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Original Article

Early enteral nutrition reduced postoperative ileus and improved the outcomes in patients with emergency intestinal surgery: results from a propensity score analysis

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Abstract: Background: Enteral nutrition (EN), especially early enteral nutrition (EEN), could effectively increase the blood flow of gut mucosa, stimulate the intestinal motility, maintain the gut integrity, decrease the incidence of infectious complications, ameliorate patient's outcome after surgery. Thus, the aim of this study was to investigate the effect of EEN in patients with nontraumatic or traumatic intestinal strangulation or perforation after emergency surgery. Methods: From January 2005 to December 2016, patients underwent emergency intestinal surgery were selected. Patients with bowel resection and/or anastomosis or primary repair with traumatic or nontraumatic intestinal perforation were all included in this retrospective study. 603 patients who either received early EN (n=101) or received late EN (N=502) was analyzed. Results: Matching of patients according to propensity score resulted in a cohort that consisted of 86patients in the EEN group and of 86 patients in the late EN group. Compared with patients in the late EN group, patients receiving EEN had reduced the time of first defecation (P=0.02), early ileus rates (P=0.04), total patients with complications (P=0.03), lengths of hospital stay (P<0.01), in hospital mortality rates (P=0.03), and lengths of ICU stay (P=0.046). Furthermore, CRP decrease was more pronounced on postoperative day 5 in the EEN group compared with the late EN group (P<0.01). The multivariate analysis with Cox regression analysis suggested that EEN was an independent risk factor for the overall survival (P=0.011). Conclusions: EEN therapy in patients with emergency intestinal surgery significantly reduced total patients with complications, early ileus, time to first defecation, length of hospital stay, mortality and increased 28-day ICU-free days.

Keywords: Early enteral nutrition, late enteral nutrition, postoperative ileus, emergency intestinal surgery

Introduction

Nutritional support is beneficial during the metabolic and inflammatory phase, assisting in the amelioration of a patient's outcome after surgery [1-3]. Early start of oral nutrition is promoted in most patients undergoing gastrointestinal surgery and is an important part of fast-track surgery protocols [4]. Enteral nutrition (EN), especially early enteral nutrition (EEN), could effectively increase the blood flow of gut mucosa, stimulate the intestinal motility, maintain the gut integrity, prevent bacterial and endotoxin translocation, and decrease the incidence of infectious complications [5-7]. Furthermore, EEN within the first 24 hours postoperatively is beneficial and is even associated with reduced mortality rate in comparison to no caloric intake [8]. In addition, EN has been recommended in several studies to be started after the surgery as soon as possible, because EN allows patients for a faster recovery [9]. However, this early approach is not successful per se in all patients. Early start of EN is generally delayed after surgery because of a number of factors including postoperative nausea and vomiting, and a potential possibility of postoperative complications, such as ileus, obstruction, or anastomotic leakage.

Postoperative ileus (POI) is a common complication in patients with gastrointestinal surgery, which is accompanied by increased patient morbidity, increased use of parenteral nutrition,

Table 1. Constituents of Peptisorb liquid (per 500 mL)

Energy	500 Kcal	Se	28.5 ug
Maltodextrin	88 g	Vitamin A	0.41 mg
Hydrolyzed whey protein peptide	20 g	Vitamin B1	0.75 mg
Lipid (vegetable oil)	8.5 g	Vitamin B2	0.8 mg
K	0.75 g	Vitamin B6	0.85 mg
Na	0.5 g	Vitamin B12	1.05 ug
Ca	0.4 g	Vitamin C	50.0 mg
Mg	0.115 g	Vitamin D	3.5 ug
P	0.36 g	Vitamin E	6.5 mg
Cl	0.625 g	Vitamin K	26.5 ug
Fe	8.0 mg	Niacin	9.0 mg
Zn	6.0 mg	Pantotenic acid	2.65 mg
Cu	0.9 mg	Folic acid	0.135 mg
Mn	1.65 mg	Biotin	0.02 mg
F	0.5 mg	Choline	0.185 g
I	0.065 mg	Carotenoids	1.0 mg
Mo	0.05 mg	Taurine	0.05 mg
Cr	33.5 ug		

prolonged hospitalization, and increased costs [3, 10]. Manipulation of the intestines leading to a local inflammatory response is thought to be causative for the development of POI. Therefore, gastrointestinal surgery is often associated with a higher risk of delayed gastric emptying or POI [11]. A considerable proportion of these patients are offered total parenteral nutrition to reach nutritional goals because oral nutrition often fails during the first week.

A large number of patients in our hospital for emergency gastrointestinal surgery are malnourished at the time of admission, and enteral nutrition is not routinely used because of the edematous and paralytic characteristics of the bowel. Several studies demonstrated that EEN is also feasible after emergency gastrointestinal surgery, only if there are no contraindications to EEN such as intestinal malabsorption, obstruction, ischemia, bleeding, multiple fistulas with high output, severe shock with impaired splanchnic perfusion, and sepsis [12, 13]. Therefore, in the present study we mainly investigated the effect of EEN in patients with nontraumatic or traumatic intestinal strangulation or perforation after surgery.

Materials and methods

Study patients

This study was approved by the institutional review board of our hospital, and informed consent was waived. Medical records of 603 patients undergoing emergency intestinal surgery from January 2005 to December 2016 were included in this single-center retrospective study. Patients with bowel resection and/or anastomosis or primary repair with traumatic or nontraumatic intestinal perforation were all included in this study. Intestinal obstruction such as strangulation was also included. Furthermore, the traumatic injuries in all cases were stab wounds. In addition, patients with postoperative shock were also included in this study, and vasopressors were stopped receiving within 2 days postoperatively in all those patients. Patients with renal, cardiac, or hepatic failure at the time of admission, and patients undergoing cholecystectomy, appendectomy, or adhesiolysis without bowel resection and/or anastomosis were excluded. In addition, patients with short bowel syndrome, uncontrolled bowel perforation, or sustained bowel ischemia were also excluded.

Study design

Clinical factors and surgical outcomes were compared between the EEN group (n=101) and late EN group (n=502). Clinical factors of gender, age, American Society of Anesthesiologists score (ASA), Acute Physiology and Chronic Health Evaluation II score (APACHE II score) on intensive care unit (ICU) admission, diagnosis, operation type, location of lesion, presence of stoma, use of supplemental parenteral nutrition (PN), and degree of achievement target calorie were recorded. Blood samples were taken on the day before surgery and on days 1, 2, 3 and 5 after surgery to measure C-reactive protein (CRP). Surgical outcomes of complication types, complication rates, ICU-free days, ventilator free days (VFDs), mortality rates, and lengths of hospital stay were also assessed. Energy requirements were calculated either through Harris–Benedict equation or simplistic formula (25-30 kcal/kg) or. The target energy requirements were divided into >80% or <80% of goal calorie within 3 to 5 days after initiation EN alone or in combination with supplemental PN. Patients in the EEN group were inserted nasogastric or nasointestinal feeding tube to have EN all postoperatively and within 48 hours, and enteral nutrition used in this study was a commercially available Peptisorb Liquid (Nutricia, Amsterdam, the Netherlands), which is composed of maltodextrin, hydrolyzed whey protein peptide, fat, vitamins and trace elements. A summary of the composition of Peptisorb Liquid is shown in **Table 1**. The calorie density was 1 kcal/mL with an osmolarity of 400 mOsm/L. Late EN was defined as enteral feeding from 3 to 6 days after surgery. ICU-free days were defined as the number of days between successful transfer to a general ward and day 28 after surgery. If the patient died before day 28 or stayed in the ICU for ≥28 days, the ICU-free days were 0. VFDs were defined as the number of days between successful weaning from mechanical ventilation and day 28 after surgery. If the patient died before day 28 or required mechanical ventilation for ≥28 days, the VFDs were 0. The criteria to start EN included secure bowel anastomosis or repair, hemodynamic stability or declining doses of vasopressors, and no bowel ischemia observed during the surgery.

Complications

We described the most common surgical complications after emergency gastrointestinal surgery, such as wound infection, anastomotic leaks, intra-abdominal or pelvic abscesses, pneumonia, urinary tract infection, bacteremia and central catheter infection, and the number of reoperations or postoperative percutaneous intervention(s). Wound infection was defined as having experienced purulent exudate of a surgical wound with positive bacterial culture. Anastomotic leakage was defined as clinical suspicion of leakage of anastomosis, confirmed by CT scan showing free abdominal air and fluids in close proximity to the anastomosis or a visually dehiscent anastomosis at the time of reoperation. The number of leaks was also added to the number of abscesses to avoid debate in interpretation. An intra-abdominal or pelvic abscess was defined as an abscess diagnosed by ultrasound or CT scan, requiring operative or percutaneous drainage with the presence of pus. Urinary tract infection was defined as clinical symptoms and bacteriuria ($>10^5$ colony-forming units/ml). Pneumonia was defined as an abnormal chest X-ray or positive culture of tracheal aspirate associated with the presence of fever (>37.5°C). A central catheter infection was defined as a positive culture of a central catheter combined with a positive blood culture.

Postoperative ileus

Daily registrations of intake, nausea, vomiting, and the presence of a nasogastric tube or reinsertion within 5 days, gastric retention, and defecation were recorded postoperatively. To include more symptoms of POI than only the return of defecation, we designed another more extensive definition of ileus. POI was defined as early, late, and prolonged. Patients had an early ileus if 1 or more of the following symptoms occurred: nausea or vomiting for more than 1 episode in the first 5 days, reinsertion of the nasogastric tube in the first 5 days, presence of the nasogastric tube for more than 4 days, no return to normal diet after 5 days, or first-time normal defecation after 7 days. Prolonged ileus was defined as an early ileus lasting more than 5 days. Late ileus was defined as nausea or vomiting after the first 5 days, influencing normal intake and defecation, or reinsertion of the nasogastric tube.

Statistical analysis

Continuous variables are presented as mean ± standard deviations (SD) or median and interquartile range, as appropriate. Categorical variables are presented as frequencies and percentages. Continuous variables were compared using a t test when normally distributed, or otherwise using the Mann-Whitney U test. The χ^2 test or Fisher exact test was used for comparison of categorical variables. Propensity score matching was performed in order to reduce biases in patient selection. Propensity scores were estimated using a logistic regression analysis. The covariates included in the calculation were age, sex, location of lesion, APACHE II score, type of surgery, presence or absence of stoma, and provision of PN. A 1:1 matched analysis using nearest-neighbor matching with a caliper distance of 0.2 without replacement was performed based on the estimated propensity score of each patient. Multivariate Cox regression analysis was used for the survival analysis. All data were analyzed using the statistical package for social sciences (SPSS) version 17.0. Results were considered statistically significant if P values were <0.05.

Table 2. Characteristics of the total study population

	EEN (n=101)	Late EN (n=502)	*P* value
Female/male	65/36	316/186	0.79
Age, years	63.7±8.7	62.8±9.1	0.36
BMI, kg/m^2	22.1±3.5	21.9±3.3	0.58
ASA II/III	32/69	192/310	0.21
APACHE II score	18.2±3.2	17.9±3.1	0.38
Diagnosis, n (%)			0.48
Obstruction/strangulation	29 (28.7)	162 (32.3)	
Perforation	72 (71.3)	340 (67.7)	
Location of lesion, n (%)			0.87
Small bowel	47 (46.5)	229 (45.6)	
Colon and rectum	54 (53.5)	273 (54.4)	
Stoma, n	36 (35.6)	157 (31.3)	0.39
Postoperative shock, n (%)	19 (18.8)	98 (19.5)	0.87
Location of feeding tubes, n			<0.01
Nasointestinal tube	19 (18.8)	23 (4.6)	
Nasogastric tube	82 (81.2)	479 (95.4)	
PN, n (%)	72 (71.3)	467 (93.0)	<0.01
Achieving goal calorie, n (%)			0.92
≥80%	91 (90.1)	454 (90.4)	
<80%	10 (9.9)	48 (9.6)	

Table 3. Characteristics of propensity score-matched population

	EEN (n=86)	Late EN (n=86)	*P* value
Female/male	54/32	52/34	0.75
Age, years	62.9±8.8	63.5±9.0	0.66
BMI, kg/m^2	22.3±3.4	22.4±3.2	0.84
ASA II/III	25/61	29/57	0.51
APACHE II score	18.6±3.1	18.2±3.3	0.41
Diagnosis, n			0.86
Obstruction/strangulation	23	24	
Perforation	63	62	
Location of lesion, n			0.76
Small bowel	39	41	
Colon and rectum	47	45	
Stoma, n	29	30	0.87
Postoperative shock, n	14	10	0.38
Location of feeding tubes, n			0.18
Nasointestinal tube	10	5	
Nasogastric tube	76	81	
PN, n	67	68	0.85
Achieving goal calorie, n			0.58
≥80%	78	80	
<80%	8	6	

Results

Clinical characteristics of the patients

A total of 603 adult patients who met the criteria for enrollment were selected for analysis in this study, and only 101 received EEN after emergency gastrointestinal surgery. EEN after emergency gastrointestinal surgery was given to 101 subjects, and late EN to the other 502 subjects. The characteristics of these 603 patients are shown in **Table 2**. Compared with patients in late EN group, patients receiving EEN tended to have a greater likelihood of receiving nasointestinal feeding tube (P<0.01), and were less likely to receive PN (P<0.01). There were no significant differences on any of the baseline by using propensity score analysis (**Table 3**). Furthermore, as shown in **Table 4**, no significant differences for each surgical approach with propensity score matched population were observed between EEN group and late EN group (P=0.98).

Postoperative ileus and clinical outcomes

As shown in **Table 5**, a shorter time to first defecation was seen in the EEN group compared with the late EN group (3.2±1.8 VS 3.9±2.1, P=0.02). In the EEN group, 24 in 86 patients (27.9%) developed a POI versus 32 in 86 patients (37.2%) in late EN group (P=0.19). Early ileus occurred in 9 patients in the EEN group versus 21 in the late EN group (P=0.04). However, there were no differences were observed for late and prolonged ileus between two groups (P>0.05).

After EEN intervention, 2 patients had an anastomotic leakage versus 5 patients in the late EN group (P=0.25), and all underwent surgical repair (**Table 5**). Furthermore, all patients with anastomotic leakage also had an intra-abdominal or pelvic abscess, of which some could be managed by percutaneous drainage. However, complications occurred in 25 of 86 patients receiving EEN and in 39 of 86 patients given late EN, with significant differences (P=0.03).

Plasma CRP levels were not different between both groups before surgery and

Table 4. Surgical procedures in the propensity score-matched population

Surgical procedures	EEN (n=86)	Late EN (n=86)	*P* value
Primary repair	15	12	0.98
Wedge resection	2	2	
Small bowel resection with anastomosis	23	27	
Ileostomy or jejunostomy	19	18	
Colon resection with anastomosis	16	17	
Hartmann procedures or colostomy	11	10	

Table 5. Postoperative ileus and outcome characteristics in the propensity score-matched population

	EEN (n=86)	Late EN (n=86)	*P* value
Complication, n (%)			
Surgical wound infection	15 (17.4)	22 (25.6)	0.19
Wound dehiscence	4 (4.7)	6 (7.0)	0.52
Anastomotic leakage	2 (2.3)	5 (5.8)	0.25
Intra-abdominal or pelvic abscess	6 (7.0)	9 (10.5)	0.42
Pneumonia	5 (5.8)	9 (10.5)	0.27
Positive central catheter	4 (4.7)	6 (7.0)	0.52
Culture			
Bacteremia	5 (5.8)	7 (8.1)	0.55
Urinary tract infection	5 (5.8)	9 (10.5)	0.27
Total patients with complications, n (%)	25 (29.1)	39 (45.3)	0.03
number of reoperations, n (%)	2 (2.3)	5 (5.8)	0.25
POI, n (%)			
Early ileus	9 (10.5)	21 (24.4)	0.04
Late ileus	7 (8.1)	5 (5.8)	0.22
Prolonged ileus	8 (9.3)	6 (7.0)	0.21
Time to first defecation	3.2±1.8	3.9±2.1	0.02
Length of hospital stay, d	14.5±3.8	16.4±4.1	<0.01
ICU-free days, d	26.8±1.8	26.2±2.1	0.046
VFDs, d	27.2±1.4	27.0±1.2	0.32
Mortality, n (%)	3 (3.5)	11 (12.8)	0.03
Re-hospitalization, n (%)	11 (12.8)	10 (11.6)	0.82

on postoperative days (POD 1 and POD 2), but were higher in the late EN group on POD 3 (129.4±42.1 vs 148.9±60.2, P=0.03). On POD 5, both groups showed a reduction in CRP, with a more distinctive decrease in the EEN group (96.4±36.8 vs 126.7±34.2, P<0.01, **Figure 1**).

Compared with late EN group, patients receiving EEN had reduced lengths of hospital stay (14.5±3.8 VS 16.4±4.1, P<0.01), inhospital mortality rates (3 VS 11, P=0.03), and more 28-day ICU-free days (26.8±1.8 VS 26.2±2.1, P=0.046) in the propensity score-matched population (**Table 5**). However, no difference was seen for rehospitalization between both groups (11 VS 10, P=0.82).

As shown in **Table 6**, the multivariate analysis with Cox regression analysis suggested that EEN was an independent risk factor for the overall survival.

Discussion

In this propensity-matched study, we focused on effects of EEN after emergency intestinal surgery in patients with bowel resection and/or anastomosis or primary repair. The findings of this study suggest that EEN is safe and previously reported detrimental complications, such as ischemia of the small bowel or aspiration pneumonia, were not observed [14, 15]. Furthermore, EEN within 48 hours after emergency intestinal surgery was associated with reduced time to first defecation, early ileus rates, incidence of total patients with complications, in-hospital mortality rates, lengths of hospital stay, and more 28-day ICU free days.

EN has benefits on modulating the metabolic and systemic immune response, as well as preserving intestinal barrier function [16, 17]. However, EN is traditionally started until bowel motility has recovered after elective surgery on the gastrointestinal tract, which caused delays in enteral feeding after emergency surgery compared with elective surgery [18]. On the one hand, patients with emergency gastrointestinal surgery have an edematous or ischemic bowel, anastomosis healing is usually delayed, which can result in anastomotic disruption or leakage. On the other hand, poor enteral intake can lead to malnutrition or delayed bowel mucosa growth and increase postoperative morbidity and mortality. Recently, EN has been recommended to be initiated as early as possible unless contraindicated by

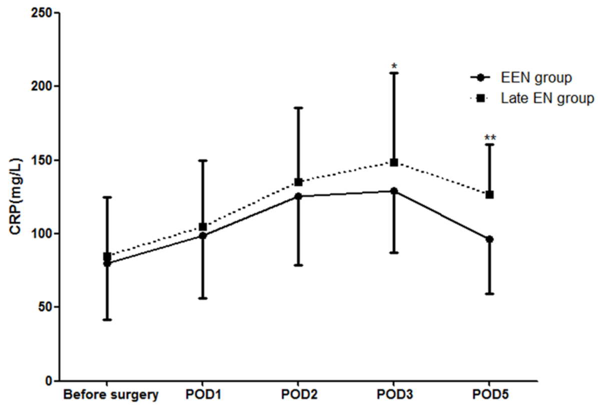

Figure 1. Evolution of CRP levels in the propensity score-matched population. Data are mean ± SD. POD, Postoperative day; *P<0.05 and **P<0.01 versus EEN group.

Table 6. The multivariate analysis with Cox regression analysis for the overall survival

	Overall survival		
Parameter	HR	95% CI	*P* value
Age	0.77	0.42-1.68	0.553
Gender	1.13	0.55-1.79	0.783
Location of lesion	1.27	0.34-2.33	0.675
Tumor size	1.52	0.73-3.31	0.204
Presence or absence of stoma	2.21	0.68-4.23	0.187
Provision of PN	0.44	0.12-4.13	0.331
EEN	0.08	0.02-0.64	0.011

several guidelines [19, 20]. Osland *et al.* [21] showed in a meta-analysis that compared with traditional postoperative feeding practices, EEN was associated with reductions in total complications, and does not negatively affect clinical outcomes such as anastomotic dehiscence, resumption of bowel function, hospital length of stay, or mortality. Another meta-analysis showed that enteral feeding that started within 24 hours after the surgery may be of benefit, such as assisting in a reduction of infection risk or reduction of length of hospital stay [8]. In addition, Petra *et al.* [3] demonstrated in a randomized controlled trial that EEN is associated with reduction in length of stay and anastomotic leakage in patients undergoing elective rectal surgery. However, these results primarily focused on elective gastrointestinal surgery, and few studies have addressed the beneficial effects of EEN after emergency gastrointestinal surgery. Hyung *et al.* [13] demonstrated that early feeding within 48 hours was feasible after emergency gastrointestinal surgery and was associated with reductions in length of stay in the intensive care unit and pulmonary complications. Furthermore, Navneet *et al.* [22] demonstrated in a prospective study that early enteral feeding through a nasoenteric tube was well tolerated by patients with nontraumatic perforation peritonitis and helped to improve energy and protein intake, reduce the amount of nasogastric aspirate, the duration of postoperative ileus, and the risk of serious complications. Another prospective study showed immediate postoperative feeding is feasible in patients with nontraumatic intestinal perforation and peritonitis, and reduces septic morbidity [12].

Although many studies reported many beneficial effects of EEN in surgical patients, EEN was not associated with reduction of mortality [23, 24]. However, despite the mechanism was not well clear, several studies also demonstrated EEN within the first 24 hours revealed a statistically significant reduction of mortality in trauma patients and patients with gastrointestinal surgery [8, 25]. Therefore, our present study focused on assessing the effect of EEN in patients undergoing emergency intestinal surgery. In this study, EEN decreased the length of hospital stay, in-hospital mortality rate, and had a longer 28-day ICU-free day compared with patients with LEN in the propensity-matched population. Furthermore, the multivariate analysis with Cox regression analysis suggested that EEN was an independent risk factor for the overall survival. Although the exact mechanism of how EEN reduced in-hospital mortality is not known, some studies relating severe peritonitis and pancreatitis reported that EEN was associated with decreased in-hospital mortality [17, 26, 27]. Hence, multi-center randomized controlled studies with a larger number of patients with EEN after emergency intestinal surgery are necessary to strengthen our finding.

The beneficial effects of enteral nutrition on POI in this study were remarkable and new, which may be explained by the effect on local inflammation. Previous study showed manipulation of the intestines during surgery triggered the POI [11]. Background mechanisms are thought to include the fact that manipulation of the intestine initiates an inflammatory cascade starting with activation and degranulation of mast cells and activation of macrophages leading to invasion of neutrophils [3]. Invaded neutrophils release of nitric oxide and prostaglandins, which directly impair intestinal smooth muscle cell contractility [11, 28]. The formation of an inflammatory infiltrate not only impairs motility in the manipulated areas but also leads to generalized hypomotility of the gastrointestinal tract via activation of inhibitory adrenergic neural pathways [29] Inhibition of the inflammatory response has been shown to be important for reducing POI. Major surgery induces a systemic immuno-inflammatory response with increased concentrations of CRP (as a marker of inflammatory response) [7]. In this study, CRP was higher immediately after the operation and recovered better after enteral nutrition in comparison to the late EN group. Therefore, EEN may also reduce the inflammatory response and thereby reduce POI in present study.

EN has been shown to reduce postoperative complications after elective gastrointestinal surgery in recent meta-analysis [21, 30]. Moreover, EN should be started as soon as possible after the surgery, which has been recommended by several studies because of a faster recovery in patients with EN [31]. However, EN is often delayed because of reasons including a potential possibility of postoperative complications, such as ileus, or anastomotic leak. A previous prospective randomized controlled trial demonstrated that EEN is safe and associated with less anastomotic leakage in patients undergoing extensive rectal surgery [3]. In addition, EEN also have been reported to reduce pulmonary complications in patients with emergency gastrointestinal surgery [13, 32]. However, in this study, the rates of anastomotic leak and pneumonia were similar in EEN group and late EN group, which may be explained by different patient population. Moreover, we found that incidence of total patients with complications were significantly lower in patients with EEN compared with patients with late EN. These findings may result from modifications of nutritional and inflammatory status after EEN.

There are several limitations to our study. First, this was a single-center, retrospective study. Second, early feeding was started when the patient demonstrated hemodynamically stable status and secure bowel anastomosis was performed, rather than according to the gastrointestinal motility of the patients. Consequently, there was no intergroup difference in gastric residual volume before feeding in our study. Third, the results of this study were based on an intent-to-treat analysis; whether or not EN was initiated within 48 hours after surgery. Although 90.7% of patients reached more than 80% of their nutritional goal within 3 to 5 days after initiation of EN, our database did not have enough information regarding the target calorie, protein delivery, and rate of advancement. Fourth, our study was unable to assess the effects of EEN on fluid balance. Fifth, practitioners are likely to initiate EN as late as possible in more severe patients. Thus, the impact of EEN on reducing length of hospital stay and ICU stay requires further research, including severely-ill patients with long length of stay in the ICU.

In conclusion, EEN therapy in patients with emergency intestinal surgery significantly reduced total patients with complications, early ileus, time to first defecation, length of hospital stay, mortality and increased 28-day ICU-free days. However, we suggest that a prospective and multi-center study be undertaken to strengthen our findings.

Acknowledgements

WHG, WY, TY, JJG and LQH carried out the surgery, and drafted the manuscript. ZJ, XHL, THY and WHG participated in the design of the study and performed the statistical analysis. LQH, XHL and ZJ conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. This work was supported partly by funding from the National Natural Science Foundation of China (Grant no. 81600434), Jiangsu Natural Science Foundation (Grant no. BK20160572) and Jiangsu Provincial Medical Youth Talent (QNRC2016-514).

Disclosure of conflict of interest

None.

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