Effects of Early Enteral Nutrition on Patients After Emergency Gastrointestinal Surgery

A Propensity Score Matching Analysis

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Abstract: Early postoperative enteral feeding has been demonstrated to improve the outcome of patients who underwent surgery for gastrointestinal (GI) malignancies, trauma, perforation, and/or obstruction. Thus, this study was conducted to assess the efficacy of early postoperative enteral nutrition (EN) after emergency surgery in patients with GI perforation or strangulation.

The medical records of 484 patients, admitted between January 2007 and December 2012, were reviewed retrospectively. Patients were divided into 2 groups: the early EN (EEN, N = 77) group and the late EN (LEN, N = 407) group. The morbidity, mortality, length of hospital, and intensive care unit (ICU) stays were compared between the 2 groups. Propensity score matching was performed in order to adjust for any baseline differences.

Patients receiving EEN had reduced in-hospital mortality rates (EEN 4.5% vs LEN 19.4%; $P = 0.008$), pulmonary complications (EEN 4.5% vs LEN 19.4%; $P = 0.008$), lengths of hospital stay (median: 14.0, interquartile range: 8.0–24.0 vs median: 17.0, interquartile range: 11.0–26.0, $P = 0.048$), and more 28-day ICU-free days (median: 27.0, interquartile range: 25.0–27.0 vs median: 25.0, interquartile range: 22.0–27.0, $P = 0.042$) than those receiving LEN in an analysis using propensity score matching. The significant difference in survival between the 2 groups was also shown in the Kaplan–Meier survival curve ($P = 0.042$). In a further analysis using the Cox proportional hazard ratio after matching on the propensity score, EEN was associated with reduced in-hospital mortality (hazard ratio, 0.03; 95% confidence interval, 0.01–0.49; $P = 0.015$).

EEN is associated with beneficial effects, such as reduced in-hospital mortality rates, pulmonary complications, lengths of hospital stay, and more 28-day ICU-free days, after emergency GI surgery.

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Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, ASA = American Society of Anesthesiologists, EEN = early enteral nutrition, GI = gastrointestinal, ICU = intensive care unit, LEN = late enteral nutrition, PN = parenteral nutrition, VFDs = ventilator-free days.

INTRODUCTION

Nutritional support is useful during the inflammatory and metabolic phase, assisting in the improvement of a patient's outcome after surgery.[1–4] In particular, enteral nutrition (EN) has been shown to reduce the length of hospital stay and postoperative complications after elective gastrointestinal (GI) surgery in recent meta-analysis.[5–7] Moreover, several studies have recommended that EN should be started as soon as possible after the surgery because EN allows patients for a faster recovery.[5,8] However, EN is often delayed because of reasons including a potential possibility of postoperative complications, such as ileus, obstruction, or anastomotic failure. In fact, the practice of delaying EN until the passing of flatus or stools is a conservative practice that arose out of valid concern about stressing a fresh anastomosis; however, the benefits of this practice has not been confirmed in clinical studies. EN has rather significant beneficial effects, such as reduction in infectious complications, bacterial translocation or aspiration, and severity of multiple organ dysfunction syndrome in surgical patients.[5–7,9,10] Recent studies have suggested that early EN (EEN) is also feasible and/or beneficial after emergency GI surgery,[11–14] if there are no contraindications to EEN such as intestinal obstruction, malabsorption, multiple fistulas with high output, intestinal ischemia, severe shock with impaired splanchnic perfusion, and fulminant sepsis.[8] However, although the provision of EEN has been demonstrated to show several beneficial effects in surgical patients, the majority of these studies have focused primarily on elective GI surgery. Thus, this study was conducted to assess the efficacy of early postoperative EN after surgery in patients with traumatic or nontraumatic GI perforation or strangulation.

MATERIALS AND METHODS

This study was based on a retrospective review of the medical records of 484 patients that underwent emergency GI surgery from January 2007 to December 2012. The study was approved by the Severance Institutional Review Board (IRB No. 4–2014–0505).

Patient Selection

Patients considered for inclusion in this study had all undergone bowel resection and/or anastomosis or primary repair with traumatic or nontraumatic intestinal perforation. The traumatic injuries in all cases were stab wounds. In addition, intestinal obstruction such as strangulation was also included. Additionally, patients with postoperative shock were included in this study, and those patients stopped receiving vasopressors within 2 days postoperatively. Patients that underwent appendectomy, cholecystectomy, or adhesiolysis without bowel resection and/or anastomosis were excluded, as well as patients with sustained bowel ischemia, uncontrolled bowel perforation, or short bowel syndrome.

Clinical Assessment

Clinical factors and surgical outcomes were compared between the 2 groups (EEN = 77 vs late EN [LEN] = 407). Clinical factors consisted of age, gender, American Society of Anesthesiologists score, Acute Physiology and Chronic Health Evaluation II score on intensive care unit (ICU) admission, diagnosis, location of lesion, operation type, presence of stoma, degree of achievement target calorie, and use of supplemental parenteral nutrition (PN). Surgical outcomes consisted of complication rates, complication types, mortality rates, ventilator-free days (VFDs), ICU-free days, and lengths of hospital stay. Energy requirements were calculated either through simplistic formula (25–30 kcal/kg) or Harris–Benedict equation.[15,16] 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. EEN was defined as having had oral provision or EN through nasogastric (NG) or jejunal feeding tube and gastrostomy tube, all postoperatively and within 48 hours. LEN was defined as an oral provision or enteral feeding from 3 to 6 days postoperatively. All feeding tubes were placed in the proximal portion of the anastomotic or primary repair site. VFDs were defined as the number of days between successful weaning from mechanical ventilation and day 28 after surgery. VFDs were 0 if the patient died before day 28 or required mechanical ventilation for ≥28 days. ICU-free days were defined as the number of days between successful transfer to a general ward and day 28 after surgery. ICU-free days were 0 if the patient died before day 28 or stayed in the ICU for ≥28 days. The criteria to start EN included hemodynamic stability or declining doses of vasopressors, secure bowel anastomosis or repair, and no bowel ischemia observed during the surgery. Postoperative pulmonary complications included pneumonia, atelectasis, pleural effusion, and acute respiratory distress syndrome. Wound complications were defined as having experienced a discharge of pus and positive bacterial culture from the surgical sites. Postoperative ileus was defined as sustained nonmechanical obstruction for >4 days after the operation and confirmed by simple abdominal radiography. Infectious complications were defined as a complication accompanying infections, such as pneumonia, wound infection, and sepsis in this study. Newly developed sepsis was defined as a sepsis diagnosed during the periods of stability or improvement from previous septic conditions.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, and continuous variables as medians and interquartile ranges. The analyses were conducted using a χ^2 test for categorical variables and a Mann–Whitney U test for continuous 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, 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. Survival curves were constructed using a Kaplan–Meier survival analysis with comparisons between the curves based on a log-rank χ^2 statistic. In addition, survival was analyzed using a Cox proportional hazard regression model. The proportional hazards assumption was confirmed by inspection of the log curves and examination of time-dependent covariates. Statistical significance was accepted for 2-sided P values of <0.05.

Statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Co, Armonk, NY). Propensity score matching was performed with IBM SPSS version 20.0 and R version R 2.12.1 (R Foundation for Statistical Computing).[17]

RESULTS

Patient Characteristics

Among the 484 adult patients eligible for analysis, 77 (15.9%) received EEN after emergency GI surgery. The baseline characteristics according to when EN was first started are summarized in Table 1. There were significant differences in use of PN and type of feeding route between the 2 groups in an unmatched analysis ($P = 0.001$ and 0.007, respectively). However, there were no significant differences on any of the baseline after matching for propensity score. In addition, there were no significant differences for each surgical approach between the 2 groups with unmatched (EEN = 77 vs LEN = 407; $P = 0.953$) and with propensity score matched patients (EEN = 67 vs LEN = 67; $P = 0.99$) (Table 2).

Clinical Outcomes

Table 3 illustrates the clinical outcomes based on the time of initial start of EN. Patients receiving EEN had reduced in-hospital mortality rates, lengths of hospital stay, pulmonary complications, and more 28-day ICU-free days than those receiving LEN in an unmatched analysis. In the propensity-matched cohort, the EEN group had significantly lower in-hospital mortality rates (4.5% vs 19.4%; $P = 0.008$), pulmonary complications (4.5% vs 19.4%; $P = 0.008$), reduced lengths of hospital stay (median: 14.0, interquartile range: 8.0–24.0 vs median: 17.0, interquartile range: 11.0–26.0, $P = 0.048$), and more 28-day ICU-free days (median: 27.0, interquartile range: 25.0–27.0 vs median: 25.0, interquartile range: 22.0–27.0, $P = 0.042$) than the LEN group. The significant difference in survival between the 2 groups was also shown in the Kaplan–Meier survival curve ($P = 0.042$; Figure 1). The difference in survival between the 2 groups was evident after the second week of surgery, which remained constant throughout the first 28 days of follow-up after surgery. Furthermore, Cox proportional hazard analysis showed that EEN was associated with reduced in-hospital mortality (adjusted hazard ratio, 0.03; 95% confidence interval, 0.01–0.49; $P = 0.015$) (Table 4).

DISCUSSION

In this study, EEN within 48 hours from the completion of emergency GI surgery was associated with reduced in-hospital mortality rates, pulmonary complications, lengths of hospital stay, and more 28-day ICU-free days. Despite the presence of heterogeneity in the population, EEN has seen consistent

TABLE 1. Baseline Characteristics of the Total Population and Matched Population

	Total Population			Propensity Matched Population		
Characteristic	**EEN (N = 77)**	**LEN (N = 407)**	***P* Value**	**EEN (N = 67)**	**LEN (N = 67)**	***P* Value**
Age, y	64 (50–75)	61 (50–71)	0.377	62 (49–74)	66 (54–74)	0.232
Sex, N (%)			0.765			0.859
M:F	50 (64.9): 27 (35.1)	257 (63.1): 150 (36.9)		41 (61.2): 26 (38.8)	42 (62.7): 25 (37.3)	
Body weight, kg	58.0 (49.6–67.3)	60.0 (53.1–66.4)	0.348	60.0 (55.0–65.0)	60.0 (54.0–68.0)	0.616
BMI, kg/m^2	21.7 (20.0–23.8)	22.2 (20.1–24.2)	0.567	22.0 (20.9–23.8)	22.8 (20.8–24.6)	0.265
ASA score	3 (2–3)	3 (2–3)	0.525	3 (2–3)	3 (2–3)	0.619
APACHE II score	18 (15–23)	17 (14–24)	0.482	19 (16–24)	19 (15–26)	0.997
Diagnosis, N (%)			0.131			0.294
Perforation	56 (72.7)	327 (80.3)		50 (74.6)	55 (82.1)	
Obstruction/strangulation	21 (27.3)	80 (19.7)		17 (25.4)	12 (17.9)	
Location of lesion, N (%)			0.679			0.833
Stomach and duodenum	18 (23.4)	115 (28.3)		18 (26.9)	15 (22.4)	
Small bowel	27 (35.1)	134 (32.9)		22 (32.8)	23 (34.3)	
Colon and rectum	32 (41.5)	158 (38.8)		27 (40.3)	29 (43.3)	
Stoma, N (%)	29 (37.7)	128 (31.4)	0.286	23 (34.3)	24 (35.8)	0.856
Postoperative shock, N (%)	14 (18.2)	71 (17.4)	0.876	13 (19.4)	8 (11.9)	0.235
Feeding routes, N (%)			0.007			0.274
Gastric: postpyloric	70 (90.9): 7 (9.1)	396 (97.3): 11 (2.7)		61 (91.0): 6 (9.0)	65 (97.0): 2 (3.0)	
Parenteral nutrition, N (%)	54 (70.1)	377 (92.6)	0.001	54 (80.6)	54 (80.6)	1.000
Achieving goal calorie, N (%)			0.824			0.531
<80%:≥80%	8 (10.4):69 (89.6)	38 (9.6):359 (90.4)		7 (6.1):60 (89.6)	4 (6.1):62 (93.9)	

ASA = American Society of Anesthesiologists, APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, EEN = early enteral nutrition, LEN = late enteral nutrition. Values are expressed as median (interquartile range).

effects, such as reduced in-hospital mortality rates, pulmonary complications, lengths of hospital stay, and more 28-day ICU-free days after matching on the propensity score.

EN has several benefits, such as modulating the metabolic and systemic immune response, as well as preserving gut integrity.[18] For these reasons, EN has been recommended to be initiated as early as possible unless contraindicated.[8,15] Moreover, previously published meta-analysis with regard to this concept showed that EEN was associated with significant reductions in total complications compared with traditional postoperative feeding practices, and does not negatively affect outcomes such as mortality, anastomotic dehiscence, resumption of bowel function, or hospital length of stay.[7] 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.[6]

However, these results primarily focused on elective GI surgery. To date, the study comparing EEN and LEN in patients undergoing emergent surgery was rarely reported. Of these, a retrospective study concluded that early feeding within 48 hours after emergency GI surgery may be feasible in patients without severe shock or bowel anastomosis instability.[11] Moreover, one prospective study reported that immediate postoperative feeding through the feeding jejunostomy is feasible in patients with perforative peritonitis, which may reduce septic morbidity.[14] Another prospective study showed that early enteral feeding through a nasoenteric tube is well tolerated by patients with nontraumatic perforation peritonitis, improving energy and protein intake. It also showed that EEN reduces the amount of NG aspirate, the duration of postoperative ileus, and the risk of serious complications.[12]

In general, there was no difference in mortality between the EEN and the LEN groups in patients who underwent GI

TABLE 2. Surgical Procedures in the Total Population and Matched Population

	Total Population		Propensity Matched Population	
Type of Procedure	**EEN (N = 77)**	**LEN (N = 407)**	**EEN (N = 67)**	**LEN (N = 67)**
Primary repair	19 (24.7)	106 (26.0)	15 (22.4)	13 (19.4)
Wedge resection	2 (2.6)	9 (2.2)	1 (1.5)	1 (1.5)
Gastrectomy (subtotal or total)	4 (5.2)	25 (6.1)	4 (6.0)	5 (7.5)
Small bowel resection with anastomosis	14 (18.2)	92 (22.6)	14 (20.9)	14 (20.9)
Colon resection with anastomosis	9 (11.7)	47 (11.5)	9 (13.4)	9 (13.4)
Ileostomy or jejunostomy	17 (22.1)	78 (19.2)	16 (23.9)	16 (23.9)
Hartmann procedures or colostomy	12 (15.6)	50 (12.3)	8 (11.9)	9 (13.4)

Total population, $P = 0.953$; propensity score matched population, $P = 0.99$.
Values are expressed as number (%).

TABLE 3. Outcome Characteristics in the Total Population and Matched Population

	Total Population			Propensity Matched Population		
	EEN (N = 77)	LEN (N = 407)	*P* Value	EEN (N = 67)	LEN (N = 67)	*P* Value
Length of hospital stay, d	16.0 (9.0–27.8)	20.0 (13.0–35.5)	0.006	14.0 (8.0–24.0)	17.0 (11.0–26.0)	0.048
ICU-free days, d	26.0 (18.5–27.0)	25.0 (19.0–26.0)	0.030	27.0 (25.0–27.0)	25.0 (22.0–27.0)	0.042
VFDs, d	27.0 (20.0–28.0)	27.0 (24.0–27.0)	0.274	27.0 (24.0–28.0)	27.0 (24.5–28.0)	0.295
Complications, N (%)						
Anastomotic leakage	4 (5.2)	21 (5.2)	0.990	1 (1.5)	1 (1.5)	1.000
Infectious	5 (6.5)	58 (14.3)	0.064	5 (7.5)	9 (13.4)	0.259
Wound complication	9 (11.7)	57 (14.0)	0.587	8 (11.9)	8 (11.9)	1.000
Newly developed sepsis	1 (1.3)	22 (5.4)	0.120	1 (1.5)	4 (6.0)	0.172
Pulmonary	3 (3.9)	49 (12.0)	0.034	3 (4.5)	13 (19.4)	0.008
Postoperative ileus	2 (2.6)	9 (2.2)	0.835	2 (3.0)	3 (4.5)	0.649
Overall complications, N (%)	28 (36.4)	196 (48.2)	0.057	14 (20.9)	23 (34.3)	0.082
Mortality, N (%)	3 (3.9)	50 (12.3)	0.031	3 (4.5)	13 (19.4)	0.008

EEN = early enteral nutrition, ICU = intensive care unit, LEN = late enteral nutrition, VFDs = ventilator-free days.
Values are expressed as median (interquartile range).

surgery.[7,12,14,19,20] In other words, research in surgical patients has reported many beneficial effects of EEN, but has not shown that EEN was associated with reduction of mortality. However, despite the mechanism not being clear, a meta-analysis demonstrated that EEN within the first 24 hours postoperatively is beneficial, and may even be associated with reduced mortality rate in comparison to 'nil by mouth' after GI surgery.[6] Meta-analysis with regard to EEN in trauma patients also revealed a statistically significant reduction in mortality attributable to the provision of EN within 24 hours of injury.[21] Thus, we recognized that further studies are required to assess the effect of EEN in patients undergoing emergency GI surgery.

This study demonstrated that EEN was associated with the reduction of in-hospital mortality rate, pulmonary complication, length of hospital stay, and a longer 28-day ICU-free day when compared with LEN in the matched analysis. Moreover, despite the minimal degree reduction, a 3% reduction in 28-day mortality was found in the EEN group in accordance to the multivariate Cox proportional hazard regression analysis after adjusting for covariates. Nevertheless, we were not able to demonstrate any of the benefits that have been reported about EEN, such as reduction of infectious complications.[9] Although the exact mechanism by which EEN contributes to the reduction of in-hospital mortality and pulmonary complication is difficult to determine, some studies relating to septic conditions, such as severe pancreatitis and peritonitis, demonstrated that EEN was associated with decreased in-hospital mortality or pulmonary complication.[22–25] As such, there is clinical evidence supporting the benefits of EEN for patients undergoing emergency GI surgery,[12–14,26] although it is still controversial whether EEN is associated clinical benefits in this specific patient population. Thus, our study has important implications on the nutritional support after emergency GI surgery, and will motivate future studies to conduct adequately powered, randomized controlled clinical trials.

Our sample size was adequately powered to address the primary study objectives using a 2-sided log-rank test, $\alpha = 0.05$ and 80% power. Considering the sample size, our study has validated that EEN may in fact be associated with reduction of in-hospital mortality in patients undergoing emergency GI surgery. Using a propensity score matching method, we also generated comparison groups of patients who had similar factors that affected physicians' decisions regarding EN, as in a randomized trial. However, although matching by propensity score creates a homogenous patient group, we cannot control for all variables

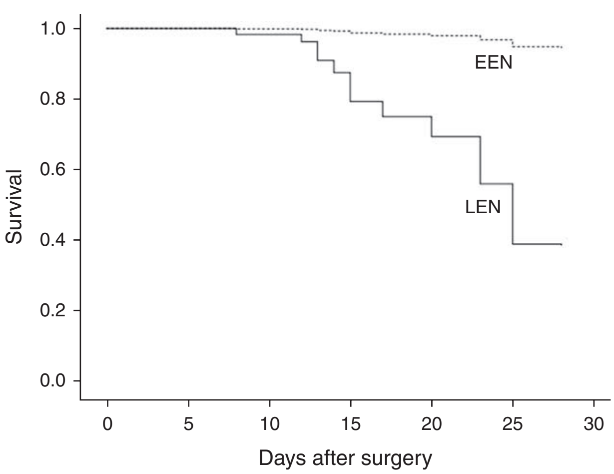

FIGURE 1. Kaplan–Meier curve showing time to death in the early and late enteral nutrition groups among propensity score-matched patients (log-rank test, $P = 0.042$). EEN = early enteral nutrition, LEN = late enteral nutrition.

TABLE 4. Association Between Early Enteral Nutrition and Mortality According to Cox Proportional Hazards Regression Analyses

Model	Hazard Ratio (95% CI)	*P* Value
Unmatched	0.26 (0.03–2.22)	0.219
Propensity matched		
Adjusted for propensity and all covariates	0.03 (0.01–0.49)	0.015

APACHE II = acute physiology and chronic health evaluation II, CI = confidence interval.
Each analysis was done after adjusting for each of complications as well as age, APACHE II score, presence or absence of postoperative shock, and parenteral nutrition.

and unmeasured variables. These unmeasured variables may have affected our results as residual confounders.

There are several limitations to our study. First, this is a retrospective, single-center study. Second, 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. Third, potential confounding by indication is an important consideration. Practitioners are likely to initiate EN as late as possible in more severe patients. In other words, the decision to initiate EN was not conducted randomly. Fourth, 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 88.4% 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. Therefore, our results need to be carefully interpreted.

CONCLUSION

This study comparing EEN with LEN shows that EEN is associated with beneficial effects, such as reduced in-hospital mortality rates, pulmonary complications, lengths of hospital stay, and more 28-day ICU-free days in patients undergoing emergency GI surgery.

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