compared with results of a previous study conducted in the same center (Masih Daneshvari Hospital). In the previous study, pH changes were higher in the groups receiving pantoprazole suspension and omeprazole suspension than the intravenous pantoprazole group, while the present study reported that pH changes were close to that of the intravenous pantoprazole group ($p = 0.00$).

Results: In this study twenty-nine critically ill patients (14 male, 15 female, mean age: 60.41±15.35 years) were followed for the control of the gastric pH.

On each of the 4 trial days, the mean of the gastric pH alteration was +1.48±1.2. The rate of upper gastrointestinal bleeding was 10.34%.

Discussion: Statistical analysis of the results showed no significant differences between 4 groups in terms of the prevalence of ventilator-associated pneumonia ($p = 0.97$). Based on results of this analysis, gender, risk factors of sepsis and coagulopathy, the presence of coffee ground in the gastric juice sample was related to post-administration gastric pH and all had a direct and significant relationship with post-administration gastric pH. In the previous study, GI bleeding was evident in 3 cases, of which 2 (11.1%) were in the group receiving intravenous pantoprazole solution and 1 (5.6%) was in the omeprazole oral suspension group. In the present study, the rate of GI bleeding was shown only in 3 (10.43%) patients.

Conclusion: this study showed no significant difference between the group studied here and three groups evaluated in the previous study in terms of prevalence of bleeding.

Keywords: SRMD; omeprazole; suspension; GI bleeding; nosocomial pneumonia.

1. INTRODUCTION

Stress-related mucosal damage (SRMD) is a gastric corrosive inflammation with uncertain pathophysiology which can occur immediately after trauma, surgery, burn or sepsis. SRMD is seen in 75 to 100% of critical patients within 24 hours after admission to ICU [1,2]. Mortality rate increases with prevalence and severity of SRMD. In two prospective multicenter studies, Cook et al. observed a significant difference in the mortality rate of patients with and without gastrointestinal bleeding [3]. In this study, mortality rates were 49% and 46% in patients who had gastrointestinal bleeding due to SRMD, while mortality rates were 9% and 21% in patients who did not have gastrointestinal bleeding ($P<0.01$ and $p<0.001$, respectively). This data was consistent with another study on the effect of cimetidine on prevention and treatment of SRMD. In this study, the mortality rate of patients admitted to ICU was significantly associated with severity of the gastrointestinal mucosal injury. The results of this study showed that the prevalence of mortality was 57% in patients with definite endoscopic ulcers or upper gastrointestinal bleeding, compared to 24% in patients with non-bleeding ulcers or normal mucosal patients [4]. In summary, patients with gastrointestinal bleeding are more likely to be admitted to ICU for a longer period of time, and prevalence of mortality is higher in these patients. The role of gastric acid in the development of SRMD and the need for early intervention to prevent the potential occurrence of upper gastrointestinal bleeding has led to the preventive use of gastric acid-reducing agents in patients admitted to ICU. Many studies in the intensive care unit have shown that PPIs (proton pump inhibitors) have a more effective role in inhibiting gastric acid secretion than H2 receptor antagonists [5,6,7]. In addition, these drugs can be prescribed by mouth, nasogastric tube or intravenously. Due to the lack of suitable omeprazole formulation for patients who are unable to swallow capsules, children, and patients with nasogastric tube use methods such as pouring granules into water or apple puree. Surveys carried out outside the body indicate that granules in a volume of 15 or 30 milliliters of apple puree are strongly attached to each other and the nasogastric tube, which actually reduces

the effect of the drug [8]. In addition, this method disintegrates enteric coating as a result of inactivation of omeprazole in the gastric acid environment [9]. Many studies have been conducted on preparation and administration of omeprazole suspension based on sodium bicarbonate (buffering agent). In addition to reducing the decomposition of a medicinal substance in the gastric acidic environment, this compound reduces potential adhesion of granules to each other or to the nasogastric tube [10,11]. PPIs suspension form is more effective in increasing gastric pH and reducing acidity [12]. This study evaluated the effect of omeprazole oral suspension in increasing gastric pH, followed by upper gastrointestinal bleeding that may occur due to lack of proper pH control in patients admitted to ICU. Regarding the concerns about alkalizing the stomach following prophylaxis of SRMD by anti-acid drugs, another goal was to investigate the incidence of ventilator-associated pneumonia (VAP) in the studied patients admitted to the intensive care unit.

2. MATERIALS AND METHODS

The studied drug was a ready-made powder for omeprazole suspension obtained from the Noor Research and Educational Institute (TAVAN) with the following formulation:

Omeprazole	160 mg
Sodium bicarbonate	q.s
Sugar	q.s
Flavoring agent	q.s
Water	Up to 80 ml

Each 5 ml contains 10 mg omeprazole powder

The study was conducted in the National Research Institute of Tuberculosis and Lung Diseases (NRITLD) founded by Dr. Masih Daneshvari. Patients were enrolled from medical ICU and surgical ICU. This study was conducted in June 2015 to May 2016 in the intensive care unit of the Masih Daneshvari Hospital. This randomized single-blind study was a clinical trial study on 30 patients admitted to ICU of the Masih Daneshvari Hospital. Inclusion and exclusion criteria are listed below.

2.1 Inclusion Criteria

1. Patients aged 16 years
2. Prediction of at least 72 hours admission to ICU
3. Need for mechanical ventilation for more than 48 hours
4. APACHE II score larger than or equal to 11
5. A nasogastric or orogastric tube
6. At least one of the risk factors for gastrointestinal bleeding

2.2 Exclusion Criteria

1. CPR status (no cardio pulmonary resuscitation)
2. More than 48 h delay in determining inclusion criteria
3. History of gastric surgery
4. Susceptibility to omeprazole
5. Active gastrointestinal bleeding
6. Risk of swallowing blood (hemoptysis, oral ulcer, facial trauma)
7. Admission for upper gastrointestinal tract surgery
8. Upper gastrointestinal tract ulcer or potential bleeding
9. Failure to receive a nasogastric tube
10. End-stage hepatic patient

Subsequently, ICU patients who required gastrointestinal tract (GIT) prophylaxis were randomly assigned to receive at least 1 day and at most 4 days of treatment with 2 mg/ml omeprazole (40 mg or 20 ml daily). Patients were enrolled on the basis of doctor's recommendation for prophylaxis. In order to control gastric pH, samples were taken from gastric secretions of the patients before and 1 to 2.5 hours after administration, and gastric juice pH was measured by using a pH meter. In presence of coffee-grounds (which can indicate upper gastrointestinal bleeding) in samples taken, the samples were tested by gastoccult (a rapid screening test designed to detect the presence of secret blood in gastric secretions or vomiting). Participation in the trial was stopped before 4 days due to death, discharge or PO (Per Oral) of the patient (nasogastric tube was exhausted). For each patient, the filled form, APACHE II score, and CPIS were calculated.

The feeding time of patients with a nasogastric tube in two medical and surgical ICUs of the Masih Daneshvari Hospital was conducted every 3 hours (6 am, 9 am, 12 pm, 3 pm, 6 pm, 9 pm, 12 am, 6-hour rest and re-start from 6 am). The stomach should be void while administrating oral omeprazole suspension; it was decided to take a pre-administrating sample at 8 am to control gastric pH. The administration was done at 8 am after taking samples. Oral omeprazole

suspension was administered via a nasogastric tube through a 50 mg syringe. After taking a sample, the sample pH was measured immediately by a pH meter in the laboratory. The second sample was taken at least 1 hour and at most 2.5 hours after administration between 9 and 10:30 depending on the exact time of administration and the next gavage time. Gastric juice samples were taken from a nasogastric tube through a gavage syringe (50 mg syringe); then, the gastric juice was moved to Faluccane tube and its pH was measured in the laboratory using pH meter. To measure pH of gastric secretions, the AZ 86502 desktop pH meter was used (Fig. 1).

Fig. 1. AZ 86502 desktop pH meter

Every day before starting pH measurement, the device was calibrated. Calibration was done at three points using buffers 4, 7 and 9. According to main objectives of this study, information of patients admitted to ICU including demographic characteristics and clinical characteristics of patients (APACHE II score, risk factors, baseline pH and CPIS) at baseline was obtained by a special form. All information was analyzed by SPSS software (version 22) after initial calculations. This study used the coding system, which is a common method in qualitative information processing, to process information for statistical analysis. In order to examine the results more closely and to see how different the study was from the previous study, the intravenous pantoprazole used in the previous study was used here as control considering that both studies had the same inclusion criteria and variables. The results were compared with two groups studied previously (pantoprazole suspension and omeprazole suspension) using analysis of variance (ANOVA) calculator. The previous study used Extemporaneous made in Masih Daneshvari Hospital (M) and the present study used the ready-made powder of omeprazole suspension made in the TAVAN Company (T).

3. RESULTS

The qualified patients were treated with 2 mg/ml oral omeprazole suspension; their juice content was aspirated for at least 1 day and at most 4 days to control gastric pH. Samples were taken from 16 out of 29 qualified patients (55.2%) until the fourth day and their pH was controlled. The most common reason for quitting the study before the end of four days was the removal of nasogastric tube (PO) or intolerance to hold the nasogastric tube, bleeding and patient death. Fig. 2 shows the reasons for quitting the study separately.

In this study, 29 patients were enrolled, of which 17 (58.62%) were male and 12 (41.77%) were female. The mean age was 60.4 years (Fig. 3).

3.1 Clinical Variables of Patients at Baseline

Clinical variables of the patients at baseline, including APACHE II score, risk factors for incidence of SRMD, CPIS and baseline gastric pH were evaluated. Table 1 shows clinical variables of patients.

Table 1. Clinical variables of patients at baseline

Variable	Mean ± SD
APACHE II score	23.11 ± 8.29
CPIS	6.69 ± 1.32
Baseline pH	5.4 ± 1.46
Risk factors	%/(N)
• Trauma	0/(0)
• Surgery	3.44/(1)
• Sepsis	6.89/(2)
• Renal failure	17.21/(5)
• Infectious diseases	24.14/(7)
• Respiratory failure	48.32/(15)

According to Table 1, the mean and standard deviation of APACHE II score was 23.11 ± 8.29. Seven risk factors of SRMD, including trauma, surgery, respiratory failure, shock and sepsis, renal failure and coagulopathy were investigated at baseline. Among these risk factors, 48.32% had respiratory failure, 1% had sepsis, 5% had renal failure, 7% had infectious diseases and

none showed trauma. The mean of CPIS was 6.69 ± 1.32 in the T omeprazole suspension group. The mean of CPIS was 6.8 ± 1.2 in the control group (intravenous pantoprazole) (P = 0.77). The mean of CPIS was 6.83 ± 1.15 in the pantoprazole suspension group (P = 0.70). The mean of CPIS was 6.47 ± 1.42 in the omeprazole suspension group (M) (P = 0.59). Fig. 3 compares CPIS in four groups.

3.2 Baseline pH Distribution (Pre-administration) in the Studied Patients

According to Table 2, the mean and standard deviation of baseline pH was 5.4 ± 1.46 in the T suspension group. The mean and standard deviation of baseline pH was 5.38 ± 1.08 in the control group (intravenous pantoprazole) (P = 0.96). The mean and standard deviation of baseline pH was 5.68 ± 0.92 in the pantoprazole suspension group (P = 0.45). The mean and standard deviation of baseline pH was 5.48 ± 1.19 in the omeprazole suspension group (M) (P = 0.84).

Fig. 5 compares baseline pH changes and pH changes in each of four days between four groups.

3.3 Changes in Post-administration Gastric Juice pH

According to Table 3, the mean and standard deviation of pH changes was 1.48 ± 1.2 after four days in the T omeprazole suspension group. As shown in Fig. 5, pH changes were higher in the first days than the last day. The mean and standard deviation of pH changes was 1.16 ± 0.66 in the control group (intravenous pantoprazole) (P = 0.30). In Fig. 6, the mean and standard deviation of pH changes was 2.88 ± 0.88 in the pantoprazole suspension group (P = 0.00). The mean and standard deviation of pH changes was 2.35 ± 1.05 in the omeprazole suspension group (M) (P = 0.01).

3.4 Average Time for a Unit of pH Increase in the Studied Patients

To determine the time required for the effectiveness of the drug, the time when pH difference (in comparison with baseline pH) was greater than and equal to 1 was calculated. Analysis showed that the time to acquire at least 1 unit of change from the lower pH to the higher pH was 1. 21 ± 0.64 days. Additionally, 87% of the patients acquired this pH with the first dose of the drug.

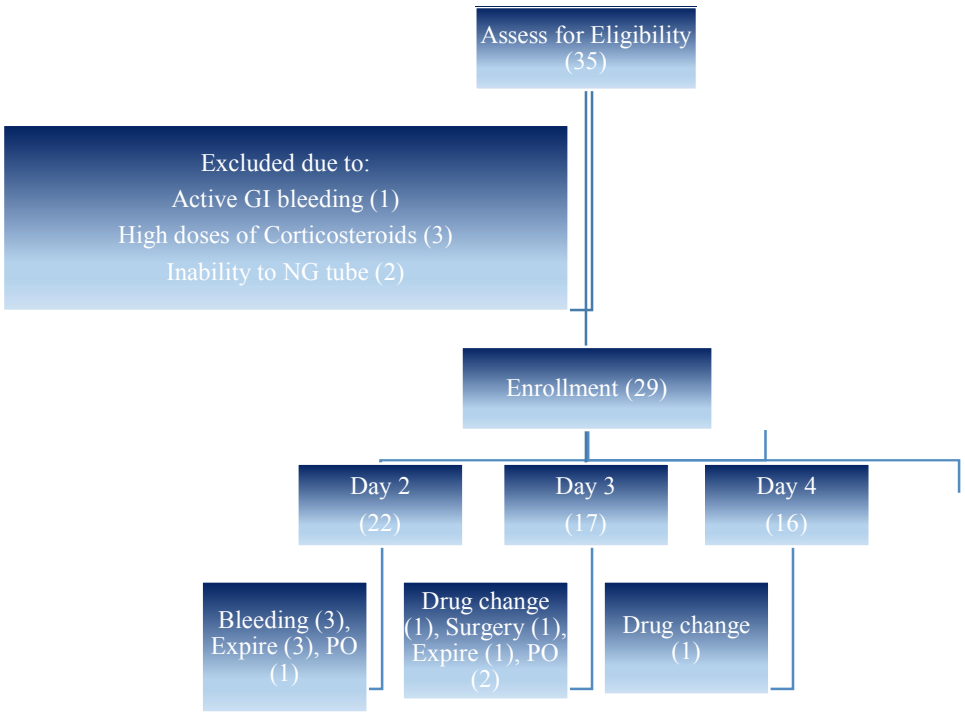

Fig. 2. Reasons for quitting the study before 4 days

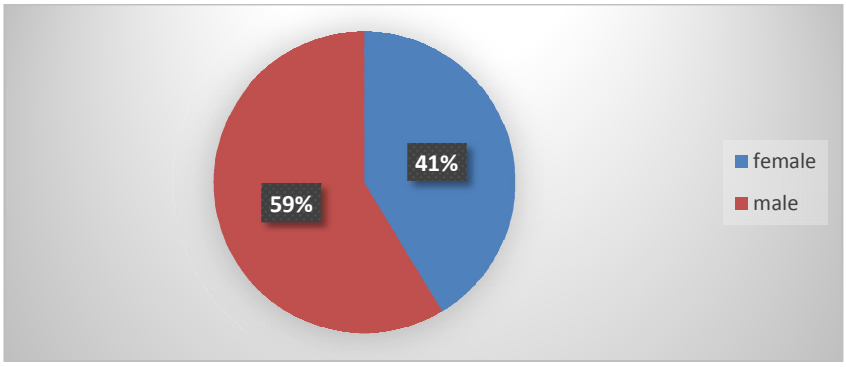

Fig. 3. Gender distribution

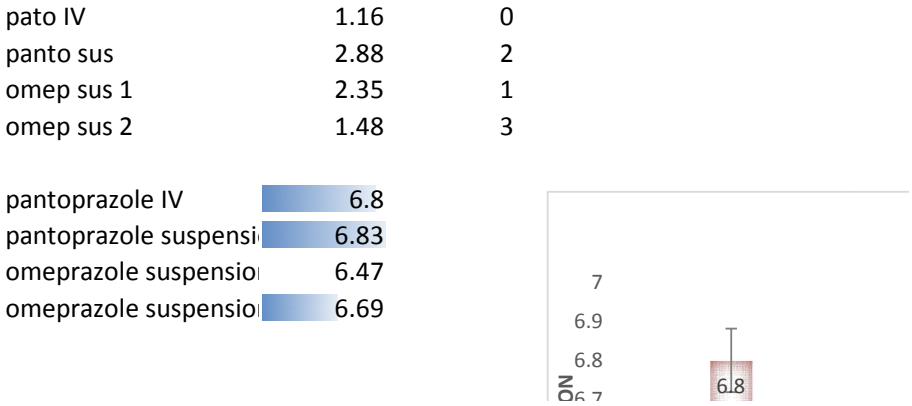

Fig. 4. Comparison of CPIS in four groups

Table 2. Baseline pH distribution if the T omeprazole suspension group

Days (n)	Mean ± SD of baseline pH	patients with pH≤4 N (%)
Day 1 (n = 29)	5.42 ± 1.17	1 (4.34)
Day 2 (n = 22)	5.43 ± 1.11	1 (5.26)
Day 3 (n=17)	5.52 ± 1.03	0
Day 4 (n = 16)	5.55 ± 1.16	0

Table 3. pH changes in the T omeprazole suspension group

Days	Mean ± SD
Day 1	1.85 ± 1.0
Day 2	1.58 ± 0.46
Day 3	1.36 ± 0.50
Day 4	1.2 ± 0.48

3.5 Prevalence of Upper Gastrointestinal Bleeding

According to Fig. 7, only 3 out of 29 patients (10.43%) had upper gastrointestinal bleeding. In the control group (intravenous pantoprazole), none of 18 patients had to bleed. In the pantoprazole suspension group, only 2 out of 20 patients (11.1%) had to bleed. In the M omeprazole suspension group, only 1 out of 18 patients (5.6%) had to bleed.

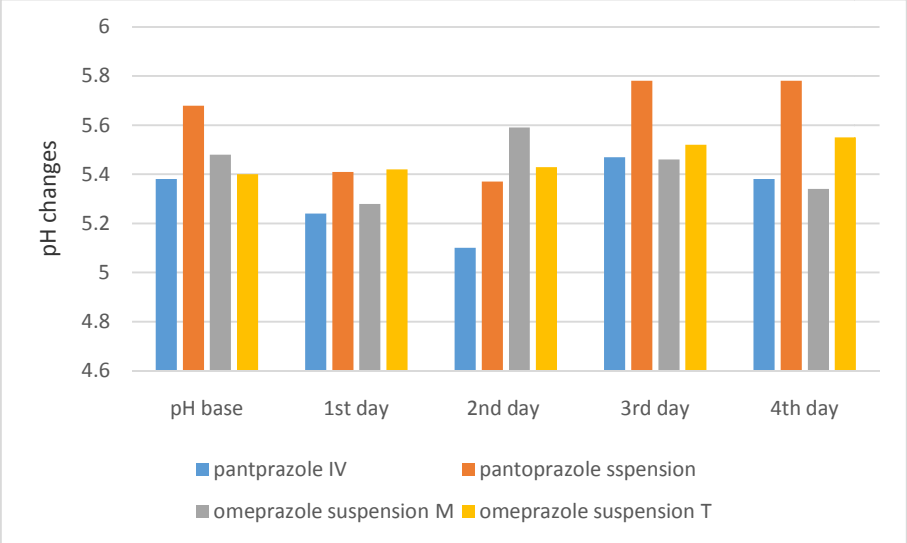

Fig. 5. Comparison of baseline pH changes and pH changes in each of four days between four groups

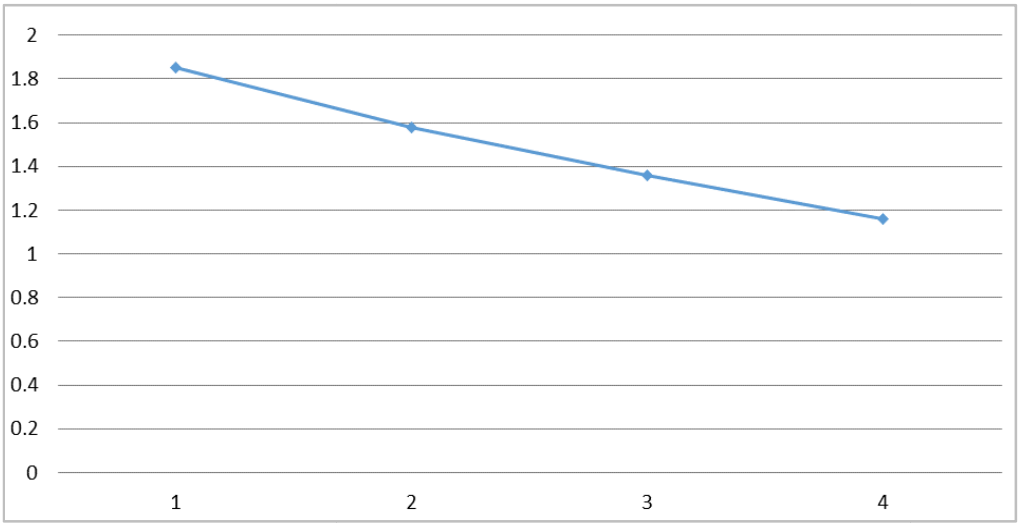

Fig. 6. pH changes in four days in the T suspension group

4. DISCUSSION AND CONCLUSION

The present study was done on 29 hospitalized patients to evaluate the effect of an oral powder formulation of 2 mg/ml omeprazole suspension (40 mg daily) on gastric pH. Samples were taken from patients treated with the drug for at least 1 day and at most 4 days to measure gastric pH. The most common causes of exclusion before 4 days were mortality (30.76%), followed by nasogastric tube discharge (23.07%) and gastrointestinal bleeding (23.07%). At baseline, baseline clinical characteristics including demographic characteristics, APACHE II score, the prevalence of risk factors (trauma, surgery, respiratory failure, shock, sepsis, renal failure and coagulopathy), CPIS, and mean baseline pH were recorded for each patient. The studied population included 17 men (58.62%) and 12 women (41.37%) aged 60.41 ± 15.35 years. The mean APACHE II score was 23.11 ± 8.29. Risk factors included surgery (1%), sepsis (2%), renal failure (5%), and infectious diseases (7%); none of the patients had a risk factor for trauma and shock.

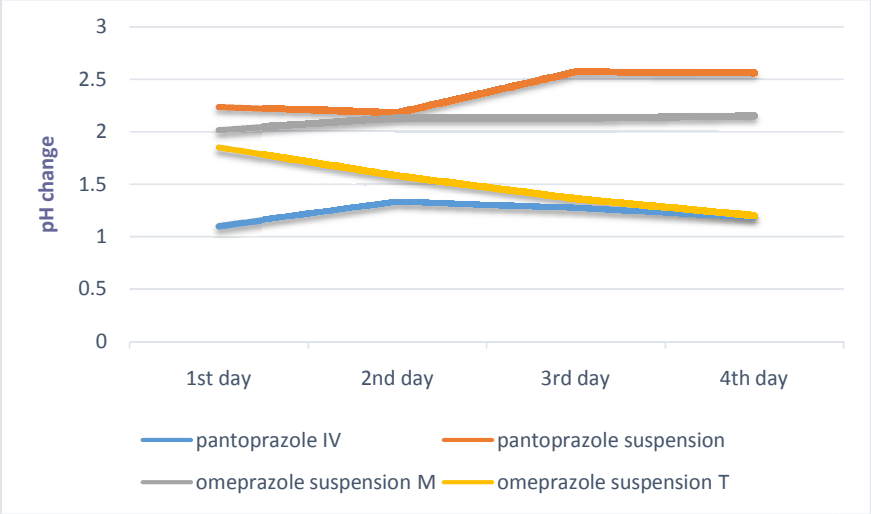

Fig. 7. pH changes in four days between four groups

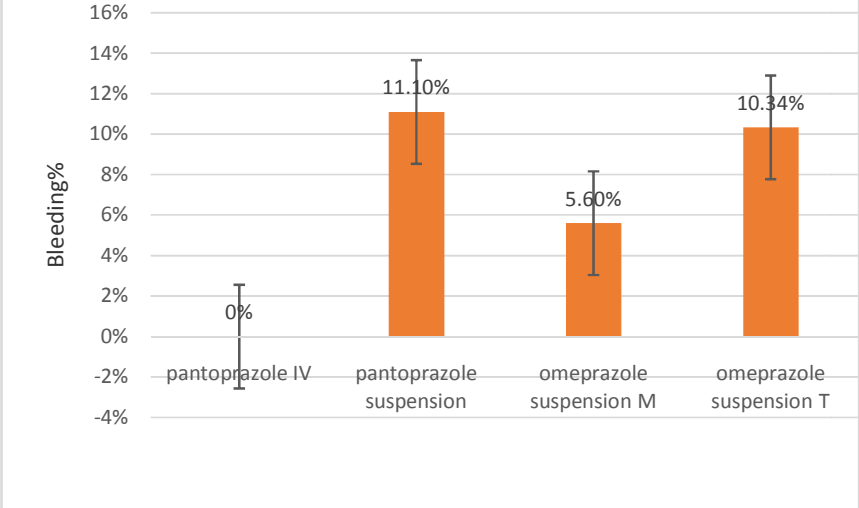

Fig. 8. Comparison of bleeding (%) between four groups

In a study by Conard et al. to compare oral omeprazole suspension and continuous cimetidine infusion in preventing upper gastrointestinal bleeding, the two groups were in most cases matched, although the mean APACHE II score (indicating the severity of deterioration) was higher in the group receiving omeprazole suspension. Concerning that characteristic of patients were similar in the Conard's study, it can be concluded that baseline characteristics of the patients had no effect on post-administration gastric pH, which indicates drug effectiveness (4). In case of proton pump inhibitors, pH monitoring is useful in selecting the proper doses. The use of PPIs is restricted for deteriorating patients admitted to ICUs. All proton pump inhibitors are inactivated by gastric acid, which is why they should be taken as enteric-coated granules in gelatin capsules (omeprazole).

One of the drawbacks of PPIs is the unavailability of the liquid formulation. This formulation is particularly important for patients who cannot swallow (13). An immediate-release omeprazole formulation is available containing omeprazole capsules and sodium bicarbonate. Some studies have shown that these Extemporaneous formulations may cause blockage or fading of a nasogastric tube (14),

altering bioavailability [1,2]. Omeprazole suspension, in which sodium bicarbonate is used as a suspending agent, solves this problem. This formulation also requires patients to have adequate absorption capacity, which is variable in ICU patients due to immobilization of gastrointestinal tract [3]. Moreover, immediate-release omeprazole formulation contains sodium bicarbonate, which should be cautiously used for patients who have a constraint on the use of sodium [15].

The superiority of proton pump inhibitors compared with H2RA has been proven in many studies. In a double-blind study by Conard et al. to compare the effect of oral omeprazole suspension and intravenous cimetidine solution on upper gastrointestinal bleeding in ICU patients, oral omeprazole suspension was found to be more effective in increasing gastric pH and preventing upper gastrointestinal bleeding than intravenous cimetidine solution [5]. Considering the greater effectiveness of PPIs in increasing gastric pH and in preventing upper gastrointestinal bleeding compared to H2 receptor antagonists, this study only addressed one of the most widely used PPIs, namely omeprazole.

Pharmaceutical care unit of the Masih Daneshvari Hospital is the first center in Iran to provide patients with nonsterile hospital pharmacy manufacturing since 2011. This hospital pharmacy manufacturing system combines, mixes or changes pharmaceutical raw materials to provide the patients with the considered drug according to their specific needs; thus, this system plays a very important role in treating patients who cannot take their medicines in the form of drugs available in the market for any reason. As noted, NPO patients, patients who cannot swallow capsules or have digestive tract disorder, cannot use PPIs as pills (pantoprazole) or capsules (omeprazole). Many studies have shown that oral omeprazole suspension can be effective in controlling gastric juice pH and preventing upper gastrointestinal bleeding.

Few studies compared the effectiveness of two or more PPIs in increasing gastric pH. In a study to compare immediate-release omeprazole suspension and slow-release pantoprazole tablet in controlling night-time reflex of GERD patients, a gastric pH monitoring at 24 h showed that oral omeprazole suspension once a day was more effective than pantoprazole tablet once or twice a day in controlling gastric acidity [16].

Because the acid in lumen plays an important role in SRMD, keeping the gastric pH on a higher level theoretically reduces the progression of mucosal damage as well as upper gastrointestinal bleeding in ICU patients [5]. In a study by Martin et al, only two characteristics of hematemesis (bright red blood in the gastric juice sample which does not disappear after NG tube adjustment and 5-10 min normal saline lavage) and presence of coffee ground for 8 constant hours which does not disappear by 100 ml lavage or it is associated with a 5% reduction in hematocrit was considered in definition of GI bleeding [17].

The patients were also examined for prevalence of VAP. In a study by Cook et al, prophylaxis by an anti-acid or H2RA did not increase the incidence of VAP [18]. However, at least theoretically, prophylactic agents which have greater effectiveness in reducing the upper gastrointestinal bleeding (H2RA and PPIs) are associated with a higher incidence of VAP; moreover, weaker gastric acid suppressants (sucralfate) have not shown a lower incidence of VAP. Thus, it is recommended that the choice of proper drug for prophylaxis of SRMD considers whether prevention of upper gastrointestinal bleeding has a higher clinical value or reduction of pneumonia symptoms. However, it seems more feasible to choose the drug based on the lower risk of upper gastrointestinal bleeding, at least until the relationship between prophylactic drug and prevalence of VAP is confirmed by more and stronger clinical studies. This is why in practice, H2RA or PPIs are often used for prophylaxis of SRMD [15].

To evaluate the results more accurately, the results were compared with results of a previous study conducted in the same center (Masih Daneshvari Hospital). In the previous study, the changes in pH of the groups receiving pantoprazole suspension and omeprazole suspension were higher than the intravenous pantoprazole group, while in the present study, pH changes were close to that of the intravenous pantoprazole group ($p = 0.00$). Considering that suspension form of pantoprazole and omeprazole in the previous study was more effective in increasing gastric acid, the risk of pneumonia was similar in four groups. Statistical analysis of the results indicated no significant differences between 4 groups in terms of the prevalence of VAP ($p = 0.97$). Therefore, it can be concluded that omeprazole suspension was similar to previous treatment group in terms of

the risk of VAP. Based on results of this analysis, gender, sepsis, and coagulopathy, the presence of coffee ground in the gastric juice sample was related to post-administration gastric pH, all of which had a direct and significant relationship with post-administration gastric pH. In the previous study, GI bleeding was evident in 3 cases, of which 2 (11.1%) received intravenous pantoprazole solution and 1 (5.6%) received oral omeprazole suspension. In the present study, GI bleeding was shown only in 3 (10.43%) patients. The results showed no significant difference between the current study group and three groups of the previous study regarding the prevalence of GI.

CONSENT

As per international standard or university standard, the patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard was written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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