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ORIGINAL ARTICLE

Comparison of the efficacy of esomeprazole and famotidine against stress ulcers in a neurosurgical intensive care unit

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Summary *Background:* To compare the efficacy of esomeprazole and famotidine against stress ulcers and the association of these prophylactic agents with ventilator-associated pneumonia in patients admitted to neurosurgical intensive care unit (ICU).
Patients and Methods: Sixty patients were randomly allocated into two groups (the esomeprazole and famotidine groups; $n = 30$ each) to receive prophylaxis medication for 7 days within 24 hours of admission in a neurosurgical ICU. Patients in the esomeprazole group received esomeprazole (40 mg) dissolved in water once a day through a nasogastric tube, whereas patients in the famotidine group received an intravenous infusion of famotidine (20 mg) every 12 hours. We then compared the occurrence of overt upper gastrointestinal bleeding and ventilator-associated pneumonia between these two groups.
Results: One patient in the famotidine group had overt upper gastrointestinal bleeding (3.3%), whereas the bleeding was not observed in patients in the esomeprazole group. Ventilator-associated pneumonia occurred in one patient (3.3%) from each group. One patient died within 30 days (3.3%) in the esomeprazole group and three patients (10%) died in the famotidine group. There was no difference in the occurrence of overt upper gastrointestinal bleeding ($p = 1.000$), ventilator-associated pneumonia ($p = 1.000$), and 30-day mortality ($p = 0.612$) between these two groups.
Conclusion: In this small-scale study, the effect of administration of esomeprazole through a nasogastric tube on stress ulcer was similar to that of intravenous famotidine infusion in neurosurgical ICU patients. In addition, the association between prevalence of ventilator-associated

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pneumonia and administration of esomeprazole was also similar to that observed with famotidine infusion.

Introduction

With improvements in critical care, the occurrence of stress ulcer bleeding has decreased recently. However, it still occurs and is associated with a high mortality rate in critically ill patients with risk factors, including respiratory failure requiring mechanical ventilation, sepsis, coagulopathy, shock, severe burning injury, head injury or intracranial surgery, and hepatic or renal failure that require major surgery [1,2]. Although treatment with prophylactic agents for stress ulcer in these patients is still recommended, there is still no consensus on the choice of drug [3—5].

Stress ulcer is a common complication in neurosurgical intensive care unit (ICU), often referred as Cushing's ulcers. Besides hemodynamic disturbance in critically ill patients, hypersecretion of gastric acid caused by injury to the central nervous system plays an important role in the pathogenesis of Cushing's ulcers [2,6]. Acid suppression using histamine-2 receptor antagonists (H2RA) has proven to be more effective than placebo for stress ulcer and is most popular in clinical use [3,5,7,8]. Proton pump inhibitors (PPIs) are more potent in acid suppression than H2RA and have been increasingly used for treatment of stress ulcers recently [9]. A meta-analysis reported by Pongprasobchai et al [10] demonstrated the superiority of PPI over H2RA in decreasing clinically important bleeding in critically ill patients; however, another meta-analysis revealed a different result [11]. Therefore, this study was conducted to directly compare the effect of esomeprazole and famotidine on stress ulcer in neurosurgical ICU.

Patients and methods

From March 2007 to March 2010, we enrolled those patients who were admitted to the neurosurgical ICU of the Far Eastern Memorial Hospital, New Taipei, Taiwan for post-surgical care or management of severe cerebrovascular accident. Most patients received surgical treatment for intracranial hemorrhage. After explaining the study purpose and obtaining written consent from their family members, prophylactic medication was initiated within 24 hours after admission. We excluded those who were aged less than 18 years, who had history of allergy to either famotidine or esomeprazole, who could not be fed through a nasogastric tube, and who already had gastrointestinal bleeding on admission. This study was approved by the Research Ethics Review Committee of the Far Eastern Memorial Hospital and was monitored during execution.

The patients were randomly allocated to two groups. The patients in the first group received esomeprazole (40 mg; Nexium, AstraZeneca, Sodertaije, Sweden) dissolved in water through a nasogastric tube once per day for 7 days (the esomeprazole group); the patients in the second group (the famotidine group) received intravenous famotidine (20 mg; Gaster, Astellas, Shizuoka, Japan) infusion every 12 hours for 7 days. Most of these patients started their enteral feeding after admission to the neurosurgical ICU if not contraindicated. We recorded the demographic data, operation time, and baseline data of Glasgow Coma Scale (GCS, last score prior to the operation or on admission for those without surgery), Acute Physiology and Chronic Health Evaluation II Score (AP-II), and intracranial pressure. We counted 1 point for the patients with endotracheal intubation in the verbal category of GCS. We recorded vital signs including body temperature, heart rate, and blood pressure every day for 1 week; patient's complete blood cell count and chest X-ray (CXR) were reviewed every other day; and stool occult blood was tested twice a week for 1 week. Besides, we surveyed the ICU admission days and 30-day survival rates. We also monitored and recorded the characteristics of nasogastric tube drainage, sputum, and stool every day for 1 week. We focused on the prevention of overt upper gastrointestinal bleeding in patients receiving stress ulcer prophylactic agents and defined upper gastrointestinal bleeding as tarry stool, hematemesis, drainage of more than 60 mL coffee ground substance from nasogastric tube, or decreased hemoglobin level more than 2 g/dL with proved lesions by endoscopic examination. We also defined positive stool occult blood test as occult bleeding. Guaiac stool occult blood test was carried out twice a week. If no stool sample was available on the scheduled day, it would be checked when the patient passed a stool on the following days during the study period. We defined ventilator-associated pneumonia as pneumonia occurring after 48 hours of ventilator use that fulfills three or more of the following four criteria: (1) presence of persistent ($>$48 hours) or new onset infiltration in CXR; (2) positive sputum smear (with $<$10 epithelial cells per low-power field, 100$\times$, and $>$25 white blood cells per low-power field or presence of polymorphonuclear cells with phagocytosis); (3) fever with body temperature $>38.3^{\circ}C$; and (4) leukocytosis $>12 \times 10^9$/L.

All data were analyzed with the statistical software SPSS for Windows (SPSS Inc., Chicago, IL, USA). Significant difference for sex was compared with the Chi-square test, whereas significant differences for age, operation time, GCS, intracranial pressure, and ICU admission days were compared with the Mann—Whitney *U* test. We used Fisher's exact tests to evaluate the differences for apparent upper gastrointestinal bleeding and microscopic bleeding, ventilator-associated pneumonia, and 30-day mortality between these two groups.

Results

A total of 60 patients participated in the study, with 30 allocated to the esomeprazole group and 30 to the famotidine group. In the esomeprazole group, 26 patients were

operated for intracranial hemorrhage, one for massive cerebral infarct, one received transarterial embolization for intracerebral hemorrhage, and two received intracranial pressure monitoring for intracranial hemorrhage. In the famotidine group, 26 patients were operated for intracranial hemorrhage, one for brain tumor, and three received intracranial pressure monitoring for intracranial hemorrhage. Every patient received ventilator support and nasogastric feeding when admitted to the ICU. In the esomeprazole group, there were 20 male and 10 female patients, with a mean age of 56.2 ± 18.4 years. The average baseline GCS was 8.0 ± 4.5, AP-II was 16.4 ± 5.6, intracranial pressure was 15.2 ± 13.3 cmH_2O. The average operation time was 235.7 ± 168.1 minutes. In the famotidine group, there were 16 male and 14 female patients, with a mean age of 59.2 ± 15.0 years. The baseline GCS was 7.3 ± 4.1, AP-II was 17.7 ± 6.2, intracranial pressure was 12.4 ± 9.4 cmH_2O. The average operation time was 293.0 ± 246.8 minutes. There was no significant difference for sex ($p = 0.292$), age ($p = 0.473$), GCS ($p = 0.599$), AP-II ($p = 0.370$), intracranial pressure ($p = 0.667$), and operation time ($p = 0.232$) between these two groups (Table 1).

In the esomeprazole group, none of the patients had overt upper gastrointestinal bleeding, 10 (33%) had occult bleeding, and one (3.3%) had ventilator-associated pneumonia. By contrast, in the famotidine group, one patient (3.3%) had overt upper gastrointestinal bleeding, 10 (33%) had occult bleeding, and one (3.3%) had ventilator-associated pneumonia. The patient with overt upper gastrointestinal bleeding did not undergo endoscopic examination due to concern of significant risk during the immediate postoperative period. There was no difference for overt upper gastrointestinal bleeding ($p = 1.000$), occult bleeding ($p = 1.000$), and ventilator-associated pneumonia ($p = 1.000$) between these two groups. The ICU admission days were 23.6 ± 12.40 days in the esomeprazole group and 23.3 ± 12.14 days in the famotidine group and no statistical difference was noted ($p = 0.842$). One patient died (3.3%) within 30 days in the esomeprazole group, whereas three patients (10%) died in the famotidine group. The 30-day survival rate showed no statistical difference ($p = 0.612$; Table 2).

Table 1 Distributions of baseline characteristics in the two study groups.

Baseline characteristics	Esomeprazole ($n = 30$)	Famotidine ($n = 30$)	p*
Male	20 (66.7)	16 (53.3)	0.292
Age (y)	56.2 ± 18.4	59.2 ± 15.0	0.473
GCS	8.0 ± 4.5	7.3 ± 4.1	0.599
AP-II	16.4 ± 5.6	17.7 ± 6.2	0.370
ICP (cmH_2O)	15.2 ± 13.3	12.4 ± 9.4	0.607
OP time (min)	235.7 ± 168.1	293.0 ± 246.8	0.232

Data are presented as n (%) or mean ± SD.
* Comparisons between two groups: Chi-square test was used to examine the difference in sex and Mann–Whitney U test was used for other variables.
AP-II = Acute Physiology and Chronic Health Evaluation II Score; GCS = Glasgow Coma Scale; ICP = intracranial pressure; OP = operation.

Table 2 Outcome evaluations in the two study groups.

Outcome evaluations	Esomeprazole ($n = 30$)	Famotidine ($n = 30$)	p*
Overt UGI bleeding	0 (0)	1 (3.3)	>0.99
Occult bleeding	10 (33.3)	10 (33.3)	>0.99
Ventilator-associated pneumonia	1 (3.3)	1 (3.3)	>0.99
ICU admission days	23.6 ± 12.40	23.3 ± 12.14	0.842
30-day survival	29 (96.7)	27 (90.0)	0.612

Data are presented as n (%) or mean ± SD.
* ICU admission days were compared with Mann–Whitney U test and Fisher's exact test was used for other variables.
ICU = intensive care unit; UGI = upper gastrointestinal.

Discussion

In our small study group, none of the patients in the esomeprazole group had overt upper gastrointestinal bleeding; by contrast, one patient (3.3%) in the famotidine group had overt upper gastrointestinal bleeding, but no significant difference was found between the two groups. The incidence rate was similar to that of previous studies (between 3% and 6% for clinically important bleeding) that used prophylactic agents for treating stress ulcer [12,13]. There was also no difference in the occurrence of ventilator-associated pneumonia between the esomeprazole and famotidine groups (3.3% in both groups). Although occult bleeding does not predict the development of clinically significant bleeding [14], it was also evaluated in this study. A significant proportion of patients (33%) in neurosurgical ICU developed occult bleeding in both the esomeprazole and famotidine groups; however, no difference was found between the two groups.

At present, proton pumper inhibitors are the most potent acid inhibitors available. They have gained more popularity as stress ulcer prophylactic agents recently despite the absence of strong evidence supporting their use. Conrad et al [15] demonstrated that omeprazole oral suspension provided better acid control than intravenous cimetidine in critically ill patients. A previous small pilot study revealed a better efficacy of omeprazole over ranitidine for treating stress ulcers [16]. A meta-analysis reported by Pongprasobchai et al [10] also showed the superiority of PPI over H2RA in decreasing clinically important bleeding in critically ill patients. However, another meta-analysis by Lin et al [11] revealed a different result. A randomized controlled study performed by Kantorova et al [17] demonstrated that omeprazole, famotidine, and sucralfate prophylaxis could not affect the already very low incidence of clinically important stress-related bleeding in surgical ICU when compared with the placebo.

Early enteral nutrition has been promoted in critically ill patients in recent years, with probable benefits for treating stress ulcer [18,19]. This strategy was adapted in our neurosurgical ICU and might have contributed to the low incidence of apparent upper gastrointestinal bleeding in our patients. Marik et al [20] concluded in their meta-analysis that treating stress ulcer with H2RA may not be needed in those patients receiving enteral feeding, and such therapy may actually increase the risk of pneumonia

and death. However, these studies were not well designed and thus definite recommendations regarding the role of enteral feeding in treating stress ulcer are not possible [18,19]. Therefore, the use of enteral feeding as the only therapeutic approach for stress ulcer prophylaxis should not be encouraged until definite data are available [19].

Stress ulcer prophylaxis has become a standard of care for critical patients for more than two decades. However, there were some reports concerning its overuse in critical settings [21] and even in general medical patients [22,23]. The issues of overutilization of PPIs for gastroesophageal reflux disease and stress ulcer prophylactic agents were also proposed [9]. Considering its cost effectiveness and potential risk, judicious use of stress ulcer prophylactic agents in high-risk patients is important for critical care. From the literature review to-date, no significant difference in efficacy and risk of nosocomial pneumonia was demonstrated when comparing different drugs for stress ulcer [24,25]. Our study had a similar result and provided a cheaper regimen of an oral form of esomeprazole given through a nasogastric tube in suitable patients.

There are several limitations in our study. The case number is relatively small to draw a strong conclusion. It was carried out in only one hospital and the studied results cannot be generalized for practice. We did not collect all the relevant clinical data for analysis, such as history of ulcer or bleeding, use of nonsteroid anti-inflammatory drugs, aspirin, and steroids. Besides, we only provided prophylactic agents to those patients for the initial 7 days after admission, and the following days were not considered in the analysis.

In conclusion, our small-scale study demonstrated that esomeprazole given through a nasogastric tube could provide a simple, effective approach for the treatment of a stress ulcer without an increased risk of ventilator-associated pneumonia in patients admitted to neurosurgical ICU.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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