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## Comparison between the Preventive Effects of Ranitidine and Omeprazole on Upper Gastrointestinal Bleeding among ICU Patients

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### ABSTRACT

**Background:** Critically ill patients may develop visible gastric mucosal injury and stress ulcer soon after admission to an intensive care unit causing upper gastrointestinal bleeding as an important complication. Histamine-2 receptor antagonist (H2RA) prophylactic therapy has been documented to significantly decrease the incidence of upper GI bleeding in critically ill patients. This study was carried out in order to compare the effects of intravenous doses of ranitidine and enteral form of omeprazole suspension on preventing GI bleeding among ICU patients.

**Materials and Methods:** This study was a double-blind randomized clinical trial conducted on patients admitted to the ICU at the Imam Hossein Hospital in Tehran, Iran. The patients were randomly divided into two groups of A and B. In group A, ranitidine was used as the prophylactic drug against GI bleeding with the dosage of 50 mg two times a day accompanied by placebo gavages through nasogastric tube. In group B, 20 mg of a suspension of omeprazole two times a day was gavaged in addition to 2<sup>cc</sup> of a parenteral placebo drug. Of 198 patients admitted to the ICU, 69 patients did not meet the inclusion criteria and a total of 129 patients enrolled in this study.

**Results:** During the study 14(20.58%) cases in the ranitidine group and 3(4.9%) in the omeprazole group developed significant GI bleeding. Incidence of GI bleeding showed a significant difference between the two groups using the chi-square test. Of the 68 patients receiving ranitidine, 44 (67.7%) died. This rate was 38 in those receiving omeprazole (62%). Of the patients given ranitidine who faced overt GI bleeding, 12 (85.7%) died. This rate was 3 in the omeprazole group (100%).

**Conclusion:** This study showed a statistically significant difference between omeprazole and ranitidine in preventing overt GI bleeding among ICU patients; but it failed to indicate any difference in prophylaxis of clinically important GI bleeding between the two drugs. (Tanaffos 2009; 8(4): 37-42)

**Key words:** Gastrointestinal bleeding, ICU, Stress ulcer, Prophylaxis, Omeprazole, Ranitidine

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## INTRODUCTION

Stress-induced upper gastrointestinal (GI) bleeding is a well-recognized complication in critically ill patients, particularly in those requiring mechanical ventilation (1,2). Most critically ill patients, develop visible gastric mucosal injury soon after admission to an intensive care unit (3-6). Although stress-induced gastric injury seems to begin with impairment of mucosal defense and repair, presumably due to local ischemia, experimental studies suggest that, the presence of acid in the gastric lumen, is critical for the production of gross mucosal damage and bleeding (6-9).

Gastrointestinal bleeding due to stress ulceration is an important complication in critically ill patients (2,10,11) which may lead to high rates of mortality, morbidity and ICU stay (12-14). On the basis of the positive results of randomized trials (15-27), prophylactic measures such as neutralization of gastric acid and reduction of gastric acid secretion with Histamine-2 Receptor Antagonist Therapy (H2RA) have been documented to significantly decrease the incidence of upper GI bleeding in critically ill patients (10,28). Many randomized clinical trials were done to evaluate the preventive effects of cimetidine, ranitidine, and sucralfate on GI bleeding in different settings among which a double-blind, placebo-controlled, randomized trial on 131 critically ill patients in 1993 (10) showed that patients treated with intravenous cimetidine, had a significantly lower rate of upper GI bleeding than the placebo-treated group.

Proton pump inhibitors produce a more potent and longer-lasting inhibition of gastric acid and also have less interaction with other drugs than H2RAs. Proton pump inhibitors (PPI), such as omeprazole, have recently proved efficacious for stress-related GI bleeding prophylaxis and are used in many settings (11,28-30). Omeprazole is commercially available as a delayed-release capsule containing enteric-coated granules to protect against acid degradation.

Since mechanical ventilation is a major independent risk factor for GI bleeding in ICU patients, this study was carried out in order to compare the efficacy of intravenous doses of ranitidine and enteral omeprazole suspension to prevent overt and clinically important GI bleeding among mechanically ventilated ICU patients.

## MATERIALS AND METHODS

This study was a double-blind randomized clinical trial conducted on patients admitted to the ICU from June 2000 to January 2001 at the Imam Hossein Hospital in Tehran, Iran.

ICU patients, who had been under mechanical ventilation for a minimum of 48 hours, were recruited in this study. Using the table numbers randomly, all ICU beds were divided into two groups of A and B. This randomization design was used to avoid the patient selection bias by the ICU personnel. All the participants had nasogastric tube (NGT), which is a suitable monitoring for confirming the upper GI bleedings, if occur. Patients with pneumonia, current upper GI bleeding, previous gastrectomy, current usage of 2 doses of prophylaxis, and those transported from another ICU ward were all excluded from the study. Written consents signed by the patients or their family members were obtained for participation in the study. Of the 198 patients admitted to the ICU, 69 patients did not meet the inclusion criteria and as a result, 129 patients enrolled in this study.

Internal and surgical cases were not separated in this study because being an internal or a surgical case per se, is not a major risk factor for gastrointestinal bleeding based on Cook's study (2).

In group A, intravenous ranitidine was used with 50 mg dosage two times a day accompanied by placebo gavages through nasogastric tube. In group B, 20 ml of a suspension of omeprazole two times a

day was gavaged in addition to 2cc of a parenteral placebo drug.

Omeprazole suspension was prepared by adding omeprazole granules gathered from the original drug shape (capsules) and water to apple sauce prepared with chopped apple. This substance prevents degradation of omeprazole granules by optimizing gastric acidity.

Two types of GI bleeding including overt and clinically important bleedings were evaluated in this study. If one of the following happens, the situation is called “overt GI bleeding”: hematemesis, coffee ground in NGT, melena or hematochezia. Overt bleeding in addition to at least one of the following items is called “clinically important GI bleeding”:

- A 20 mmHg decrease in systolic or diastolic blood pressure during the first 24 hours after bleeding
- A 20 bpm increase in heart rate or 10 mmHg in systolic blood pressure in a standing position
- A 2 gr/dl decrease of Hb or 6% HCT during the first 24 hours after bleeding
- Lack of increase in Hb after infusing 2 units of packed cell

Blood pressure, heart rate, respiratory rate, oral and auxiliary temperature, antibiotic usage, major surgery, dialysis, total parenteral nutrition, gastric gavage, corticosteroid usage, trauma, coagulation profile (PT, PTT and platelet count), sepsis profile (ESR, CRP) and renal function (BUN, Creatinine) were recorded along with demographic data, impressions, past medical and drug history. All medications prescribed for patients were adjusted according to their renal and hepatic functions.

SPSS11 software was used for data analysis.

## RESULTS

Of the 129 participants, 68 were included in group A (ranitidine group), and the remaining (61) in group B (omeprazole group). Patients' age in group A,

ranged from 5 to 85 yrs with the mean age of 49.19 yrs. Group B patients were in the age range of 5 to 95 yrs with a mean age of 52.41 yrs. No significant difference was found between the two groups in this regard. In the omeprazole group, there were 32(52.5%) males and 29(47.5%) females. These numbers were 35(51.5%) males and 33(48.5%) females in the ranitidine group.

Throughout the study 14(20.58%) given ranitidine and 3(4.9%) given omeprazole faced overt GI bleeding and this difference between the two groups was statistically significant using the chi square test ( $p < 0.05$ ). The frequencies of the two types of bleeding are demonstrated in Table 1.

Table 1. The frequency of the two types of bleeding among patients

Bleeding Group	Overt *		Clinically Important(%)
	Positive(%)	Negative(%)	
A	14(20.58)	54(79.41)	4(28.57)
B	3(3.9)	58(96.1)	1(33.34)

\* P value < 0.05

Average duration of hospitalization in ICU was 7.67 days ( $7.67 \pm 7.2$ ) in the omeprazole group and 6.16 days ( $6.16 \pm 8.04$ ) in the ranitidine group. This difference was not statistically significant. Table 2 shows the duration of hospitalization and mechanical ventilation.

Table 2. Mean ICU hospitalization days and mean duration of mechanical ventilation

Case Group	ICU Hospitalization(day)	Mechanical Ventilation(day)
A	$6.16 \pm 8.04$	$4.96 \pm 7.94$
B	$7.67 \pm 7.2$	$6.54 \pm 6.94$

P value > 0.05

Of the 68 patients receiving ranitidine, 44 (67.7%) died. This rate for patients receiving omeprazole was 38(62%). Of 14 patients given ranitidine who faced overt GI bleeding 12 (85.7%) died. This rate was 3

(100%) for the omeprazole group. Fisher exact test showed no significant difference in the mortality rate between the two groups.

Considering some major risk factors of GI bleeding including renal failure and coagulopathy, fisher exact test showed that the incidence of renal failure and coagulopathy was not significantly different between the two groups. Other risk factors showed no significant difference between the two groups either as demonstrated in Table 3.

Table 3. Major risk factors in patients

Groups Risk factors	Ranitidine	Omeprazole	Significance
Hx of GI bleeding	10(14.7%)	9(14.8%)	0.99
Coagulopathy	5(7.4%)	3(4.9%)	0.57
Hypotension	3(4.4%)	4(6.6%)	0.7
Sepsis	6(8.8%)	8(13.1%)	0.43
Renal failure	9(13.2%)	5(8.2%)	1.0
Gavage	34(50%)	37(60.7%)	1.0
Corticosteroid	39(57.4%)	28(45.9%)	0.19
Major surgery	40(58.8%)	34(55.7%)	0.72
Dialysis	4(5.9%)	2(3.3%)	0.8
TPN	1(1.5%)	1(1.6%)	1.0
Hx of anti ulcers	13(19.1%)	8(13.1%)	0.36
Head trauma	19(27.9%)	12(19.7%)	0.27
Multiple trauma	8(11.8%)	4(6.6%)	0.31

P-value > 0.05

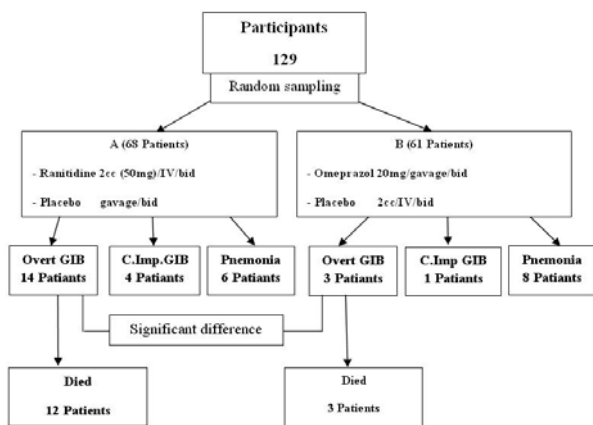


Figure 1. Flow diagram of the subjects' progress through the phases of the study

## DISCUSSION

Based on current findings, GI bleeding is one of the major causes of increased mortality and morbidity rates as well as ICU hospitalization and its related costs. Many researchers have tried different preventive strategies and various medications to solve the mentioned complications of GI bleeding. The majority of these studies only got conflicting results in this regard.

In a survey by Daley and colleagues (31) in America on 2000 physician members of the society of critical care medicine (SCCM), it was shown that H2RAs were the initial therapy for preventing GI bleeding between 1995 and 1999 which have been replaced by PPIs during the recent years because of their permanent effects on parietal cells, increased availability and marketing and also flexibility in administering different formulations.

Jung and co-workers (32) in their study in 2002 stated that PPIs could be an alternative therapy for H2RAs in preventing GI bleeding among mechanically ventilated ICU patients.

We designed this study according to the randomized control trial conducted by Cook D.J. (33, 34) and colleagues comparing the prophylactic effects of ranitidine and sucralfate on upper gastrointestinal bleeding among ICU patients in 1998. NG tube monitoring was applied for confirming upper GI bleeding besides the defined criteria to identify this problem. We, (like many previous studies on this topic specially Cook's work) did not evaluate gastric acidity and only focused on the degradation effect of gastric acid on omeprazole granules. Apple sauce-based omeprazole suspension solved this problem by optimizing the PH in the stomach. Our randomized control trial supported the priority of omeprazole in preventing stress ulcer and overt upper GI bleeding among ICU patients in comparison to ranitidine.

There was no significant difference between the two drugs in preventing the clinically important GI

bleedings. However, omeprazole might be a better choice for preventing upper GI bleeding considering its ability to suppress gastric acidity more efficiently (6-10 times) compared to H2-blockers in non-ICU settings, exceeding interactions of H2-blockers with other drugs, no need for adjustment in renal failure cases, and less drug tolerance compared to H2-blockers. The recent increase in usage of PPIs mentioned by Daley and their aforementioned merits would make them more popular prophylactic agents compared to H2RAs, although there was a low significant difference between PPIs and H2RAs in terms of effectiveness.

In this study we only focused on the rate of GI bleeding after prescribing the two drugs and not their availabilities, mechanisms of effects or difficulties of usage. The other most important limitations of the current study were the low sample size and being single-central which did not allow us to generalize our findings. Therefore, further studies with larger sample sizes through multi-central clinical trials are required on this matter.

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