

# The impact of early enteral nutrition on pediatric patients undergoing gastrointestinal anastomosis: a propensity score matching analysis

Qingjuan Shang, MD<sup>a</sup>, Qiankun Geng, MD<sup>b</sup>, Xuebing Zhang, BN<sup>d</sup>, Hongfang Xu, BN<sup>d,\*</sup>, Chunbao Guo, MD, PhD<sup>a,c,\*</sup>

## Abstract

This study was conducted to assess the clinical advantages of early enteral nutrition (EEN) in pediatric patients who underwent surgery with gastrointestinal (GI) anastomosis.

EEN has been associated with clinical benefits in various aspect of surgical intervention, including GI function recovery and postoperative complications reduction. Evaluable data documenting clinical advantages with EEN for pediatric patients after surgery with GI anastomosis are limited.

We retrospectively reviewed the medical records of 575 pediatric patients undergoing surgical intervention with GI anastomosis. Among them, 278 cases were managed with EEN and the remaining cases were set as late enteral nutrition (LEN) group. Propensity score (PS) matching was conducted to adjust biases in patient selection. Enteral feeding related complications were evaluated with symptoms, including serum electrolyte abnormalities, abdominal distention, abdominal cramps, and diarrhea. Clinical outcomes, including GI function recovery, postoperative complications, length of hospital stay, and postoperative follow-up, were assessed according to EEN or LEN.

Following PS matching, the baseline variables of the 2 groups were more comparable. There were no differences in the incidence of enteral feeding-related complications. EEN was associated with postoperative GI function recovery, including time to first defecation ( $3.1 \pm 1.4$  days for EEN vs  $3.8 \pm 1.0$  days for LEN, risk ratio [RR], 0.62; 95% confidence interval [CI] 0.43–1.08,  $P = .042$ ). A lower total episodes of complication, including infectious complications and major complications were noted in patients with EEN than in patients with LEN (117 [45.9%] vs 137 [53.7%]; OR, 0.73, 95% CI 0.52–1.03,  $P = .046$ ). Mean postoperative length of stay in the EEN group was  $7.4 \pm 1.8$  days versus  $9.2 \pm 1.4$  days in the LEN group ( $P = .007$ ). Furthermore, the incidence of adhesive small bowel obstruction was lower for patients with laxative administration compared with control, but no significant difference was attained ( $P = .092$ ).

EEN was safe and associated with clinical benefits, including shorten hospital stay, and reduced overall postoperative complications on pediatric patients undergoing GI anastomosis.

**Abbreviations:** ASBO = adhesive small bowel obstruction, CRP = C-reactive protein, EEN = early enteral nutrition, LEN = late enteral nutrition, POD = postoperative days, POI = postoperative ileus, PS = propensity score.

**Keywords:** early enteral nutrition, gastrointestinal anastomosis, gastrointestinal function, postoperative complications, postoperative hospital stay

## 1. Introduction

Evidence suggests that postoperative nutritional support could diminish the postoperative complications and ameliorate the

clinical outcome in many types of surgical treatment.<sup>[1–3]</sup> Specifically, following the major intestinal surgery, early start of enteral nutrition (EN) within the first 24 hours postoperatively is beneficial, such as reduction in infectious complications,

Editor: Leonidas G. Koniaris.

The research was supported by National Natural Science Foundation of China (No: 30973440, 30770950), and the key project of the Chongqing Natural Science Foundation (CSTC, 2008BA0021, cstc2012jjA0155).

Authors' contributions: YW, QG, YY designed, analyzed the data, and evaluated the manuscript; QS performed the statistic measurement and analyzed the data; CG analyzed the data and wrote the article.

The authors report no conflicts of interest reported.

<sup>a</sup> Department of Pathology, Linyi People's Hospital, Linyi, Shandong province, <sup>b</sup> Department of Pediatric General Surgery, Children's Hospital, <sup>c</sup> Ministry of Education Key Laboratory of Child Development and Disorders, Children's Hospital, Chongqing Medical University, <sup>d</sup> Department of Pediatric General Surgery, Children's Hospital of Chongqing Medical University, Chongqing, P.R. China.

\* Correspondence: Hongfang Xu, Department of Pediatric General Surgery, Children's Hospital of Chongqing Medical University, 136 Zhongshan 2nd Rd., Chongqing 400014, P.R. China (e-mail: 3256525@qq.com), Chunbao Guo, Department of Pediatric General Surgery and Liver Transplantation, Children's Hospital of Chongqing Medical University, 136 Zhongshan 2nd Rd., Chongqing 400014, P.R. China (e-mails: guochunbao@cqmu.edu.cn; guochunbao@foxmail.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:9(e0045)

Received: 9 May 2017 / Received in final form: 19 October 2017 / Accepted: 7 February 2018

<http://dx.doi.org/10.1097/MD.00000000000010045>

bacterial translocation or aspiration, and severity of multiple organ dysfunction syndrome and is even associated with reduced postoperative mortality rate after gastrointestinal (GI) surgery.<sup>[4,5]</sup> In addition, EN is suggested to be safer and less expensive than parenteral nutrition (PN). Another benefits of early enteral nutrition (EEN) come from the amelioration oxidative stress after surgery.<sup>[6,7]</sup> Therefore, physicians have become interested in feeding patients as soon as possible. Many clinicians continue to feed patients later to the first week for the consideration of the potential risks, hemodynamic instability, which has been considered a relative or absolute contraindication to EEN. Early start of oral nutrition is associated with an increase in splanchnic blood flow. So, it is critical for EN for the hemodynamic condition without an increase in overall cardiac output, termed as the “steal” phenomenon.<sup>[8,9]</sup> In patients whose hemodynamic condition is unstable, EN has been related with gut ischemia, which was confirmed in a study of rats with occlusion of the mesenteric artery.<sup>[10]</sup>

Moreover, the benefits of this early approach is not successful per se in all patients and been confirmed in clinical studies. Postoperative total enteral feeding is associated with complications such as postoperative nausea, vomiting, diarrhea, abdominal distention, and abdominal cramps, which is often delayed because of these reasons. These symptoms might be worsen with increasing caloric intake, and this often necessitates prolonged gastric decompression and enteral nutritional support, even lead to discontinuance of enteral feeding.<sup>[11,12]</sup> In fact, another valid concern for EEN is the stressing a fresh anastomosis with stools, so a conservative management is still practiced. A considerable proportion of these patients is offered total parenteral nutrition to reach nutritional goals until the passing of flatus or stools during the first week.

Although the EEN has been demonstrated to show several beneficial effects in surgical patients, clinical data in pediatric patients in severe abdominal infection are very limited. Thus, on the basis of our experience and the findings of previous studies, we sought to assess the efficacy of early postoperative EN after surgery in patients with traumatic or nontraumatic GI perforation or strangulation in a retrospective controlled clinical trial.

## 2. Materials and methods

The study was designed as a retrospective, single-center review of the clinical records for 484 patients who underwent intestinal anastomosis on emergency or electively laparotomy from January 2007 to December 2012. Computerized medical records were thoroughly reviewed with clinician and nurse notes, surgical records, laboratory tests, imaging examinations, and histopathology results. Specifically, the following variables were recorded in all patients on admission and on days 1, 4, and 8 after surgery: age, body weight, sex, hemoglobin, C-reactive protein (CRP), procalcitonin, and total lymphocyte count. Operating time, intraoperative blood loss, transfusion rate and necessity for reoperation were also recorded. This protocol was approved by the institutional review board of the Chongqing Medical University (IRB, No.: CHMU2011–039) and conducted by the department of surgery, in accordance with the ethical standards prescribed by the Helsinki Declaration of the World Medical Association. Inclusion criteria were patients undergoing primary repair of intestinal perforation, bowel resection and anastomosis, as well as repair of intestinal strangulation and obstruction. Exclusion criteria included patients with postoperative shock and patients with ongoing infection. Additionally, to

minimize severity differences in the study population, patients managed in the intensive care unit (ICU) for >3 days were excluded. The primary endpoint of this research, postoperative ileus (POI), was defined as time (in days) to first defecation. Secondary endpoints were clinical outcome, including postoperative complications, and length of hospital stay.

### 2.1. Nutrition care protocol

The patients in this study were managed with same care protocols, including total parenteral nutrition, cessation of enteral feeding. The nasogastric tubes (Flocare Nutricia Ltd., 140-cm long) were inserted into the first jejunal loop through the nose.

EEN project depended on the patient condition and physician's preference because some physicians in our institution considered that it might be safe and beneficial and to promote the recovery of GI function. On postoperative day (PID) 1, ambulation was encouraged; Postoperatively, all patients were allowed to drink and eat as soon as possible. Liquids and solid food were usually offered in proper order from POD 1 to 2 to progress to normal diet on the basis of tolerance. If kept in place after surgery, the nasogastric tube was removed 24 hours after surgery. According to standard care protocols, patients received parenteral nutrition through a central venous catheter in the jugular vein. Total parenteral nutrition (TPN) was given 24 h/d from the first day after surgery for 3 days. The nitrogen intake was 0.25 g/kg body weight per day, caloric intake was 125.4 kJ/kg/d and lipid intake was 1.1 g/kg/d. Usually, TPN was offered to reach nutritional goals 24 h/d for the first 3 days postoperatively, which was set as late enteral nutrition (LEN) group.

Medical reasons, adverse events, or patient's wishes could cause deviation to the protocol and were recorded. Pocrustic agents, probiotics, or atropine, when appropriate, were symptomatically used for diarrhea and abdominal cramping or bloating. Other adverse symptoms were managed as indicated clinically. The PN solutions were prepared under aseptic conditions according to the weight of each patient by a clinical pharmacist. The nutrition mixture was administered via a central venous catheter, including amino acids, fat emulsion, dextrose, electrolytes, vitamins, and trace elements.

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.

### 2.2. Clinical assessment

Daily registrations of postoperative GI symptoms, including abdominal bloating, abdominal cramps, intake, diarrhea (defined as more than three bowel movements per day), nausea, vomiting, gastric retention, and defecation, were recorded within the first 5 days. Before the hospital stay, >1 episode of nausea or vomiting was defined as early ileus. We described the surgical outcomes, including ventilator rates, ICU-stay rates, and total lengths of hospital stay (the number of days from the day of operation until the date of discharge) and most common postoperative complications, including complication rates, complication types, such as wound infection, intra-abdominal or pelvic abscesses, anastomotic leaks, and the number of reoperations. Wound complications consisted of wound dehiscence, erythema, swelling, and pus. Infectious complications were confirmed with microbiological analyses and positive cultures.

### 2.3. Statistical analysis

To minimize the biases in patient selection, propensity score (PS) matching was accomplished using a multivariable logistic regression model. The 1:1 matched analysis with a caliper distance of 0.2 without replacement was performed using SPSS 20.0 (IBM, Armonk, NY) or R software 3.1.2 (The R Foundation for Statistical Computing) and the MatchIt package. We further measured the interaction among all pre-test covariates. The linear assumption was checked using the generalized additive model.

After PS matching, the matched PGE1 treatment patients and controls were subjected to statistical comparisons using SPSS 20.0 (IBM, Armonk, NY). Continuous and categorical variables were presented as means  $\pm$  SDs and frequencies (percentages), respectively. The analyses were conducted using a Mann-Whitney U test for continuous variables and a  $\chi^2$  test for categorical variables. The relative risks for postoperative variables were measured with cross-tabulation (odds ratio [OR]) or multivariate logistic regression analysis (risk ratio [RR]). Statistical significance was considered if 2-sided *P* values were less .05.

## 3. Results

### 3.1. Patient characteristics

At the time of the analysis, a total of 575 pediatric patients were eligible for analysis according to the intention-to-treat principle. Among them, 278 (48.3%) received EEN and 297 (51.7%) did not. The baseline features of the pediatric patients according to EEN or LEN are shown in Table 1. With respect to demographic and preoperative clinical data and intraoperative factors, no significant differences were observed between the 2 groups, like causes of operation, operation time, blood loss, CRP at admission, and transfused patients (*P* > .05). In addition, there were no significant differences in surgical approach between the 2 groups with unmatched and PS-matched patients (Table 1).

Under PS-matching, 255 patients with EEN were well matched to 255 patients without EEN. The variables entered were very similar and comparable between the patients with EEN and LEN (Table 1) because the values of absolute standardized mean differences reduced from 0.01 to 0.07. Several variables, including postoperative shock, became more comparable after PS-matching (Table 1).

### 3.2. Clinical outcomes

Table 2 illustrates the clinical outcomes based on EEN and LEN. The mean durations of parenteral nutrition were  $2.3 \pm 1.6$  and  $3.2 \pm 0.7$  days for patients with EEN and LEN, respectively (risk ratio [RR], 0.75; 95% confidence interval [CI] 0.41–1.16, *P* = .002). All types of nutritional support were well tolerated in both groups. In the propensity-matched cohort, the time to first defecation in the EEN group was  $3.2 \pm 1.4$  days, and  $3.8 \pm 1.0$  days in the LEN group, respectively (RR, 0.62; 95% CI, 0.43–1.08, *P* = .082). In the LEN group, 33.3% (85/255) developed a POI versus 40.8% (104/255) in the LEN group (RR, 0.73; 95% CI, 0.51–1.04, *P* = .049). POI includes early ileus late and prolonged ileus. Early ileus occurred in 27 patients in the EEN group versus 46 in the LEN group (RR, 0.54; 95% CI, 0.32–0.90, *P* = .011). No differences were seen for late and prolonged ileus. The enteral feeding-related complications were evaluated with symptoms, including serum electrolyte abnormalities, abdominal distention, abdominal cramps, and diarrhea. There were no differences in the incidence of these symptoms between the 2 groups. These symptoms were alleviated by slowing down the speed of enteral transfusion or by the administration of medications. None of the patients discontinued enteral feeding, and no enteral feeding-related complications were noted in the LEN group. For nutritional variables (albumin and prealbumin, Table 2), no significant differences were found between the 2 groups at POD 5. In patients with EEN, CRP returned more distinctively to normal than patients with LEN. On POD 5, a

**Table 1**

**Baseline characteristic of eligible population entered into the propensity score matching analysis.**

	Total population			Propensity matched population		
	EEN (n = 278)	LEN (n = 297)	<i>P</i>	EEN (n = 255)	LEN (n = 255)	<i>P</i>
Age, y	3.8 $\pm$ 2.1	4.1 $\pm$ 2.3	.23	3.9 $\pm$ 1.7	4.0 $\pm$ 1.6	.28
Male:female	163:115	171:126	.45	149:106	150:105	.50
Body weight, kg	12.8 $\pm$ 7.9	13.4 $\pm$ 8.3	.32	12.9 $\pm$ 6.4	13.2 $\pm$ 7.1	.43
Albumin, g/L (normal range, 35–50)	32.6 $\pm$ 5.6	33.8 $\pm$ 4.9	.48	33.1 $\pm$ 4.9	33.4 $\pm$ 4.7	.51
Prealbumin, mg/dL (normal range, 20–40)	19.5 $\pm$ 4.8	18.4 $\pm$ 4.6	.25	19.2 $\pm$ 4.3	18.8 $\pm$ 4.5	.44
Hemoglobin, g/L	103.4 $\pm$ 12.4	99.8 $\pm$ 13.3	.23	102.3 $\pm$ 11.9	101.4 $\pm$ 12.1	.34
WBC, (10 <sup>9</sup> cells/L)	19.3 $\pm$ 5.3	18.7 $\pm$ 5.8	.27	19.1 $\pm$ 4.8	18.9 $\pm$ 5.2	.18
CRP, mg/L (normal value: 0–10)	16.2 $\pm$ 5.5	15.8 $\pm$ 5.7	.33	16.0 $\pm$ 4.9	15.9 $\pm$ 5.1	.47
Postoperative shock, N (%)	41 (14.7)	65 (21.9)	.018	39 (15.3)	42 (16.5)	.40
Duration of surgery, min	84.9 $\pm$ 8.9	92.5 $\pm$ 11.2	.063	86.8 $\pm$ 8.5	88.7 $\pm$ 10.4	.35
Estimated blood loss, mL	19.3 $\pm$ 5.3	19.5 $\pm$ 4.8	.12	19.4 $\pm$ 4.9	19.5 $\pm$ 4.7	.46
Transfused patients, N (%)	66 (23.7)	95 (32.0)	.026	63 (24.7)	67 (26.3)	.38
Causes of operation, N (%)						
Bowel strangulation or Perforation	76 (27.3)	93 (31.3)	.17	67 (26.3)	69 (27.1)	.46
Intestinal intussusception	152 (54.7)	141 (47.5)	.050	140 (54.9)	136 (53.3)	.40
Pancreatic duct dilation	13 (4.7)	9 (3.0)	.21	9 (3.5)	8 (3.1)	.50
Trauma	37 (13.3)	54 (18.2)	.068	39 (15.3)	42 (16.5)	.40
Operation type, N (%)						
Small bowel anastomosis	116 (41.7)	110 (37.0)	.1483	109 (42.7)	105 (41.2)	.39
Stomach and duodenum anastomosis	24 (8.6)	31 (10.4)	.28	23 (9.0)	28 (11.0)	.28
Colon and rectum anastomosis	138 (49.6)	156 (52.5)	.2781	123 (48.2)	122 (47.8)	.50

CRP = C-reactive protein, EEN = early enteral nutrition, LEN = later enteral nutrition, WBC = white blood cell.

**Table 2**  
**Gastrointestinal function and early outcome in the matched population (multivariate logistic regression).**

	EEN (n=255)	LEN (n=255)	P	Risk ratio (95% CI)
Duration of parenteral nutrition, days, mean ±SD	2.3±1.6	3.2±0.7	.002	0.75 (0.41–1.16)
First defecation, days, mean ±SD	3.1±1.4	3.8±1.0	.042	0.62 (0.43–1.08)
POI, N (%)	85 (33.3)	104 (40.8)	.049	0.73 (0.51–1.04)
Early ileus, N (%)	27 (10.6)	46 (18.0)	.011	0.54 (0.32–0.90)
Abdominal distension after POD 5, N (%)	41 (16.1)	34 (13.3)	.23	1.25 (0.76–2.04)
Serum electrolyte abnormalities, N (%)	13 (5.1)	11 (4.3)	.42	1.19 (0.52–2.71)
Abdominal cramps, N (%)	52 (20.4)	43 (16.9)	.18	1.26 (0.81–1.98)
Diarrhea, N (%)	23 (9.0)	29 (11.4)	.23	0.77 (0.43–1.38)
Albumin, g/L (normal range, 35–50)	34.8±4.6	35.3±5.2	.37	0.79 (0.51–1.34)
Prealbumin, mg/dL (normal range, 20–40)	22.6±3.1	23.1±3.3	.13	0.64 (0.44–1.27)
CRP at POD 5, mean ±SD	11.2±8.7	17.6±9.4	.086	0.68 (0.44–1.83)
Postoperative hospital stay, days, mean ±SD	7.4±1.8	9.2±1.4	.045	0.46 (0.37–1.15)

CI = confidence interval, EEN = early enteral nutrition, LEN = later enteral nutrition, POD = postoperative days, POI = postoperative ileus, SD = standard deviation.

marginal decrease in CRP levels in patients receiving EEN was observed (RR, 0.68; 95% CI, 0.44–1.83,  $P = .086$ ). Analysis of liver and kidney function did not demonstrate any alterations in TPN (data not shown). The mean length of hospital stay ( $8.6 \pm 1.2$  days) in patients receiving EEN was significantly less than that ( $9.4 \pm 1.3$  days) in patients with LEN (RR, 0.46; 95% CI, 0.37–1.15,  $P = .045$ ) (Table 2).

### 3.3. Postoperative complications

According to established criteria, postoperative complications are summarized in detail in Table 3. The total complication episodes were significantly reduced in the EEN group, compared with the LEN group, with an OR of 0.73 (95% CI, 0.52–1.03;  $P = .046$ ), representing a trend toward a 27% relative risk reduction for the complications. Fifty-one of 255 patients (8.3%) with EEN developed at least 1 complication, which was marginal less than the 67 of 255 patients (17.3%) with LEN who developed complications (OR, 0.71; 95% CI, 0.47–1.08,  $P = .067$ ). Following EEN, 14 patients reported late ileus versus 27 patients in the LEN group (OR, 0.49; 95% CI, 0.25–0.96,  $P = .025$ ), suggesting a reduction trend toward Late ileus. There were no statistically significant differences between groups for anastomotic leakage, hemoperitoneum and incision dehiscence, which should be subjected to surgical intervention. In the EEN group, 14 patients underwent a total of 27 perioperative reoperations versus 16 patients in the LEN group undergoing

30 reoperations ( $P = .28$ ). Moreover, there were no significant differences among the incidences of reoperation, including incision dehiscence, postoperative bleeding, abdominal abscess, and intestinal leak or obstruction. A reduction trend for postoperative infectious complications (pneumonia, wound, abdominal, and systemic infection) was indicated in patients receiving EEN compared with the patients receiving LEN (OR, 0.69; CI, 0.43–1.11,  $P = .077$ ) (Table 3), although there were no statistically significant differences between groups for any of the individual infectious complications.

### 3.4. Follow-up and recurrence rates

All the patients were followed at least 2 months (a half over 6 months of follow-up) and the median follow-up was 8 months (range, 2–29 months). The incidence of constipation in the patients with EEN was significantly lower compared with that in the control (OR, 0.57; 95% CI, 0.31–1.05;  $P = .037$ ), which was not expected (Table 4). During the follow-up, the incidence of adhesive small bowel obstruction (ASBO) was lower for patients with laxative administration compared with control, but no significant difference was attained ( $P = .092$ ). The patients using EEN suffered almost similar hospital readmission compared with the patients who were subjected with LEN ( $P = .0001$ ). The most common reason for the hospital readmission was surgery-related ASBO. The median time of first recurrence was 3.6 months (range 2.5–12 months) for patients with EEN and 2.8 months

**Table 3**  
**Postoperative complications in the matched population ( $\chi^2$  test).**

	EEN (n=255)	LEN (n=255)	P	Odds ratio (95% CI)
Total episodes of complications, N (%)	117 (45.9)	137 (53.7)	.046	0.73 (0.52–1.03)
Total cases with at least 1 complication, N (%)	51 (20.0)	67 (26.3)	.067	0.71 (0.47–1.08)
Major complications, N (%)	26 (10.2)	35 (13.7)	.14	
Anastomotic leakage, N (%)	3 (1.2)	9 (3.5)	.071	0.33 (0.09–1.22)
Hemoperitoneum, N (%)	5 (2.0)	6 (2.4)	.50	
Incision dehiscence, N (%)	11 (4.3)	9 (3.5)	.41	
Reoperation	23 (9.0)	28 (11.0)	.28	
Infectious complications, N (%)	36 (14.1)	49 (19.2)	.077	0.69 (0.43–1.11)
Surgical wound infection, N (%)	22 (8.6)	19 (7.5)	.37	
Pneumonia, N (%)	11 (4.3)	18 (7.1)	.13	
Sepsis, N (%)	3 (1.2)	8 (3.1)	.11	
Peritonitis or abscess, N (%)	14 (5.5)	22 (8.6)	.11	

CI = confidence interval, EEN = early enteral nutrition, LEN = later enteral nutrition.

**Table 4**  
**Follow-up and recurrence rates in the matched population ( $\chi^2$  test).**

	EEN (n=255)	LEN (n=255)	P	Odds ratio (95% CI)
Constipation, N (%)	18 (7.9)	30 (25.9)	.037	0.57 (0.31–1.05)
ASBO, N (%)	27 (14.8)	38 (19.6)	.092	0.68 (0.40–1.15)
Hospital readmission, N (%)	22 (11.6)	31 (18.5)	.12	
Time of first recurrent ASBO, mo, median (range)	3.6 (2.5–12)	2.8 (1.7–15)		
Reoperation for ASBO, N (%)	5 (2.1)	11 (5.8)	.10	

ASBO=Adhesive small bowel obstruction, CI=confidence interval, EEN=early enteral nutrition, LEN=later enteral nutrition.

(range 1.7–15 months) for patients with LEN. During the follow-up period (1–29 months), of the 16 patients who required surgical treatment for ASBO, 5 patients with EEN had emergency surgery performed within 24 hours after admission because of suspected bowel strangulation. Laparotomy confirmed strangulation in 3 of them. Whereas for the control, 11 patients with LEN had emergency surgery and confirmed strangulation in 6 of them. The diseased bowel segments were resected in 2 cases in the EEN group, and in 6 in LEN group (Table 4).

#### 4. Discussion

After PS matching to control the confounders of heterogeneity in this multivariate population, the present study demonstrated that EEN within 48 hours from the completion of GI anastomosis can promote rapid postoperative intestinal function recovery (first defecation) in patients undergoing major intestinal surgery and was associated with reduced postoperative complications and lengths of hospital stay. This improvement might result from the redistributes fluid from the interstitium to the enteric cavity spaces, which relieve the postoperative intestinal edema formation.

Compared with traditional postoperative feeding practices, EEN was proved with several benefits by previously published meta-analysis, including reduction of the postoperative septic complications, and improvement of glucose tolerance, protein kinetics, and wound healing.<sup>[13,14]</sup> In this retrospective review, after adjusting for covariates, the time to first defecation was shorter with EEN after GI anastomosis for pediatric patients. Moreover, despite the minimal degree reduction, EEN was associated with the reduction of postoperative complications and length of hospital stay when compared with LEN. Importantly, EEN was associated with a lower occurrence of anastomotic leakage and reduced readmission rate, which might come from modulating the metabolic and systemic immune response, as well as preserving gut integrity.<sup>[15]</sup> 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.<sup>[16]</sup>

Moreover, postoperative total enteral feeding is associated with complications such as diarrhea, abdominal distention, and abdominal cramps. These symptoms worsen with increasing caloric intake and can lead to discontinuance of enteral feeding.<sup>[17–19]</sup> EEN was safe and previously reported detrimental complications, such as ischemia of the small bowel or aspiration pneumonia, were not observed here in this research. On the first 3 days after surgery in this study, the amount of EN increased slowly to avoid severe GI complications. EEN does not negatively affect outcomes of enteral feeding-related complications. Twenty-nine cases in the EEN group had symptoms, like resumption of bowel function, which were alleviated by slowing down the speed

of enteral transfusion or by the administration of medications, and none of the patients discontinued enteral feeding or dropped out of the study. There was concern that in the early postoperative phase, caloric target as set by nutritional societies is a matter of dispute for EEN, which should be made up by parenteral supplements to obtain caloric aims. The EEN group received less calories of artificial nutrition than the LEN group, probably associated with the frequent protocol deviations encountered in the EEN group. It is unknown whether the observed effects can be attributed to the caloric intake. In certain patient populations, like intensive care population and acute pancreatitis patients, it was in favor of parenteral nutrition for a reduced mortality rate compared with oral diet nutrition.<sup>[20,21]</sup>

Owing to its shorter half-life, prealbumin is more sensitive than albumin for evaluating protein synthesis in the liver. In this study, the prealbumin was observed slightly decrease in the EEN groups on the POD 5. Thus, there is clinical evidence in our research supporting the benefits of EEN for pediatric patients, although it is still controversial whether EEN is associated with the reduction synthesis of prealbumin in this specific patient population. The question of whether we underfed the EEN group therefore arises. The issue remains whether possible “underfeeding” in this case is harmful or beneficial. Moreover, to avoid ischemia of the small bowel, EN was not started early in hemodynamically unstable patients. Our results are in accordance to other results of feeding in the ICU: patients receiving lower amounts of feeding recovered better than patients receiving the highest permitted amount of calories.<sup>[22]</sup> It seems that the amount of calories is not as important as the route and timing of artificial nutrition. Our study has important implications on the nutritional support in pediatric patients and will motivate future studies to conduct adequately powered, randomized controlled clinical trials. The main pillars of enhanced recovery after surgery (ERAS) programs include optimal postoperative pain management and early enteral feeding and mobilization after surgery. ERAS implementation has also resulted a similar reduction in complication rates along with a modest reduction in length of stay (LOS), in different surgical populations in adult patients.<sup>[23]</sup> The ERAS implementation would be useful to applicability in the paediatric setting.

GI blood flow is reduced in patients after various types of critical illnesses and conditions. Manipulation of the intestine initiates the pathogenesis of intestinal edema, which might be involved in GI blood flow unstable, inflammatory cascade, and activation of macrophages leading to invasion of neutrophils. Many investigators have reported that EN may dampen the inflammatory response and thereby reduce POI, whereas another mechanism may be the stimulation of bowel movements by the input of nutritional liquids.<sup>[24,25]</sup> The formation of an inflammatory infiltrate not only impairs motility in the manipulated areas but also leads to generalized hypomotility of the GI tract via activation of inhibitory adrenergic neural pathways. Inhibition of

the inflammatory response has been shown to be important for reducing POI.<sup>[15]</sup> Compared with the LEN group, the rate of infectious complication in the EEN group was significantly decreased.<sup>[15]</sup> In this study, CRP was higher immediately after the operation and recovered better after EN in comparison to the LEN group. Early dampening of this local inflammation via postpyloric nutrition may explain the results found. With regard to anastomotic leakage, the local inflammatory response is also important. EEN may also reduce the inflammatory response and thereby reduce anastomotic leakage. In the experimental setting, EN prevents adverse structural and functional alterations of the anastomotic position by improving the intestinal blood flow, and modulating the systemic and local immune response.<sup>[26]</sup>

EN may also improve splanchnic blood flow and ischemic injury. In fact, although feeding increased GI oxygen consumption, the concomitant increase in oxygen delivery led to better delivery to consumption ratio in the fed versus the unfed state. Histological evidence has proven that EN preserved the gut flora architecture, prevented GI mucosa atrophy, and inhibited microbial translocation from the gut to the blood stream. This hypothesis about effect of EN on splanchnic blood flow or GI oxygen consumption was not investigated in this study, which was suggested in previous research.<sup>[27]</sup> Although the exact mechanism is difficult to determine in the clinical setting, these results may be explained by an effect of EN on local inflammation and edema recovery.

Our study was limited in several ways. First, it is a retrospective, single-center design analysis, and the decision to initiate EEN was based on intent-to-treat, so not randomly designed. Retrospectively, the days to first defecation were extracted from patient records, which might not be fully accurate. In practice, although there is no executable guideline, possibly, sicker patients were not fed because of their condition, and feeding may simply be a marker of a less ill patient, which might be associated with intestinal edema, long procedure time, more fluid loss, and tend to transfer into ICU care. Also, if a physician is more likely to initiate EN early, he or she would also be more likely to follow other measures to improve outcome or initiatives to decrease rates of health care-associated infection. Owing to the fact that this is a retrospective study, it is not possible to distinguish whether advantageous outcome is simply associated with EN early or a causative factor of awareness of ERAS protocols. Our study does demonstrate that LOS was independently associated with EEN even after controlling for other potential confounders. Lastly, our database does not include any information regarding the type of enteral formulas that patients received, mainly whether they received immune-enhancing formula or standard formula. The study does not take into account patients' total caloric intake, rate of advancement, and whether disruptions in the feeding occurred. Our database did not have enough information regarding the target calorie, protein delivery, and rate of advancement. Therefore, our results need to be carefully interpreted. To limit the influence of confounding variables on the actual effects of EEN, we attempted to control for this possibility by using PS matching to generate comparison groups of patients who had similar baseline factors.

In summary, this comparison of EEN with LEN suggests that the beneficial effect of EEN was embodied in decreasing the POI, infectious complications, and shorten postoperative hospital stay for patients undergoing major intestinal surgery. In addition, we found no evidence of harm because of the EEN. We acknowledge that these results are based on a heterogeneous group of patients, although we performed a PS matching analysis. These results

provide justification for an adequately powered, randomized controlled clinical trials in the future to further address this controversial this modality in pediatric patients.

## Acknowledgments

The authors thank Prof. Xianqing Jin for providing technical assistance and for insightful discussions during the preparation of the manuscript and Dr Xiaoyong Zhang at the Wistar Institute, USA, for help with the linguistic revision of the manuscript.

## References

- [1] Lee SH, Jang JY, Kim HW, et al. Effects of early enteral nutrition on patients after emergency gastrointestinal surgery: a propensity score matching analysis. *Medicine* (Baltimore) 2014;93:e323.
- [2] Klek S, Kulig J, Sierzega M, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. *Ann Surg* 2008;248:212–20.
- [3] Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care* 2010;19:261–8.
- [4] Marimuthu K, Varadhan KK, Ljungqvist O, et al. A meta-analysis of the effect of combinations of immune modulating nutrients on outcome in patients undergoing major open gastrointestinal surgery. *Ann Surg* 2012;255:1060–8.
- [5] Lewis SJ, Egger M, Sylvester PA, et al. Early enteral feeding versus “nil by mouth” after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ* 2001;323:773–6.
- [6] Martindale RG, Warren M. Should enteral nutrition be started in the first week of critical illness? *Curr Opin Clin Nutr Metab Care* 2015;18:202–6.
- [7] Kotzampassi K, Kolios G, Manousou P, et al. Oxidative stress due to anesthesia and surgical trauma: importance of early enteral nutrition. *Mol Nutr Food Res* 2009;53:770–9.
- [8] Yang S, Wu X, Yu W, et al. Early enteral nutrition in critically ill patients with hemodynamic instability: an evidence-based review and practical advice. *Nutr Clin Pract* 2014;29:90–6.
- [9] Wells DL. Provision of enteral nutrition during vasopressor therapy for hemodynamic instability: an evidence-based review. *Nutr Clin Pract* 2012;27:51–6.
- [10] Kozar RA, Schultz SG, Hassoun HT, et al. The type of sodium-coupled solute modulates small bowel mucosal injury, transport function, and ATP after ischemia/reperfusion injury in rats. *Gastroenterology* 2002;123:810–6.
- [11] Shankar B, Daphnee DK, Ramakrishnan N, et al. Feasibility, safety, and outcome of very early enteral nutrition in critically ill patients: Results of an observational study. *J Crit Care* 2015;30:473–5.
- [12] Llaguna OH, Kim HJ, Deal AM, et al. Utilization and morbidity associated with placement of a feeding jejunostomy at the time of gastroesophageal resection. *J Gastrointest Surg* 2011;15:1663–9.
- [13] Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2016;20:117.
- [14] Li JY, Yu T, Chen GC, et al. Enteral nutrition within 48 hours of admission improves clinical outcomes of acute pancreatitis by reducing complications: a meta-analysis. *PLoS One* 2013;8:e64926.
- [15] Hao F, Guo H, Zhong J, et al. Effects of prostaglandin E1 on patients undergoing major gastrointestinal surgery. *Ann Surg* 2017;Jan 24. doi: 10.1097/SLA.0000000000002152.
- [16] Lewis SJ, Andersen HK, Thomas S. Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. *J Gastrointest Surg* 2009;13:569–75.
- [17] Yang H, Feng Y, Sun X, et al. Enteral versus parenteral nutrition: effect on intestinal barrier function. *Ann N Y Acad Sci* 2009;1165:338–46.
- [18] Ralls MW, Demehri FR, Feng Y, et al. Enteral nutrient deprivation in patients leads to a loss of intestinal epithelial barrier function. *Surgery* 2015;157:732–42.
- [19] Feng Y, Teitelbaum DH. Tumour necrosis factor-induced loss of intestinal barrier function requires TNFR1 and TNFR2 signalling in a mouse model of total parenteral nutrition. *J Physiol* 2013;591:3709–23.
- [20] Elke G, Wang M, Weiler N, et al. Close to recommended caloric and protein intake by enteral nutrition is associated with better clinical outcome of critically ill septic patients: secondary analysis of a large international nutrition database. *Crit Care* 2014;18:R29.

- [21] Wereszczynska-Siemiakowska U, Swidnicka-Siergiejko A, Siemiakowski A, et al. Early enteral nutrition is superior to delayed enteral nutrition for the prevention of infected necrosis and mortality in acute pancreatitis. *Pancreas* 2013;42:640–6.
- [22] Hise ME, Halterman K, Gajewski BJ, et al. Feeding practices of severely ill intensive care unit patients: an evaluation of energy sources and clinical outcomes. *J Am Diet Assoc* 2007;107:458–65.
- [23] Liu VX, Rosas E, Hwang J, et al. Enhanced recovery after surgery program implementation in 2 surgical populations in an integrated health care delivery system. *JAMA Surg* 2017;152:e171032.
- [24] Powell JJ, Murchison JT, Fearon KC, et al. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. *Br J Surg* 2000;87:1375–81.
- [25] Boelens PG, Heesakkers FF, Luyer MD, et al. Reduction of postoperative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. *Ann Surg* 2014;259:649–55.
- [26] de Aguilar-Nascimento JE, Dock-Nascimento DB, Bragagnolo R. Role of enteral nutrition and pharmacconutrients in conditions of splanchnic hypoperfusion. *Nutrition* 2010;26:354–8.
- [27] Braga M, Gianotti L, Gentilini O, et al. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med* 2001;29:242–8.