

The Effectiveness of Standard Single Dose Omeprazole vs. High Dose Continuous Infusion in High-risk Critically Ill Patients

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Abstract

Objectives: The present study was carried out to investigate the beneficial effects of high dose omeprazole versus standard low dose as a prophylaxis against upper GIT bleeding in high risk critically ill patients.

Methods: A hundred and ten high risk critically ill patients were divided into two groups, fifty-five patients each. Group A received intravenous (IV) omeprazole 40 mg bolus dose once daily followed by normal saline infusion. Group B received IV bolus of 80 mg omeprazole followed by 8 mg/h infusion. The treatment was for the whole period of ICU stay. Early morning gastric pH, residual gastric volume, signs of significant upper GIT bleeding, ICU stay Hb, number of ICU days without ventilator, ICU stay hemoglobin (Hb), number of red cell units transfused in ICU, ICU stay, and numbers of ICU survivors were recorded.

Results: Gastric pH was higher in group B compared to group A ($p < 0.05$). The number of patients developed significant upper GIT bleeding were significantly higher in group A. Group A had lower ICU Hb levels and used significant higher number of RBC units. ICU stay was significantly higher in group A compared to group B ($p = 0.02$). There were no statistical differences regarding the number of ICU days without ventilator and ICU survivors between both groups ($P < 0.05$).

Conclusions: High dose PPI continuous infusion can reduce the incidence of upper GIT bleeding in high risk critically ill patients. High dose PPI can reduce ICU stay with no effect on ICU survivor rate.

Keywords: Proton pump inhibitor; Gastric pH; Upper gastrointestinal bleeding; Critically ill patients

Abbreviations: GIT: Gastrointestinal Tract; IV: Intravenous; ICU: Intensive Care Unit; Hb: Haemoglobin; PPI: Proton Pump Inhibitor

Introduction

Stress may result in upper gastrointestinal (GIT) mucosal damage and bleeding [1-3]. The pathophysiology behind gastric mucosal damage is not completely understood. Inadequate perfusion, disruption in mucosal blood flow, increase in gastric acidity, and inadequate cellular oxygenation can lead to stress ulcers [3]. The incidence of gastric bleeding can be reduced by early enteral feeding and with the prophylaxis use of antacids [4,5].

It has been reported that up to 25% of the critically ill patients can develop significant GIT bleeding with haemodynamic instability at one stage during ICU stay [3]. Mortality rate is higher in critically ill patients with significant gastrointestinal bleeding (48.5%) compared to 9.1% in non-bleeders [6].

Prophylaxis against upper GIT bleeding has been recommended by many guidelines and the surviving sepsis campaign in the critical care setting [7]. Sucralfate, histamine-type 2 receptor antagonists, and proton pump inhibitors (PPIs) have been recommended as prophylaxis against stress ulcer and bleeding [8,9].

PPIs are more potent than other medications due to its mechanism of action. PPIs do not show acid anti-secretory tolerance [10]. PPIs can inhibit the parietal cells with an intravenous bolus dose. Continuous infusion can provide a steady plasma level of the drug to inactivate proton pump stimulation by histamine, food, or gastrin [6].

The present study was carried out to compare the benefits of daily standard single shot of intravenous (IV) omeprazole versus continuous IV infusion in upper GIT bleeders high-risk critically ill patients.

Methods

The local ethics committee at El-Menoufia university hospital approved this prospective randomized study. Informed written consent was taken from the first of kin for all patients included in the study. The study was performed on critically ill patients admitted to our intensive care unit (ICU) and met the inclusion criteria. The study is registered on Clinicaltrial.gov number under number NCT03388463.

A hundred critically ill patients of both genders, aged between 21 and 70 years old with high-risk for stress ulcer were included in the study. Mechanically ventilated patients were identified as high-risk patients. Patients with nasogastric tube inserted as part of their medical care were included in the study. Exclusion criteria included: ICU patients admitted because of upper GIT re-bleeding, patients who were not scheduled for early enteral nutrition during the first 24 h of ICU admission, patients with bleeding disorders, renal replacement

therapy, history of gastric ulcer, gastric surgery, and the use of gastric antacids before ICU admission.

Patients who met the inclusion criteria were randomized into two groups using computerized software to fifty patients in each group. Group A received a daily IV single standard bolus dose of omeprazole intravenously and group B received a daily high dose continuous IV infusion of omeprazole. All patients received omeprazole during the first hour of ICU admission and for the whole duration of ICU stay.

Study Design

The study was a randomized double-blind study. Independent pharmacists prepared the omeprazole bolus and infusion syringes. Patients were randomized using a computerized computer program. Patients, ICU nurses, investigators, and ICU physicians were blinded to the study medications.

Omeprazole regimens

Group A received omeprazole 40 mg bolus once a day followed by continuous saline infusion (50 ml 0.9% normal saline). Group B received 80 mg bolus as a loading dose followed by continuous infusion of 8 mg/h (200 mg omeprazole diluted in 0.9% normal saline to form a total of 50 ml). Both groups received the continuous infusions at a rate of 2 ml/h [6,11,12].

All patients were on our unit's enteral nutrition protocol. The enteral nutrition protocol started within six hours of patients meeting the enrollment criteria. The feeding was given at a constant rate of 50 to 150 ml/hr and rest the bowel for 8 h during night through nasogastric tube. Gastric aspirate was taken before starting the enteral feeding to measure the baseline admission gastric pH. Aspiration of gastric fluid was done every morning to measure the amount of overnight residual gastric volume.

For measuring gastric pH, 5 mL of early morning gastric fluid from the gastric fundus was aspirated. The position of the nasogastric tube was confirmed by chest and upper abdomen X-ray according to our unit's protocol. Gastric fluid was transported as rapid as possible to the laboratory. Gastric juice was centrifuged (3,000 rpm, 5 min), and supernatant was collected; then, pH was measured using a glass electrode. Gastric pH was measured twice daily until ICU discharge. Gastric fluid was aspirated and measured after the overnight eight hours rest from enteral feeding to measure the residual gastric volume.

All patients were followed up for clinically significant GIT bleeding. Clinically significant GIT bleeding was defined if a patient had an episode of overt sign of bleeding accompanied by reduction in mean arterial blood pressure ≥ 20 mmHg in the absence of another clinical cause, reduction in hemoglobin ≥ 20 g/L without another obvious source of bleeding, or the need for endoscopic or surgical intervention to stop GIT bleeding. Overt signs of bleeding were diagnosed if the patient had fresh blood from the nasogastric tube, haematemesis, melena or haematochezia.

Patients' demographic data were collected. Signs of clinically significant GIT bleeding, the number of patients required endoscopic intervention, feed intolerance (residual gastric volume more than 250 mL), baseline admission Hb, daily Hb level, number of red cell units transfused, ICU stay, number of ICU days without ventilator, and ICU outcome were recorded.

End point

The study end point was to study the effect of two different methods of omeprazole on gastric pH and its effect on the number of cases with clinically significant GIT bleeding. Our secondary end points were to study ICU hemoglobin level, red cell units transfused, ICU stay and ICU survival rate.

Power analysis

Sample size was calculated using Graph pad Instant statistics version 3 depending on previous observations [13]. Previous studies showed that the use of proton pump inhibitors compared to no prophylaxis reduced the GIT bleeding. By choosing 5% significance level and power of 90%, the calculated sample size was 45. In the present study we recruited 50 patients in each group to have reliable results.

Statistical analysis

It was performed using SPSS base 17.0 package (SPSS Inc, Chicago, IL, USA). Dichotomous variables are reported as percentage and compared using the chi-square test or exact fisher test (when the expected count was <5). Quantitative variables were reported as mean \pm SD and analyzed by student t-test where P-values less than 0.05 were considered significant.

Results

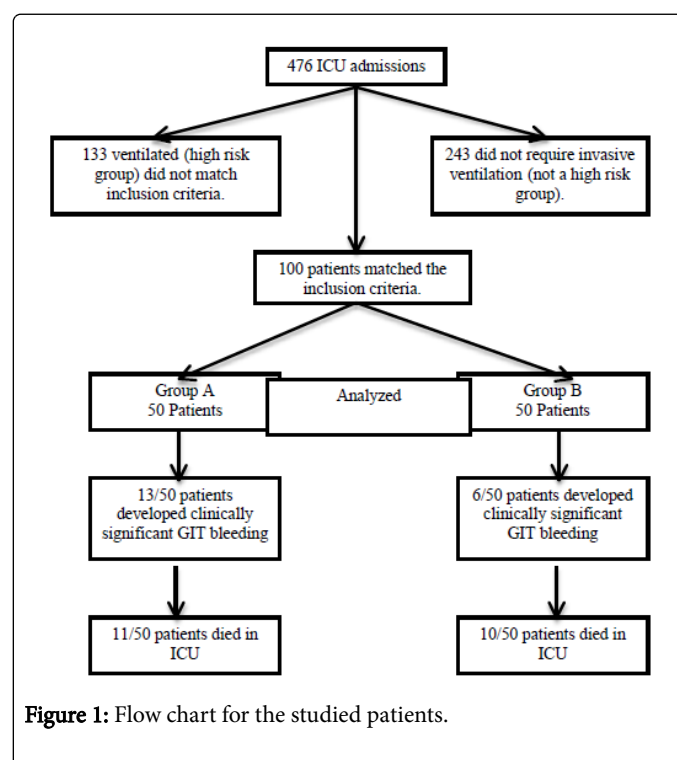


Figure 1: Flow chart for the studied patients.

A total number of 476 patients were admitted to our ICU during a nine months period, 133 were ventilated and did not match the inclusion criteria, and 243 did not require mechanical ventilation. A hundred patients followed the inclusion criteria and included in the analysis. Figure 1 shows a flow chart for patients included in the study. Patients were divided into two equal groups fifty patients each. Group

A received a daily bolus omeprazole dose and group B received omeprazole continuous infusion. There was no significance difference regarding patients' demographic data ($P > 0.05$) (Table 1).

Variables	Group A (N=50)	Group B (N=50)	P value (T-test or chi-square test χ^2)
Age (years)	58.40 ± 5.43	57.65 ± 6.15	0.47
Weight (kg)	73.45 ± 6.93	74.39 ± 5.27	0.2
Height (cm)	170.45 ± 3.37	171.87 ± 2.45	0.39
BMI	26.90 ± 2.46	26.83 ± 2.87	0.29
Gender (male/female)	27/23	26/24	0.28
Admission APACHE II score	17.57 ± 2.73	17.84 ± 2.96	0.49
Admission SOFA score	5.45 ± 1.7	5.85 ± 1.2	0.41

Table 1: Patient's demographic data. *Statistical significance (values presented as mean ± SD).

ICU admission gastric pH (mean ± SD) was 4.68 ± 0.18 and 4.66 ± 0.14 for group A and B respectively with no statistical difference ($P = 0.38$). Gastric PH was significantly lower in group A compared to group B during the whole period of ICU stay. The daily gastric pH after starting omeprazole treatment is shown in Figure 2. There was no statistical difference regarding residual gastric fluid volume between both groups at any day during ICU stay ($P > 0.05$) Figure 3.

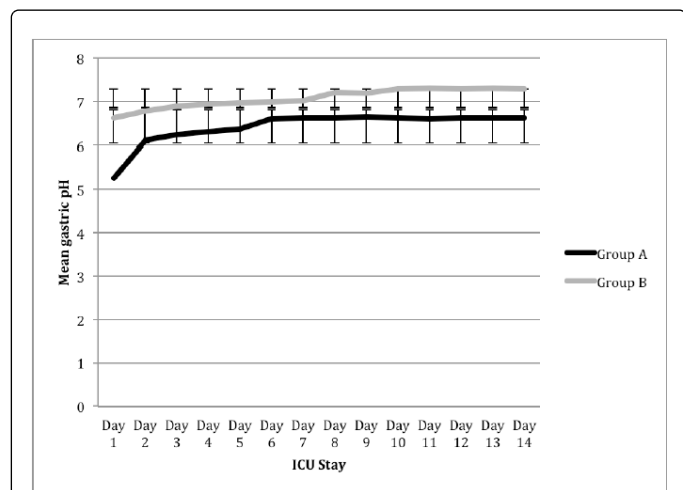


Figure 2: Mean gastric pH during ICU stay.

The number of cases developed clinically significant GIT bleeding was higher in group A compared to group B ($P < 0.05$). Different presentations of GIT bleeding and the number of cases are shown in Table 2. The number of patients required endoscopy for upper GIT homeostasis was statistically higher in group A compared to group B ($P < 0.05$). The mean ICU admission Hb level was comparable between both groups ($P = 0.65$). The mean ICU stay Hb level was significantly lower in group A compared to group B ($P < 0.05$). Group A received more RBCs units during ICU stay than group B ($P < 0.05$). The number of ICU days without ventilator was comparable between both groups

($P > 0.05$). The length of ICU stay was longer in group A compared to group B ($P = 0.02$). There was no statistical difference between the number of ICU survivors in both groups ($P = 0.24$). Table 2 shows ICU stay characteristics for both groups.

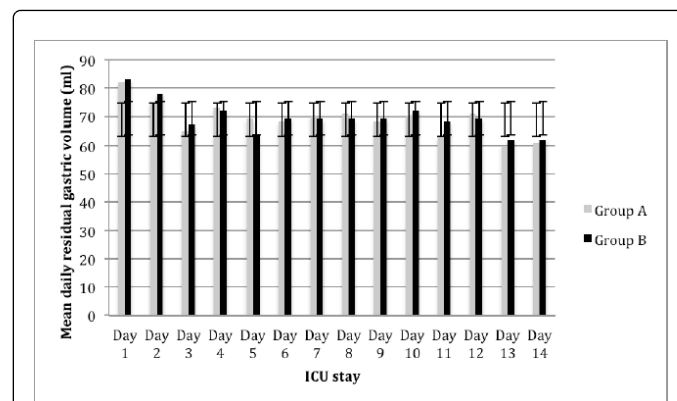


Figure 3: Mean daily residual gastric volume (ml) in ICU.

Discussion

It is not uncommon for critically ill patients to develop upper GIT bleeding at one stage of ICU stay. Increased gastric acidity is one of the risk factors for gastrointestinal bleeding due ulcers [1]. Few protocols have been established to reduce the incidence of upper GIT bleeding.

In the present study we compared the effect of low dose omeprazole versus high dose in mechanically ventilated patients. We found that patients on high dose omeprazole had higher gastric pH, lower incidence of critical significant GIT bleeding, higher ICU stay Hb, lower number of RBCs transfusion and shorter ICU stay.

Variables	Group A (50)	Group B (50)	p value
Clinical significant bleeding N (%)	13/55 (23.6%)	6/55 (10.9%)	0.02*
Nasogastric Fresh blood.	1/13 (7.7%)	0/6 (0%)	0.04*
Hematemesis	3/13 (23.1%)	1/6 (16.7%)	0.02*
Melena	8/13 (61.5%)	5/6 (83.3%)	0.01*
Haematochezia	1/13 (7.7%)	0/6 (0%)	0.04*
GIT endoscopy needed.	10/13 (77%)	3/6 (50%)	0.03*
ICU admission Hb (mean ± SD) g/dl	11.5 ± 1.8	11.6 ± 1.6	0.65
ICU stay Hb (mean ± SD) g/dl	7.5 ± 0.67	8.8 ± 0.89	0.04*
ICU red cell units transfused	6 ± 1.5	3 ± 1.2	0.03*
Number of ICU days without ventilator.	6 ± 1.7	5 ± 1.3	0.25
ICU stay (day)	12 ± 2.3	8 ± 1.5	0.02*
ICU mortality rate N (%)	11/55 (20%)	10/55 (18.2%)	0.58

Table 2: ICU stay characteristics. *Statistical significance.

Most of the studies have investigated the effect of different PPIs regimens as an adjuvant treatment for endoscopy in treating of upper GIT bleeding [14]. Very few studies have investigated the role of different antacids regimens in the prophylaxis of GIT bleeding.

Pang et al. reviewed some studies to investigate the use of PPIs in different medical scenarios [5]. The authors mentioned that PPIs are widely used in medical practice. The review did not reach a conclusion about the clinical relevance of keeping the gastric pH more than 6 in preventing upper GIT bleeding. In our study we measured gastric pH aiming to explore the clinical relevance of keeping the pH above 6. We found that higher gastric pH had a good clinical impact on decreasing the incidence of upper GIT bleeding.

Few studies have investigated the effect of different doses and medications on treatment but not the prophylaxis of upper GIT bleeding. Labenz et al. did a study to compare the effect of high dose ranitidine and omeprazole on gastric pH in patients with gastric ulcer [3]. The authors found that high dose omeprazole increased gastric pH with better patients' outcome. Our study agrees with Labenz et al. regarding the effect of high dose omeprazole on gastric pH. Platelets aggregation and better haemostasis occurs in high pH rather than low pH and bleeding. The gastric pH we achieved by treatment in our high dose omeprazole group was sufficient to reduce the incidence of gastric mucosa dysfunction.

Somberg et al. did a multicenter randomized trial to compare the use of intermittent PPI versus continuous cimetidine infusion in prophylaxis against upper GIT bleeding [15]. The advantage of our study over Somberg et al. is that we compared two different regimens of the same drug and one of these regimens is a common standard practice in most ICUs. Somberg et al. found that intermittent IV PPI is effective in controlling the gastric pH and protected patients against GIT bleeding [15]. In the present study we found that continuous PPI infusion had a superior effect than intermittent regimen.

In our literature review we could not find studies to show the effect of PPIs or gastric pH on the residual gastric volume in adults. However, Schmidt et al. studied the effect of gastric pH and its effect on gastric residual volume in children [16]. The authors found that alteration of gastric pH by fasting did not affect the residual gastric volume. Our results agree with Schmidt et al. however, we studied different group of adult patients and the pH was altered by medication and not fasting. In the present study we used a syringe pull technique, which is a weak point in the study because it might be not accurate method of measurement. Bartlett Ellis et al. did a study and concluded that syringe pull technique in estimating residual volume is inaccurate *in vivo* and should be investigated in patients [17,18].

Simon-Rudler et al. did a retrospective study to compare a high dose omeprazole versus standard dose [6]. The groups of patients studied were patients with gastric ulcer diagnosed by endoscopy. During the course of the treatment omeprazole was given orally and intravenously according to the authors' ICU protocols. The duration of omeprazole treatment was shorter than our study. The authors found that high dose omeprazole is superior to standard dose in patients with high risk GIT bleeding. Our study was similar to Simon-Rudler et al. [6]. We believe that our results are more of clinical evidence because of the study design and the uniform omeprazole formula given to both groups.

Zargar et al. [7] and Lau et al. [19] did two different randomized controlled trials to show the effect of high dose omeprazole versus placebo as an adjuvant to endoscopic treatment of duodenal ulcer. The

authors found that high dose omeprazole reduced the incidence of re-bleeding with reduction in the number of red cell units transfused. In the present study we found that high dose omeprazole decreased the number of red cell units in patients with high risk of GIT bleeding. From both studies we assume that prophylaxis and treatment of upper GIT bleeding with high dose omeprazole may have a massive impact on blood use in patients with risk GIT bleeding. None of the previous studies recorded the differences in Hb levels between groups, however, in our study we showed that ICU Hb level was higher in patients received high dose omeprazole.

In contrast to our study Sachar et al. and Wang et al. did two different systematic reviews and meta-analysis on intermittent versus continuous PPIs treatment patients with high risk of GIT bleeding [9,11]. The authors found that continuous infusion has no advantage over the standard routine bolus dose. The difference between our results and the reviews may be due to the difference in the aim of our study. The reviews primary aim was to investigate re-bleeding up to 30 days in patients with diagnosed upper GIT ulcer. In the present study we did not study the re-bleeding cases because our primary aim was to compare the prophylactic effect of different regimens of omeprazole but not a therapeutic effect.

Some authors studies the adverse effects from PPI. Osteoporosis, renal affection, pneumonia, iron and vitamins deficiency, and thrombocytopenia were reported in long-term use of PPI [20]. In the present study we did not collect data regarding PPI side effects because we studied patients for short period of time and most of the complications arise from long-term therapy.

In conclusion, gastric acid suppression is required in high-risk critically ill patients. Prophylactic high dose continuous omeprazole infusion is more effective than low standard dose to increase gastric pH and guard against upper GIT bleeding in high-risk patients in the critical care sitting. This regimen of treatment is more beneficial for patients with less bleeding, better ICU stay Hb, less red cell transfusion, and shorter time in ICU.

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