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Enteral nutrition as stress ulcer prophylaxis in critically ill patients: A randomized controlled exploratory study

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ABSTRACT

Purpose: We investigated whether early enteral nutrition alone may be sufficient prophylaxis against stress-related gastrointestinal (GI) bleeding in mechanically ventilated patients.
Materials and methods: Prospective, double blind, randomized, placebo-controlled, exploratory study that included mechanically ventilated patients in medical ICUs of two academic hospitals. Intravenous pantoprazole and early enteral nutrition were compared to placebo and early enteral nutrition as stress-ulcer prophylaxis. The incidences of clinically significant and overt GI bleeding were compared in the two groups.
Results: 124 patients were enrolled in the study. After exclusion of 22 patients, 102 patients were included in analysis: 55 patients in the treatment group and 47 patients in the placebo group. Two patients (one from each group) showed signs of overt GI bleeding (overall incidence 1.96%), and both patients experienced a drop of >3 points in hematocrit in a 24-hour period indicating a clinically significant GI bleed. There was no statistical significant difference in the incidence of overt or significant GI bleeding between groups ($p = 0.99$).
Conclusion: We found no benefit when pantoprazole is added to early enteral nutrition in mechanically ventilated critically ill patients. The routine prescription of acid-suppressive therapy in critically ill patients who tolerate early enteral nutrition warrants further evaluation.

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1. Introduction

As early as 1969, Skillman et al. described lethal gastric bleeding in patients with a triad of hypotension, respiratory failure, and sepsis [1]. We now know that splanchnic hypoperfusion and mucosal ischemia play a major role in stress-related mucosal disease, a form of erosive gastritis [2,3]. Coagulopathy and respiratory failure have been identified as important risk factors in the pathogenesis of stress-related mucosal disease [4]. Endoscopic studies have shown that up to 25% of patients have gastric erosions on admission to the intensive care unit (ICU) and up to 90% on the third ICU day [5,6]. Despite the high incidence of endoscopic findings, clinically important bleeding has a much lower incidence reported between 0.1 and 8.5% [4,7-9]. When clinically important GI bleeding occurs, it may result in hemodynamic instability, an increased need for blood transfusions, prolonged ICU stay, and an increased mortality [10].

Stress ulcer prophylaxis (SUP) in ICUs has become the standard of care with up to 70% of mechanically ventilated patients admitted to the ICU receiving SUP [11,12]. Pharmacologic prophylaxis has traditionally involved medications such as histamine-2 receptor blockers (H2RB) and proton pump inhibitors (PPI). The widespread use of gastric acid suppressing agents has raised concern over loss of the protective bacteriostatic effect of gastric acid leading to a greater incidence of ventilator-associated pneumonias [13-15]. The increasing use of gastric acid suppressive therapy together with the use of broad-spectrum antibiotics has also been associated with an increased risk of *Clostridium difficile* infection (CDI) [16-20]. Suppression of gastric acid may facilitate the growth of pathogenic flora in the gastrointestinal (GI) tract, in addition to permitting the conversion from spores to vegetative cells that ultimately produce toxins [21].

Abbreviation: CBC, complete blood count; CDI, *Clostridium difficile* infection; EN, enteral nutrition; GI, gastrointestinal; GRV, gastric residual volume; H2RB, histamine-2 receptor blocker; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; Kcal, kilocalorie; PPI, proton pump inhibitor; PTT, prothrombin time; SAPS II, Simplified Acute Physiology Score II; SMRD, stress-related mucosal disease; SOFA, Sequential Organ Failure Assessment; SUP, stress ulcer prophylaxis.

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Animal studies have shown enteral nutrition (EN) to increase GI blood flow without increasing cardiac output [22-24], and provide protection against stress related GI bleeding [25]. Two studies using a murine model suggested that continuous enteral administration of elemental formulas significantly reduced the occurrence of macroscopic mucosal lesions, compared with enteral administration of an antacid or intravenous (IV) administration of an H2RB [26,27]. It has been proposed that continuous enteral nutrition is more likely to raise gastric pH above 3.5 than H2RBs and PPIs, and that early enteral nutrition is more effective in preventing overt GI bleeding than H2RB and antacids [14].

Some early reports supported the idea that early EN may be as effective as pharmacologic SUP agents [28,29]. More recently, a retrospective cohort analysis in trauma and surgical ICU patients disclosed no added benefit of PPIs once patients were tolerating enteral feeding [30]. This finding was confirmed by the POP-UP exploratory study in medical and surgical ICU patients that revealed no added benefit with the addition of PPIs to patients on enteral feeding [31]. Definitive recommendations regarding the role of EN for SUP are deficient, and most prospective trials are limited by design flaws and lack of consistency surrounding details of the EN feeding regimen [14].

We hypothesized that early enteral feeding could potentially play a preventative role for stress-related GI bleeding and conducted a prospective randomized controlled trial to determine if early-enteral nutrition alone suffices as GI prophylaxis in critically ill patients on mechanical ventilation. We also intended to investigate the difference in incidence of CDI.

2. Materials and methods

2.1. Study population

The study was conducted over a period of three years. The study started in July 2013 in the medical ICU of University of Louisville Hospital. In July 2014, a second recruitment site (medical ICU at Jewish Hospital) was added as a site for recruitment to enhance enrollment rate. The study was completed in September 2016. The University Hospital team included an academic ICU physician, a fellow, and internal medicine residents. The Jewish Hospital team included an academic ICU physician, a fellow, and a nurse practitioner or physician assistant. Identical ICU protocols were used at both ICUs. During the study period, all eligible patients were screened for inclusion in the study. Eligible patients included those who were 18 years or older who were expected to need mechanical ventilation for >48 h with no contraindications to EN within the first 24 h after admission to the ICU. Exclusion criteria included 1) evidence of GI bleeding during the hospitalization period prior to study enrollment, 2) admission to the ICU with primary diagnosis of burn injury, 3) closed head injury or increased intracranial pressure, 4) history of partial or complete gastrectomy, and 5) pregnancy, or lactation. The study was approved by the institutional review board (IRB#11.0170), and the study was registered on *clinicaltrials.gov*. (NCT01477320). Investigators obtained informed consent using the consent forms generated for the study.

2.2. Study design and protocol

This was a prospective exploratory randomized controlled trial that was conducted on consecutive critically ill patients on mechanical ventilation who were assigned to one of two groups: placebo group or treatment group. Sealed, opaque envelopes arranged in a computer-generated random order were prepared by the study investigators and handed over to the inpatient pharmacy, where they were opened sequentially to determine the patients' treatment assignments. Study drugs, either normal saline placebo or 40 mg IV pantoprazole, were indistinguishable and dispatched from the inpatient pharmacy. The study investigators, patients, medical and nursing staff were blinded from patient randomization.

Patients randomized to the treatment group received EN and a once daily dose of 40 mg of IV pantoprazole, while those randomized to the placebo group received EN and placebo. All study patients received the same EN formula: Vital AF 1.2 Cal® (Abbott Nutrition, Columbus, OH) (a small-peptide, fish oil structured lipids with Fructo-oligosaccharides). Caloric requirements were determined by a simple weight-based equation (25–30 kcal/kg/day) [32]. Enteral nutrition was initiated within 24 h of intubation and was delivered using a volume-based feeding protocol [33].

Gastric residual volumes (GRV) were checked every 4 h. EN was paused if GRV was >400 ml on two consecutive checks. If EN was paused, GRVs were checked every 2 h until GRV was <400 ml and EN was resumed. Patients who received <25% of their caloric requirements via the EN regimen by 72 h following enrollment were considered inadequately protected against stress gastropathy and given IV pantoprazole. In the event of an episode of hypotension or hypoxemia, during which the patient might be at risk for ischemic bowel, EN was paused and resumed as deemed necessary by the medical team, but patients remained blinded. In the case of an overt GI bleed, the care and management was deferred to the medical team and the study drug (placebo or pantoprazole) was discontinued and the patients remained blinded.

Subjects were monitored per usual ICU care for signs of overt or significant GI bleeding, using complete blood counts (CBC), partial thromboplastin time (PTT), international normalized ratio (INR) and, examination of the nasogastric aspirate and stool specimens. Overt GI bleeding was defined by the presence of coffee-ground aspirate in nasogastric tube or coffee-ground emesis, bloody secretions in nasogastric tube or hematemesis, melena or hematochezia. Significant GI bleeding was defined by a 3-point decrease in hematocrit within a 24-hour period with clinical signs of overt GI bleeding, or by an unexplained 6-point decrease in hematocrit in a 48-hour period. The investigation team followed all patients enrolled until discharge from the ICU or cessation of EN and successful initiation of oral feeds. Records were made of changes in hemoglobin, volume of feeds delivered, and clinical signs of bleeding on a daily basis.

2.3. Base line assessment and data collection

Initial patient data was gathered at the time of randomization. The principal reason for ICU admission, comorbid conditions, laboratory data, as well as demographic data was recorded. The use of medications prior to enrollment, such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, antacids, H2RBs, and PPIs were noted. Illness severity scores were assessed by the Simplified Acute Physiology Score (SAPS II) and the Sequential Organ Failure Assessment (SOFA). Hemoglobin concentrations, the use of packed red-cell transfusions, presence of coffee-ground or bloody aspirate in nasogastric tube and melena or hematochezia were recorded on a daily basis. Enteral nutrition was recorded as the goal volume of EN and the percent of the goal volume delivered daily. The incidence of CDI was also recorded whenever the diagnosis of CDI was made and confirmed with a positive toxin assay.

2.4. Outcome measures

The primary outcome was the incidence of overt or significant GI bleeding. Our initial secondary outcomes were the incidence of CDI and the cost to the pharmacy for care related to stress ulcer prophylaxis and treatment of GI bleeding. Since the cost data was not available, we reported only the incidence of CDI as a secondary outcome.

2.5. Statistical analysis

Descriptive statistics were performed. Categorical variables were reported using numbers and percent; continuous variables were reported

using an IQR and median. Contingency tables were created for categorical outcomes, with Fisher's Exact tests to compare placebo and treatment groups. Wilcox rank sum tests were performed for continuous outcomes. All statistics were performed using R software version 3.2.3.

3. Results

Patients admitted to the medical ICU who were expected to need mechanical ventilation for >48 h were assessed for eligibility. Between July 2013 and September 2016, 320 patients were screened for eligibility and 124 patients were consented and enrolled in the study. Of the enrolled patients, 22 had one day or less of data (tube feed was not started in most of these patients who were extubated soon after the study enrolment) and these patients were excluded (none of these patients developed any primary or secondary outcomes). All data analyses performed included 102 patients: 47 patients in the placebo group and 55 patients in the treatment group (Fig. 1). Baseline characteristics and severity of illness scores (SAPS II and SOFA) were similar in both groups (Table 1). Nutrition was recorded as total KCal of nutrition received per day, KCal per kilogram, and the volume of nutrition received compared to the calculated goal volume. The differences in enteral nutrition received by patients in treatment and placebo group were not statistically significant (Table 2).

Of 102 patients analyzed, 2 patients (a single patient in each group) developed overt GI bleeding. Both patients experienced a >3 point drop in hematocrit within a 24-hour period indicating significant GI bleeding. No patient experienced an unexplained 6 point drop in hematocrit in the absence of overt bleeding. Thus, the overall incidence of both overt and significant GI bleeding in our study was 1.96% (n = 2). There was no statistical significant difference in the incidence of overt or significant GI bleeding between the treatment and placebo groups (1.82% vs 2.13%, p = 0.99).

There were 4 patients diagnosed with *C. difficile* infection (CDI) in the study (one patient in the treatment group and 3 patients in the placebo group). The overall incidence of CDI was 3.9% (n = 4) with no statistical difference in the incidence of CDI between the treatment and placebo groups (1.82% vs 6.38%, p = 0.33). One of the 4 patients who developed CDI was eventually diagnosed with a GI bleed.

Fifteen out of the 102 patients enrolled in the study died in the hospital (7 in the treatment group and 8 in the placebo group) with an overall hospital mortality rate of 14.71%. The in-hospital mortality was not statistically different between treatment and placebo groups (12.73% vs 17.02%, p = 0.54).

Median length of ICU stay was 6 days (IQR: 4–9.5) in the treatment group and 7 days (IQR: 3.5–11.5; p = 0.35) in the placebo group. The median length of hospital stay was 11 days in both the treatment group (IQR: 7.5–21) and the placebo group (IQR: 7–17; p = 0.61). Median hemoglobin concentration during the study period was similar between the two groups and the number of patients with hemostatic dysfunction (international normalized ratio (INR) > 1.5, partial thromboplastin time (PTT) > 40 s, or platelet count < 100,000) at any point during study was also similar between the placebo and treatment groups (Table 3).

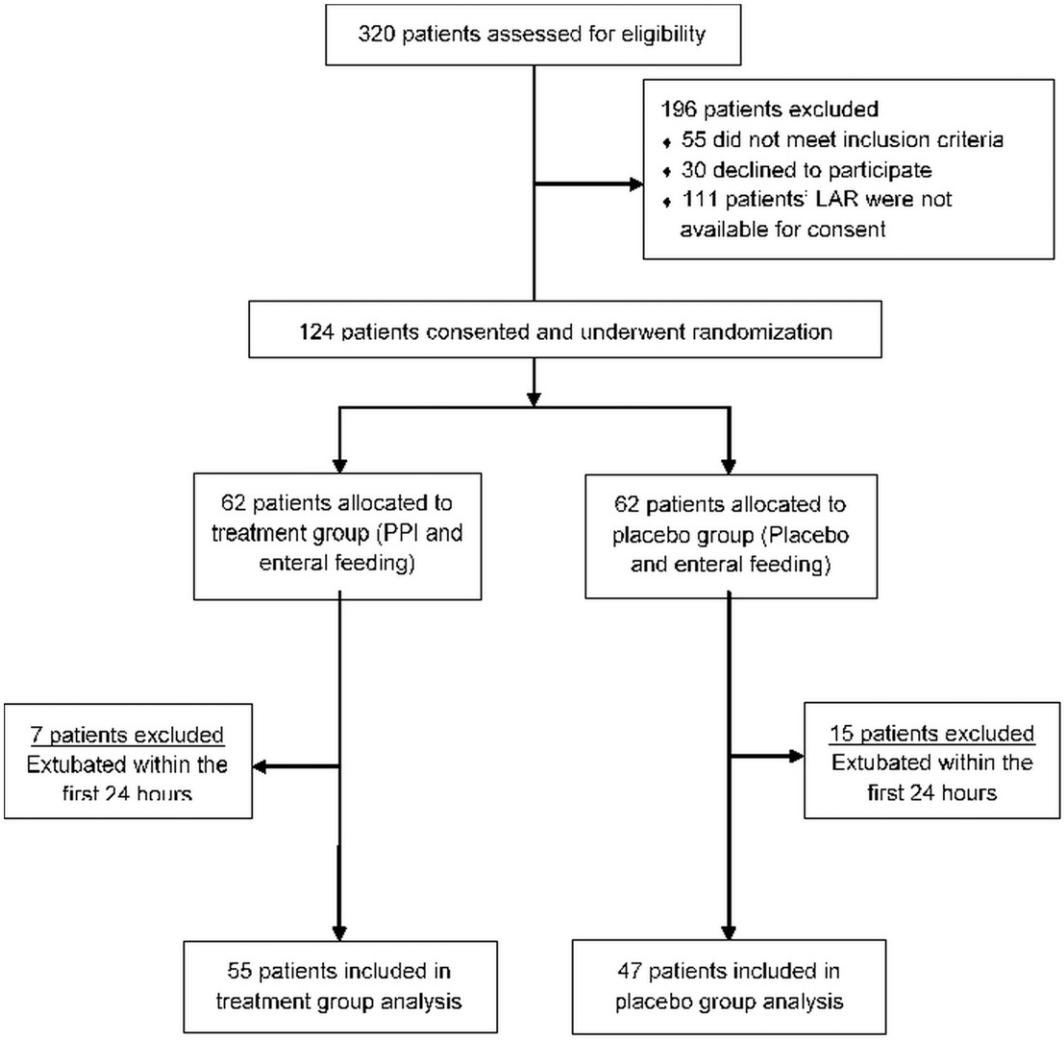

Fig. 1. Flowchart showing the enrollment process and details of patients excluded.

Table 1
Patients' characteristics at enrolment.

Data	Treatment (n = 55)	Placebo (n = 47)
Demographics		
Age, median (IQR)	62 (49.5–68)	58 (40.5–66.5)
Male gender, n (%)	30 (55)	28 (60)
BMI, median (IQR)	29.0 (22.8–34)	29.0 (23.8–34.2)
SAPS II score, median (IQR)	41.0 (34.5–53.0)	44.0 (34.0–54.0)
SOFA score, median (IQR)	7.0 (6.0–10.0)	7.0 (6.0–10.0)
Comorbidities		
CAD[a], n (%)	9 (16)	7 (15)
Heart failure, n (%)	7 (13)	12 (26)
CKD[b], n (%)	7 (13)	4 (9)
COPD, n (%)	18 (33)	7 (15)
Diabetes mellitus, n (%)	14 (25)	17 (36)
Other comorbidities, n (%)	44 (80)	38 (81)
Admission diagnosis		
Cardiac, n (%)	3 (5)	6 (13)
Neurologic, n (%)	11 (20)	9 (19)
Pulmonary, n (%)	28 (51)	25 (53)
Sepsis, n (%)	10 (18)	5 (11)
Other, n (%)	13 (24)	8 (17)
Reported pre-study history		
NSAIDS use within 1 week, n (%)	46 (84)	38 (83)
Corticosteroid use within 1 week, n (%)	52 (95)	45 (98)
Antacid use within 1 week, n (%)	53 (96)	46 (97)
PPI use within 1 week, n (%)	45 (82)	36 (78)
H2RB use within 1 week, n (%)	52 (95)	42 (91)

[a] Coronary artery disease.
[b] Chronic kidney disease.

4. Discussion

This was a prospective, randomized, double blind, exploratory study conducted over a period of three years in critically ill, mechanically ventilated patients who were admitted to the medical ICU and were expected to receive mechanical ventilation for >48 h. All patients received enteral nutrition within 24 h of intubation. Results indicated a low incidence of overt or clinically significant GI bleeding in our study (1.96%, n = 2) without a statistically significant difference between the treatment and the placebo groups.

Enteral nutrition, in addition to preventing malnutrition, has also shown to be protective against stress-related GI bleeding in animal and human studies [22-29]. A randomized-controlled trial by Selvanderan et al. studied 209 critically ill patients in medical and surgical ICUs found no benefit of pharmacologic prophylaxis with pantoprazole in critically ill mechanically ventilated patients anticipated to receive enteral nutrition in the first 24 h [31]. Of the 209 patients, there were no episodes of significant GI bleeding and a total of nine episodes of overt GI bleeding. Similar results were seen in a retrospective cohort analysis by Palm et al. with 200 patients in surgical and trauma ICUs with a 0.50% incidence of clinically significant GI bleeding after discontinuation of SUP in patients tolerating EN [30].

A meta-analysis by Krag et al. of 20 trials and over 1900 patients showed a statistically significant difference in GI bleeding in patients treated with SUP compared with those treated with placebo or no prophylaxis but this was not confirmed via trial sequential and subgroup analyses, endorsing that the quality and quantity of evidence for the use of SUP in adult critically ill patients is low and the need for larger randomized trials [34]. The REVISE trial was a pilot study that randomized 91 patients from 10 centers into pantoprazole vs placebo groups and found no difference in the rate of clinically important GI bleeding, verifying that there is no risk of increased bleeding without SUP [35]. A large multi-center trial is now underway (clinicaltrials.gov no. NCT02467621) comparing SUP to no prophylaxis, that will shed more light on the risks and benefits of SUP in the ICU [36].

The incidence of GI bleeding in the placebo group was 2.1% in our study, comparable to that reported by Krag et al. at 2.6% [12]. Other studies report a very low incidence of clinically significant GI bleeding and argue against SUP of any form. In a trial by Kantorova et al. comparing three different SUP regimens with placebo in high-risk ICU patients (mechanical ventilation >48 h and coagulopathy), no significant difference was found between treatment groups with an overall incidence of stress-related GI bleeding of 1% [37]. Zandstra et al. reported a 0.6% incidence of stress ulcer-related bleeding among 183 mechanically ventilated patients without any form of SUP [38]. Similarly, Faisy et al. disclosed a low incidence (1.1%) of clinically significant GI bleeding in patients without any form of SUP, and that SUP did not influence the incidence of clinically significant GI bleeding [39]. These studies highlight the low incidence of clinically significant GI bleeding and that pharmacologic SUP may not always be required to prevent bleeding in high-risk patients.

Stress-ulcer prophylaxis is not without risks. Acid suppressive therapy is associated with increased colonization of the upper GI tract with potentially pathogenic organisms that increase the risk of hospital-acquired pneumonia [13]. Marik et al. concluded in a meta-analysis that SUP increased the risk of pneumonia and death without reducing the risk of stress-related GI bleeding [14]. H2RBs and PPIs are often inappropriately continued after discharge from the ICU and hospital, leading to outpatient polypharmacy and additional cost [40]. Although various institutions have protocols in the ICU recommending discontinuation of SUP when enteral nutrition (EN) is started, a survey of 328 ICU physicians disclosed that only 51% discontinue pharmacologic prophylaxis when EN is initiated [41-43].

The rise in incidence of CDI in hospitalized patients during the last decade may be causally related to the generous use of gastric acid suppressive agents [44]. A dose dependent relationship has been identified between CDI and SUP that poses a greater risk after 2 days of PPI therapy [16]. In a randomized controlled trial by Lewis et al., patients taking fructo-oligosaccharide feedings were less likely to develop diarrhea than those taking the placebo [45]. We used a similar enteral nutrition formula and the incidence of CDI in our study (3.9%) was similar to the overall incidence of CDI reported in ICU patients [46]. A statistically significant difference was not seen in the incidence of CDI between the groups.

Our study had excellent randomization and blinding of all medical, research personnel, and patients to the intervention to reduce selection and performance bias. The slow enrollment was due to non-availability of legally authorized representatives (LAR) who had to be physically present in order to sign the consent for the study in the first 24 h after intubation. Although the reported usage of acid suppressive therapy prior to ICU admission was surprisingly high in our patient population, it did not translate into outcome difference between placebo and treatment group. Reporting acid suppressive therapy prior to ICU admission might have been overestimated since it was reported by family members and most of these medications are available over the counter.

Table 2
Characteristics of enteral feeding in the treatment and the placebo groups.

Enteral feeding	Treatment (n = 55)	Placebo (n = 47)	p-Value
Kcal/day delivered, median (IQR)	1728 (1584–1944)	1728 (1584–2016)	0.43
Kcal/kg/day delivered, median (IQR)	22 (17.44–26.85)	22 (18.075–25)	0.53
Daily volume received (mL), median (IQR)	699 (539.5–880)	715.5 (434–1081.9)	0.86
Total volume delivered (mL), median (IQR)	2540 (880–5493)	2914 (868–4236.5)	0.92
Percent of goal volume delivered, median (IQR)	55 (36.625–66.43)	64.38 (40.2–69.42)	0.26

Table 3
Patients' characteristics during the study.

Data	Treatment (n = 55)	Placebo (n = 47)	p-Value
Clinical data			
Duration of mechanical ventilation (days), median (IQR)	4 (2.2–7)	5 (3–8)	0.49
Hypotension (MAP < 65) at any point during study, n (%)	27 (49)	22 (47)	0.84
MAP in hypotensive patients, median (IQR)	58.8 (57–60.7)	57.8 (55.8–60.1)	0.36
Patients who received vasopressors during study, n (%)	30 (55)	19 (40)	0.17
Number of (PPI or Placebo) doses administered, median (IQR)	3 (2–7)	3 (2–6)	0.84
Patients received blood transfusions, n (%)	6 (13)	5 (14)	>0.99
Laboratory data			
Hemoglobin, median (IQR)	9.9 (8.6–11.2)	10.8 (8.9–11.5)	0.17
Hematocrit, median (IQR)	30.6 (26.7–35.9)	33.4 (29.4–36)	0.14
Platelet count, median (IQR)	195.8 (136.2–262.2)	234.8 (180.1–296.3)	0.02
INR, median (IQR)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.43
PTT, median (IQR)	34.2 (30–48.9)	34.9 (31–42.2)	1.00
Serum creatinine, median (IQR)	1 (0.8–1.8)	0.9 (0.8–1.4)	0.49
Serum albumin, median (IQR)	2.6 (2.1–3)	2.8 (2.5–3.3)	0.06
Patients who had INR > 1.5, PTT > 40, or platelet count < 100,000 at any point during study, n (%)	25 (45)	22 (47)	>0.99
Study Endpoints			
Overt GI Bleed, n (%)	1 (1.82)	1 (2.13)	0.99
Significant GI Bleed, n (%)	1 (1.82)	1 (2.13)	0.99
Incidence of CDI, n (%)	1 (1.82)	3 (6.38)	0.33

One limitation to our study is that it only included medical ICU patients on mechanical ventilation, thus these results may not be applicable to non-medical ICU patients. Another limitation is the absence of recording of antibiotic usage which can affect the incidence of CDI. Finally, larger studies are needed to confirm the findings from our exploratory study. Due to the low incidence of GI bleeding in the ICU in the current era, trials with larger sample sizes are needed to be powered to detect a statistically significant difference.

5. Conclusions

This study did not find an additional benefit of pharmacologic SUP when early EN is initiated in critically ill, mechanically ventilated patients in the medical ICU. These results add to the growing evidence supporting the protective role of early enteral nutrition in ICU. Larger clinical trials are necessary to corroborate our findings.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2017.08.036.

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