Research Article

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Comparing efficacy of enteral nutrition plus ranitidine and enteral nutrition alone as stress ulcer prophylaxis

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Aim: Adequacy of enteral nutrition (EN) alone as stress ulcer prophylaxis (SUP) is controversial. The aim of this study was to compare efficacy of EN alone and ranitidine plus EN as SUP. **Method:** Critically ill adults with indications to receive SUP were randomized to ranitidine 50 mg IV every 8 h plus EN (SUP) or EN alone (non-SUP) group for 7 days. Besides, endoscopy was performed at the time of recruitment and on day 7. **Results:** During the study period, only one patient in each group of SUP and non-SUP experienced gastrointestinal bleeding. At the time of recruitment, gastric erosion and erythema were the most endoscopic findings in the SUP and non-SUP groups. These findings did not significantly change at the end of the study (p = 0.21). **Conclusion:** EN was at least effective as ranitidine plus EN as SUP.

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Keywords: enteral nutrition • prophylaxis • ranitidine • stress ulcer

Critically ill patients are at increased risk for stress-related ulcer and subsequent gastrointestinal (GI) bleeding. Severity of acute illnesses, organ failure, medications, hemodynamic instability, hypoxemia, vasopressors, mechanical ventilation and long term fasting are main predisposing factors for stress ulcer in these patients [1–3]. Although upper GI lesions were detected within 3 days of intensive care unit (ICU) admission in most critically ill patients but bleeding was uncommon [4–7]. Depending on depth and distribution of the lesions, stress ulcers can lead to significant hemodynamic instability [8–11]. Clinically significant GI bleeding was reported in 2–4% of critically ill patients [12–15].

Catecholamine release, vasoconstriction, hypovolemia, decrease in cardiac output, inflammatory cytokines, endothelin and decrease in nitric oxide production, moves blood away from viscera to vital organs and leads to GI mucosa ischemia [17–20]. Prolonged splanchnic hypoperfusion decreases bicarbonate production, GI motility and thereafter delayed acid clearance that interfere with mucosal healing [19–26]. According to American Society of Health-System Pharmacists recommendations, ventilation more than 48 h and coagulopathy are two main predisposing factors for stress related mucosal bleeding in critically ill patients [27,28].

For more than 40 years, stress ulcer prophylaxis (SUP) was proposed to prevent mucosal damage and GI bleeding in acute illnesses [29–31]. SUP is recommended to maintain gastric pH above 4, that has been proven to reduce the risk of mucosal injury and GI bleeding [26,32]. However, widespread use of acid suppressing agents was associated with serious complications such as pneumonia and *Clostridium difficile* infection [33–36].

Following restoring of blood flow and stimulating epithelial cells renewal, enteral nutrition (EN) has critical role in preventing mucosal atrophy and GI bleeding. It is highly recommended to start EN within 24–48 h of ICU admission [30,37–39]. However, effect of EN on gastric pH has not been fully described [31,40,41].

Future Medicine

Adequacy of EN alone as SUP in critically ill patients has not been yet compared with ranitidine plus EN. The aim of this study was to compare efficacy and safety of EN alone and ranitidine plus EN as SUP in critically ill patients.

Method

Design

This open-label randomized clinical trial was performed from May 2016 to June 2017 in general ICU of Imam Khomeini Hospital Complex, a tertiary academic hospital, affiliated to Tehran University of Medical Sciences, Tehran, Iran. The study was approved by the Ethical Committee of Tehran University of Medical Sciences (Ethical code number: IR.TUMS.REC.1395.2592) and all recruited patients or one of their first-degree family members signed the study informed consent. The study also was registered as a clinical trial (IRCT code number: IRCT201604213449N21).

Patients

Adult (≥18 years old) critically ill patients were assessed within 24 h of ICU admission and who had indications to receive SUP [27,28] with no contraindication for starting EN were recruited. Patients with EN intolerance (defined as gastric residual volume more than 200 ml between the gavage schedules), severe burn, recent (during last month) GI bleeding, history of gastric ulcer, gastric or duodenal ulcer on endoscopy, receiving therapeutic dose of anticoagulants or corticosteroids and closed head trauma were excluded.

Intervention

Patients were assigned to receive either ranitidine 50 mg every 8 h as slow intravenous injection plus EN (SUP group) or only EN without ranitidine (non-SUP group) according to the simple randomization method. Random numbers were generated using excel software. Nutritional support was started within 24 h of ICU admission. Each patient received a standard EN formula (EnteraMeal product, Karen Company, Tehran, Iran) through a nasogastric tube. Each serving size (1 scoop = 33 g) of the formula provide 150 Kcal and contain 20.5 g carbohydrate, 5.3 g protein, 5.3 g total fat, vitamins and minerals. Enteral feeding was started as 50 ml every 3 h and gradually was increased to the nutritional goal (200–250 ml every 3 h or 25 kcal/kg/day) during the first 24 h. Each dose of formula was administered through nasogastric tube as intermittent bolus nutrition. The duration of intervention was 7 days and patients were followed for 28-day ICU complications.

Demographic data, baseline diseases, cause of ICU admission, severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] score), organ function (Sequential Organ Failure Assessment [SOFA] score), vital signs (temperature and hemodynamic parameters), oxygenation status (arterial blood gas [ABG]), laboratory parameters (cell blood count, partial thromboplastin time, international normalized ratio) and medications were collected from the patients' medical records and daily ICU charts. Also daily calorie and protein intakes of patients were calculated.

Bedsides, endoscopy was performed at the time of recruitment and on day 7. Primary endpoint of the study was incidence of GI bleeding. Episodes of pneumonia, diarrhea and sepsis were considered as secondary end points. Duration of ICU stay and 28-day mortality also were assessed in this study.

Patients were daily assessed for any episode of overt GI bleeding (coffee ground gastric secretions, hematemesis or melena), respiratory infections (pneumonia), sepsis and diarrhea. Coffee ground was defined as brown blood spots in gastric lavage. Criteria for pneumonia were new or progressive lung infiltration on chest imaging and at least two of the following; purulent secretions, temperature above 38.5°C, positive tracheal or plural fluid culture, leukocytosis or leukopenia [42]. If diarrhea occurred, stool was evaluated for *C. difficile* toxins using ELISA. Sepsis was considered if criteria of international guideline for management of severe sepsis and septic shock were met [43].

Statistical analysis

All statistical assessments were done using SPSS version 17 software. Normal distributions of variables were checked according Kolmogorov–Smirnov test. Continuous data were expressed as mean ± standard deviation (SD) and categorical data were presented as percentage. Independent *t*-test and χ^2 test (or Fisher's exact test in cases which more than 25% of categories had expected frequencies under 5) were used for the comparison of patients' continuous and categorical data, respectively. The $p < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics of patients†.

Parameter; mean ± SD or n (%)	SUP (n = 25)	Non-SUP (n = 25)
Age (years)	68.60 ± 15.58	60.00 ± 18.82
Sex (female:male)	11:14	9:16
Weight (kg)	71.36 ± 11.00	68.08 ± 11.33
APACHE (mean ± SD)	18.28 ± 5.31	17.12 ± 5.43
SOFA (mean ± SD)	8.76 ± 3.38	7.56 ± 2.04
Baseline diseases		
None	4 (16)	5 (20)
CVD	16 (64)	17 (68)
DM	1 (4)	9 (36)
Respiratory diseases	3 (12)	3 (12)
CKD	3 (12)	1 (4)
Neurologic diseases	2 (8)	1 (4)
Rheumatologic diseases	3 (12)	1 (4)
Causes of ICU admission		
Respiratory failure	12 (48)	10 (40)
Hemodynamic instability	9 (36)	11 (44)
Loss of consciousness	4 (16)	4 (16)

†Baseline characteristics of patients were compared. No statistically significant difference was detected between the groups. The p-values for all comparisons were over 0.05.
APACHE: Acute Physiology and Chronic Health Evaluation; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DM: Diabetes mellitus; ICU: Intensive care unit; SD: Standard deviation; SOFA: Sequential Organ Failure Assessment; SUP: Stress ulcer prophylaxis.

Results

Comparing demographic & baseline data

During the study period, 69 patients were screened for enrollment and 11 individuals did not have inclusion criteria of the study. From included patients, eight patients were excluded due to EN intolerance, ICU discharge and death (Figure 1). Finally 50 patients (25 patients in each group) completed the study period. From included patients, 30 (60%) and 20 (40%) were male and female respectively (p = 0.38). Mean ± SD of age of patients in the SUP and non-SUP groups were 68.60 ± 15.58 and 60.00 ± 18.82 years, respectively (p = 0.85). Cardiovascular diseases (66%) and diabetes mellitus (20%) were common baseline diseases and respiratory failure (44%), hemodynamic instability (40%) and loss of consciousness (16%) were main causes of ICU admission. Baseline diseases, cause of ICU admission, APACHE and SOFA scores, laboratory and clinical parameters are summarized in Tables 1 & 2. There was no statistically significant difference between the groups regarding the baseline patients' characteristics. Heparin prophylaxis (92 vs 90%), antibiotics (92 vs 100%), N-acetylcysteine (32 vs 40%), vasopressors (32 vs 28%) and antiepileptic drugs (24 vs 28%) were common administered drugs in the SUP and non-SUP groups respectively (p = 0.10).

Mean daily calorie and protein intakes in patients in SUP and non-SUP groups were comparable [(1416.80 ± 542.61 vs 1497.00 ± 551.75 Kcal/day) and (52.30 ± 18.24 vs 56.41 ± 20.46 g/day), respectively].

Primary end points

Coffee ground secretion (GI bleeding) was detected in one patient in each group of SUP and non-SUP (p = 0.75). At the time of recruitment, gastric erosion and erythema were the most endoscopic findings in the SUP and non-SUP groups (8 and 16% vs 4 and 12%, respectively, p = 0.34). These findings did not significantly change at the end of the study (12 vs 12% and 12 vs 8%, respectively, p = 0.21).

Secondary end points

There was no significant difference between the groups considering pneumonia, sepsis and diarrhea episodes (Table 3).

Days of mechanical ventilation in SUP and non-SUP groups were 11.60 ± 7.43 and 15.04 ± 7.17, respectively (p = 0.10). Length of ICU stay was comparable between the groups (15.19 ± 12.81 vs 13.00 ± 11.98 days,

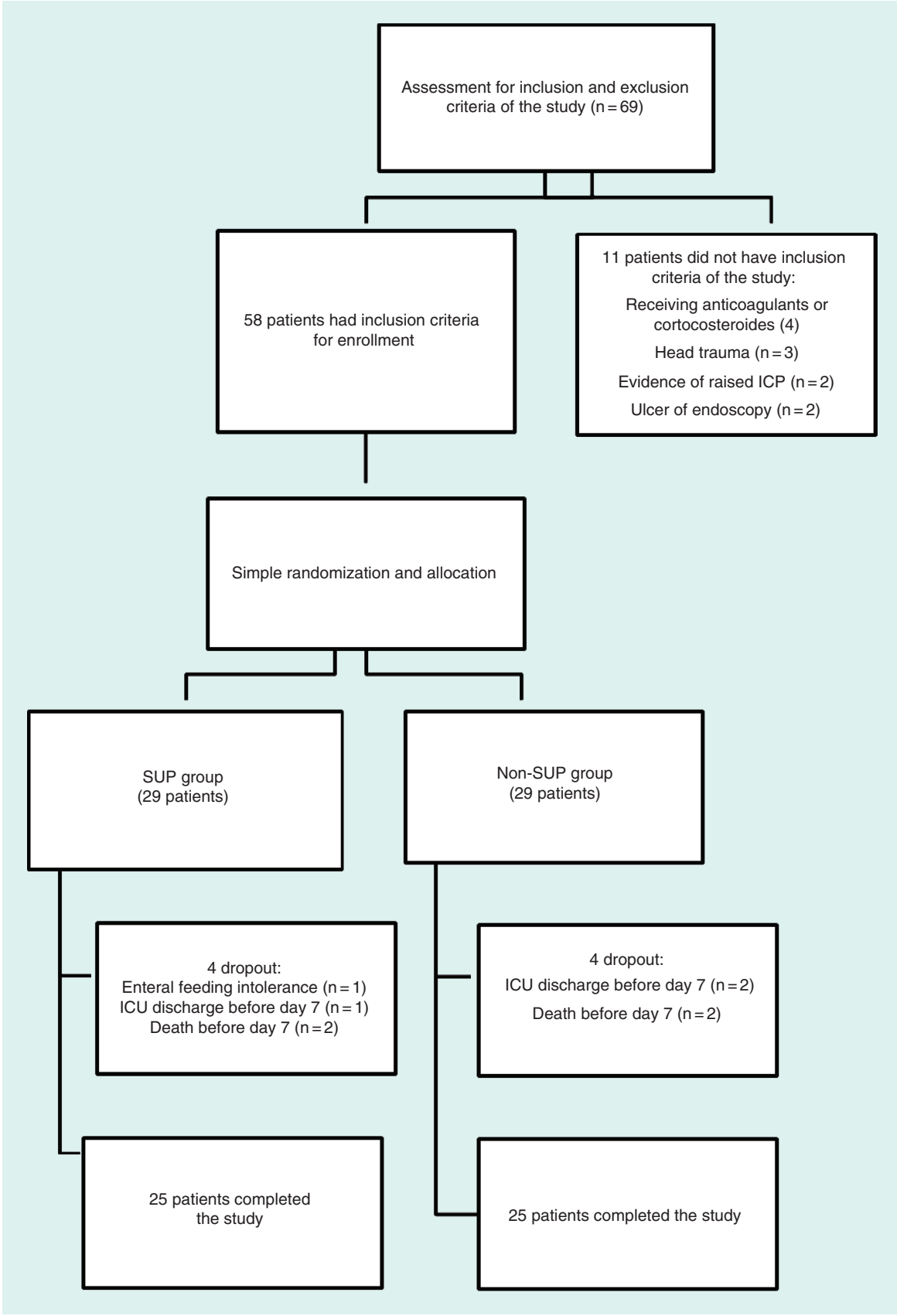

Figure 1. Consort flowchart of the study.
ICU: Intensive care unit; SUP: Stress ulcer prophylaxis.

Table 2. Laboratory parameters of patients†.

Parameter	SUP (n = 25)	Non-SUP (n = 25)
Patients with at least one episode of acidosis	8 (32)	8 (32)
Patients with at least one episode of alkalosis	17 (68)	13 (52)
Patients with at least one episode of leukopenia	4 (16)	1 (4)
Patients with at least one episode of leukocytosis	20 (80)	22 (88)
Patients with at least one episode of anemia (Hgb under 7 g/dl)	3 (12)	6 (24)
Patients with at least one episode of thrombocytopenia	10 (40)	10 (40)
Mean arterial pressure (mmHg)	91.12 ± 8.92	91.40 ± 9.10
Patients with coagulopathy	14 (56%)	11 (44)
Urea (mg/dl)	77.67 ± 42.40	53.57 ± 26.44
Serum creatinine (mg/dl)	1.33 ± 0.58	1.13 ± 0.44
INR	1.44 ± 0.41	1.30 ± 0.42
Albumin (g/dl)	2.31 ± 0.54	2.75 ± 0.56
Total bilirubin (mg/dl)	0.98 ± 0.54	0.90 ± 0.55
Alanine aminotransferase (U/l)	44.37 ± 22.87	41.16 ± 31.11
Aspartate aminotransferase (U/l)	32.80 ± 16.60	51.16 ± 28.20
Alkaline phosphatase (U/l)	241.40 ± 75.00	289.67 ± 88.19

†Laboratory parameters of patients were compared at the time of recruitment. For all comparisons p-values were more than 0.05.
Hgb: Hemoglobin; INR: International normalized ratio; SUP: Stress ulcer prophylaxis.

Table 3. Primary and secondary end points of the study†.

Endpoint	SUP (n = 25)	Non-SUP (n = 25)
Pneumonia (%)	9 (36)	7 (28)
Other infections (%)	3 (12)	6 (24)
Clostridium difficile diarrhea		
Sepsis (%)	4 (16)	3 (12)
Coffee ground	1 (4)	1 (4)
Hematemesis	–	–
Melena	–	–

†GI bleeding (coffee ground, hematemesis and melena) and infections (pneumonia, sepsis, *C. difficile* and other infections) were considered as primary and secondary end points of the study respectively. No statistically significant difference was detected between the groups. All p-values were more than 0.05.
SUP: Stress ulcer prophylaxis.

respectively; p = 0.57). In this study, 28-day ICU mortality rates in SUP and non-SUP groups were 32 and 20%, respectively (p = 0.26).

According to incidence of GI mucosal injury in critically ill patients [4–7] and considering $\alpha = 0.05$ and $\beta = 0.80$, the sample size of the study was calculated as 29 patients in each group. However, eight patients were excluded during the study period. Therefore, the power of study was calculated as 71%.

Discussion

This was the first study that compared EN alone and ranitidine plus EN in preventing stress-related mucosal injuries in critically ill patients. In this study, EN alone was effective as ranitidine plus EN as SUP. GI bleeding episodes did not differ between the SUP and non-SUP groups.

Imbalance between aggressive and defensive mucosal factors is proposed as mechanism of stress-related mucosal injury. Gastric acid overproduction and reflux of acid toward stomach are main known aggressive factors. Mucosal integrity, blood flow, bicarbonate secretion and epithelial cells renewal are the most effective defensive parameters [27,44]. Restoring blood flow to gastric mucosa has critical role in preventing mucosal damage. Early EN, adequate hydration, oxygenation and hemodynamic supports are main factors that regulate gastric mucosal perfusion [26]. Starting EN, as soon as possible, decreased incidence of stress ulcer in critically ill patients [16,45]. By enhancing gastric blood flow, increase in gastric PH and decreasing mucosal ischemia, EN showed important role

in preventing of stress ulcer in critically ill patients [5,31]. Another important effect of early EN is repairing and retaining mucosal integrity through GI tract. This property also prevents bacterial and endotoxins translocation via mucosal barriers [38,44]. Pharmacological agents (proton pump inhibitors and histamine type-2 receptors blockers) that routinely used for SUP do not have any direct effect on mucosal integrity and the defensive barriers.

Critically ill patient with trauma who received EN within 24 h of ICU admission had much lower mucosal permeability than the control group [46]. EN stimulates cell renewal pathway and epithelialization [19,47].

Protective effect of EN against stress ulcer was compared with antacids and cimetidine in 1983. In this study, EN was more effective than antacids and cimetidine in preventing GI bleeding [48]. In recent published study, pantoprazole did not add more benefit than EN for prevention of stress ulcer in critically ill patients [49].

In our study also no patient experienced significant GI bleeding. Coffee ground secretions detected in two (4%) of the patients. None of these patients had ulcers in repeated endoscopy.

In a study in 2013, Palm *et al.* discontinued SUP in critically ill patients who tolerated EN. GI bleeding was considered as endpoint of the study. In this study, the incidence of clinically important GI bleeding was 0.5%. They concluded that pharmacologic SUP can be stopped in surgical and trauma critically ill patients when tolerate EN [22]. In a randomized double-blind clinical trial in 2016, no significant difference in the incidence of overt GI bleeding, pneumonia, *C. difficile* diarrhea or days of ICU stay was detected in patients who received EN or pantoprazole [16].

However, in an old study, patients who received EN as SUP experienced more GI bleeding events. Although this study had control group but the patients were not randomly included. Patients in the EN group were older and had more predisposing factors for GI bleeding than the control group [50].

Although patients with burn or head trauma had severe stress and other risk factors for stress-related mucosal injury, but EN exhibited prophylactic effect. Severely burn patients who were under EN support had less bleeding events than those received cimetidine or antacid [51].

Comparing with parenteral nutrition, EN was more effective in preventing GI bleeding episodes in head trauma patients. Also sepsis was more common in the parenteral nutrition group than the EN group. GI tract is one of the main sources of bacteria and endotoxins that following translocation can cause nosocomial infections and sepsis. Delaying in initiation of EN may cause GI mucosal atrophy. On the other hand, acid suppressing agents promote GI bacterial replication and growth by increasing intragastric pH. These two parameters are main factors that facilitate bacterial translocation in patients who received parenteral nutrition concomitant with pharmacological SUP [47].

Respiratory tract infection (pneumonia) is the most common infection in critically ill patients. Aspiration is main route for entrance of bacteria to respiratory system. Critically ill patients are more vulnerable to aspiration pneumonia due to baseline diseases, severity of illnesses, intubation, position on bed, medications, interventions, feeding intolerance and ileus. Delay in initiation of EN was associated with increased risk of pneumonia [52].

Delay in starting EN is commonly due to concerns regarding vomiting and risk of aspiration. However, in patients with secured airway early initiation of EN is logical [53].

Correlations between use of pharmacologic SUP and increasing risk of aspiration pneumonia and *C. difficile* infection have been reported in other populations [7,54]. Gastric acidity is a natural defense against bacteria replication through GI tract. Spores of *C. difficile* bacteria but not vegetative (pathogenic) forms are stable in acidotic gastric PH. In alkaline conditions, vegetative forms were 10-fold more than spores [55]. Risk of *C. difficile* infection has not been compared between EN and acid suppressing agents in well-designed, controlled, paralleled study. However, no episode of *C. difficile* associated diarrhea was detected in our study.

Our study was first one that compared EN alone and EN plus ranitidine as SUP in critically ill patients. Also for the first time bedside endoscopy was applied for evaluation of the effectives of SUP in this setting. However, this study had some limitation. It was an open labeled, no placebo-controlled study with limited sample size. Also gastric PH monitoring was not considered in this study.

Conclusion

Few studies compared EN and acid suppressants agents as SUP in critically ill patients. Effectiveness of EN or acid suppressants agents was assessed subjectively. No study considered endoscopy findings. In our study EN was at least effective as ranitidine plus EN in preventing stress-related GI bleeding. Also risk of complications including pneumonia, sepsis and diarrhea were comparable between the groups.

Future perspective

Only few studies support efficacy and safety of EN as SUP in critically ill patients. More well-designed multicenter studies with adequate sample size are required to define efficacy and safety of EN as SUP.

Summary points

- Critically ill patients are at increased risk for stress related ulcer and subsequent gastrointestinal (GI) bleeding. In this study, effectiveness of enteral nutrition (EN) alone and ranitidine plus EN as GI bleeding prophylaxis was compared in critically ill patients.

Methods

- Patients were assigned to receive either ranitidine 50 mg every 8 h as slow intravenous injection plus EN (SUP group; n = 25) or only EN without ranitidine (non-SUP group, n = 25). Bedsides endoscopy was performed at the time of recruitment and on day 7. Primary outcome of the study was incidence of GI bleeding.

Results

- During the study period number of patients with GI bleeding were comparable between the groups (p = 0.75). At the time of recruitment, gastric erosion and erythema were the most endoscopic findings in the SUP and non-SUP groups (8 and 16% vs 4 and 12%, respectively, p = 0.34). These findings did not significantly change at the end of the study (12 vs 12% and 12 vs 8%, respectively, p = 0.21).

Conclusion

- EN was at least effective as ranitidine plus EN in preventing stress related GI mucosal injury.

Financial & competing interests disclosure

This study is the result of a PharmD student thesis and supported by Tehran University of Medical Sciences, Iran. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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