Early Enteral Nutrition Is Superior to Delayed Enteral Nutrition for the Prevention of Infected Necrosis and Mortality in Acute Pancreatitis

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Objectives: The exact time of initiation of total enteral nutrition (TEN) in severe acute pancreatitis (SAP) and its influence on the disease outcome are not well known.

Methods: An analysis of 197 cases with predicted SAP allocated to: group A (n = 97), early TEN (started within the first 48 hours after admission to hospital); and group B (n = 100), delayed TEN (started after 48 hours).

Results: Infection of necrosis/fluid collections occurred in 4 patients in group A and 18 patients in group B ($P < 0.05$). Respiratory failure and transfer to intensive care unit occurred more frequently in group B than in group A (15 vs 5 and 15 vs 3 patients; $P < 0.05$). Multiple-organ failure was observed in 9 patients in group A and 16 patients in group B ($P > 0.05$). Seven patients in group A and 11 patients in group B underwent surgery ($P > 0.05$). All 9 reported deaths occurred in group B ($P < 0.05$). The time to start TEN was a predictor of infected necrosis/fluid collection (odds ratio, 4.09; $P = 0.028$).

Conclusions: Delayed compared to early TEN is associated with higher mortality, increased frequency of infected necrosis/fluid collections, respiratory failure, and a need for intensive care unit hospitalization. Enteral nutrition in SAP should be started within 48 hours after admission to hospital.

Key Words: pancreatitis, enteral nutrition, necrosis, mortality

(*Pancreas* 2013;42: 640–646)

Approximately 75% to 80% of patients with acute pancreatitis (AP) have a self-limiting disease; in such cases, the total enteral nutrition (TEN) is unnecessary if the patients can consume normal food after 5 to 7 days, and oral feeding should be started as soon as possible. Overall, in approximately 20% of patients, AP progresses to severe AP (SAP) illness with high morbidity and mortality up to 30% associated with systemic inflammatory response syndrome (SIRS) and multiple-organ failure (MOF).[1–4] Nutritional support plays a critical role in the treatment of SAP, as it is a hypercatabolic state with a negative nitrogen balance.[5–8] Acute malnutrition may result in immunological disturbances, septic complications, and delayed healing of surgical wounds.[9] The use of either enteral (EN) or parenteral nutrition (PN) does not stimulate pancreatic secretion and, in comparison with no supplementary nutrition, is associated with a lower risk of death in AP.[10] Several randomized controlled studies and meta-analysis have shown the benefits of EN over PN in SAP, primarily in lower risk of pancreatic infections and mortality.[10–19] Moreover, in recent systematic reviews, in patients with AP, EN significantly reduced not only mortality and systemic infections, but also MOF and the need for operative intervention compared to total parenteral nutrition (TPN).[20] Prolonged fasting can potentially lead to bacterial translocation across the gut barrier and complications. The protective role of TEN in maintaining the integrity of the gut barrier has been demonstrated in a rate model of AP.[21] Therefore, EN is the recommended option for the treatment of SAP, if a patient is not expected to resume oral feeding for 5 to 7 days and should be initiated in the early phases of severe AP.[1–3,22] However, to date, there is no consensus regarding the optimal time to start enteral feeding. There is evidence that in critically ill patients hospitalized in an intensive care unit (ICU), EN administrated before 48 hours from admission is associated with a reduction of infectious complications and mortality compared with delayed nutrition.[23] According to the study of Besselink et al,[24] which demonstrated that bacteremia in AP can be detected as early as day 7, prophylactic strategies aiming to prevent infectious complications should be started in the early phases of the disease. In one systematic review of 11 randomized controlled studies on the effect of EN versus TPN in patients with AP, Petrov at al[19] noted the significant benefits of EN over TEN only if nutrition was started within the first 48 hours of admission, whereas there were no significant differences when nutritional support was started after that time. However, there have been no studies until now that have focused on direct comparisons of the early and delayed times of commencement of EN in AP. In light of these issues, the current retrospective analysis of patients with AP aimed to compare early EN (started within the first 48 hours of admission) with delayed EN (started after 48 hours of admission), with particular attention being paid to the influence of such treatment on the outcome of the disease.

MATERIALS AND METHODS

A retrospective analysis was performed on 420 consecutive patients hospitalized from 2001 to 2010 with a diagnosis of AP. Acute pancreatitis was diagnosed in patients having two of the following characteristics: upper abdominal pain, serum amylase or lipase activities at least 3 times higher than normal, and findings of abdominal contrast-enhanced computed tomography (CT), magnetic resonance imaging, or ultrasonography suggesting AP.[2,25,26] The inclusion criteria were severe AP within the first 48 hours of admission to hospital and treatment with total enteral feeding. The diagnosis of severe AP was established by the presence of one or more of the following within the first 48 hours: SIRS; Acute Physiology and Chronic Health Evaluation (APACHE) II score, 8 or greater; Bedside Index of Severity in AP (BISAP), 3 or greater; Panc 3 score; Ranson

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Received for publication June 23, 2012; accepted August 28, 2012.
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The authors declare no conflict of interest.

score, 3 or greater; Balthazar score C-E; or organ failure assessed using Sequential Organ Failure Assessment (SOFA) score.[1–3,25,27–30] The presence of SIRS was defined by 2 or more of the following parameters: temperature, more than 38°C or less than 36°C; pulse rate, more than 90/min; respiration, more than 20/min, or $PaCO_2$, 32 mm Hg or less; white blood cell count, more than 12,000 or 4000/mm or less^3) within the first 48 hours and persistence of SIRS for more than 48 hours in each study group were also noted.[3,25] Additionally, the APACHE II and SOFA scores were calculated on days 3 and 7 after admission to hospital.[1–3,29] The exclusion criteria in the study were: age, younger than 18 years; admission after 72 hours of the onset of symptoms; acute exacerbation of chronic pancreatitis; AP confirmed during laparotomy for acute abdomen; treatment with total parenteral feeding alone; early deaths of patients with severe AP who did not receive total enteral feeding. Those patients who met the inclusion were then assigned to one of the 2 treatment groups: group A: patients who started total enteral feeding within the first 48 hours after admission to the hospital ("early" nutrition); and group B: patients in whom total enteral feeding was started 48 hours after admission ("delayed" nutrition) (range, 3–7 days). A nasojejunal tube for enteral feeding was inserted by a medical staff, and the position of the tube was checked on radiographs. In patients in whom the passage of the tube tip beyond the Treitz ligament was not achieved, the tube was endoscopically inserted. Along with enteral feeding, the patients were managed by standard medical treatment in AP: intravenous fluid and electrolytes, analgesia, prophylactic antibiotics, and other supportive therapies for organ failure, as indicated. Emergency endoscopic retrograde cholangiopancreatography was performed within 24 to 72 hours on patients with suspected choledocholithiasis.

Data Collection

The following data were collected retrospectively from all patients: (1) demographic data including sex, age, etiology of pancreatitis; the number of patients transferred from other hospitals, the number of patients receiving antibiotics and additional PN; (2) laboratory data including serum levels on admission of: amylase, lipase, lactate dehydrogenase (LDH), hematocrit, bilirubin, glucose, urea, creatinine, alanine transaminase, and serum C-reactive protein (CRP) concentration on admission, day 3, and day 7; (3) radiological data including Balthazar score in CT and presence of necrosis.

In each study group, the following clinical outcomes were assessed: (1) the number of days of hospitalization; (2) the need for ICU admission; (3) the need for surgical intervention; (4) mortality; (5) local complications including acute peripancreatic fluid collections, pseudocyst, infected pancreatic/peripancreatic necrosis or fluid collection, portal/splenic/superior mesenteric vein thrombosis, and hemorrhage; and (6) systemic complications: respiratory and renal, shock, and sepsis. Multiple organ failure (defined as the failure of 2 or all of the following organs: pulmonary, renal, and cardiovascular), which persisted for more than 48 hours in each group, was also noted.[25]

Statistical Analysis

The Stata (Stata/IC version 11.0) statistical package was used for all analysis. Relative (%) frequency measurement in the qualitative variables were used for the descriptive analysis of the characteristics of the patients. The mean and SD were used for the quantitative variables with parametric distribution, and the median and interquartile range were used for variables with nonparametric distribution. The differences between qualitative variables were determined by using the χ^2 test (with the Yates correction when necessary). Comparison of quantitative variables between the 2 treatment groups was performed using the Student t test for those with parametric distribution and the Mann-Whitney U test for those with nonparametric distribution. $P < 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analyses were used for the identification of prognostic factors of mortality and infected necrosis and/or fluid collections. First, to investigate the variables at admission with potential prognostic information, those variables that were statistically significant ($P < 0.05$) in the univariate analysis were entered into a multivariate logistic regression model. The P values for the univariate tests were not corrected for multiple testing because those tests were taken as exploratory. To examine if multicollinearity is present between the variables chosen for the multivariable model, few measures were taken into consideration: tolerances, variance inflation factors, bivariate correlations, correlations of the estimated coefficients, and condition number. The offending variables were removed if necessary. The results of the stepwise multivariable logistic regression analysis as odds ratios and 95% confidence intervals were calculated. $P < 0.05$ was required for significance. To evaluate overall significance of the model (discrimination), the Hosmer-Lemeshow test was performed. For the calibration, the Nagelkerke coefficient of determination and pseudo R^2 were used. The area under the receiver operating characteristic (ROC) (c-index) curve was also calculated.

RESULTS

Characteristics of Study Patients

Of the 420 patients with AP, 197 patients (47%) met the inclusion and exclusion criteria and were considered for the final analysis. Of the 197 patients with severe AP, 97 patients (49%) were allocated to group A ("early" EN) and 100 patients (51%) were allocated to group B ("delayed" EN). The baseline characteristics of the study groups are shown in Table 1. The 2 groups were similar in all presented features except the slight difference in sex distribution (Table 1).

Comparative Analysis of Different Prognostic Scores

The assessment of the severity of AP in the study patients by using different scores is shown in Table 2. On admission to hospital, the severity of AP assessed by different scores was similar in both groups. There were no differences between the study groups in the BISAP score, the Ranson score, the Panc 3 score, the APACHE II score, and the SOFA score on day 1. In both groups, a gradual decrease in APACHE II scores over the study days was observed, with no significant difference between groups A and B on any of the measured days. In both study groups, there was also a decrease in the SOFA score over consecutive days. However, the differences in the SOFA score between groups A and B became significant after day 2 and persisted to day 7 (Table 2).

There were 52 patients (26.4%) who did not meet the criteria of SIRS, 32 patients in group A and 20 patients in group B. In the remaining 145 patients (73.4%), SIRS was observed in the first 48 hours; but in 98 patients (49.7%), SIRS persisted for more than 48 hours. There were no significant differences between groups A and B in the persistence of SIRS after 48 hours (45 vs 53 patients).

Main Clinical Outcomes

Table 3 reports on the main clinical outcomes and complications in the patients with AP. Overall, the total hospital stay

TABLE 1. Characteristics of Study Patients

	Group A (n = 97) Early Enteral Nutrition	Group B (N = 100) Delayed Enteral Nutrition	*P*
Age, median (IQR), yrs	49 (39–56)	50 (41–62.5)	0.918
Sex, M/F, n (%)	72 (74)/25 (26)	61 (61)/39 (39)	*0.048*
Etiology, n (%)			0.127
Alcohol	57 (59)	45 (45)	
Gallstone	29 (30)	43 (43)	
Other	11 (11)	12 (12)	
Antibiotic prophylaxis, n (%)	84 (87)	94 (94)	0.078
Additional parenteral nutrition, n (%)	5 (5.2)	13 (13)	0.056
Transfer from other hospital, n (%)	15 (15.5)	20 (20)	0.405
Tests on admission to hospital, median (IQR)			
Hematocrit, %	43.1 (38.4–46.6)	41.3 (37.7–45.6)	0.145
White blood cell count, $10^3/\mu L$	12.8 (9.95–15.2)	12.25 (10.1–16.3)	0.994
Creatinine, mg/dL	0.94 (0.75–1.6)	0.91 (0.79–1.2)	0.882
Urea, mg/dL	31.0 (24.0–47.0)	35.0 (27.0–46.0)	0.336
Platelet count, $10^3/\mu L$	193.0 (139.0–274.0)	217.0 (164.0–281.0)	0.138
Systolic blood pressure, mm Hg	140 (130–150)	140 (130–160)	0.847
Lipase, IU	520.0 (212.0–1501.0)	694.0 (295.5–1713.0)	0.210
LDH, IU	481.0 (355.0–667.0)	422.0 (307.0–844.0)	0.887
Glucose, mg/100 mL	118.0 (94.0–141.0)	113.5 (98.0–147.0)	0.820
Bilirubin, mg/dL	1.16 (0.82–2.04)	1.38 (0.82–2.24)	0.335
CRP, mg/L			
Day 1	101.3 (30.2–160.1)	88.6 (15.6–189.8)	0.692
Day 3	131.2 (71.4–204.0)	181.0 (96.4–262.5)	0.074
Day 7	77.8 (26.0–138.5)	86.9 (37.3–184.6)	0.172
Balthazar score, n (%)	72 (74%)	80 (80%)	
n (%) C/D/E	27 (27.8)/19 (19.6)/26 (26.8)	32 (32)/18 (18)/30 (30)	0.827

Balthazar score: C - edematous pancreatitis plus mild extrapancreatic changes; D - severe extrapancreatic changes including one fluid collection; E - multiple or extensive extrapancreatic collections.[1]

was similar between the study groups. Moreover, 18 (9.1%) of the 197 patients underwent surgical treatment during hospitalization: 7 patients (7.2%) in group A and 11 (11%) patients in group B (not significant). Surgical procedures comprised the following: debridement of necrosis with lavage and drainage of infected pseudocyst. The percentage of patients admitted to the ICU in group B was significantly higher than that in group A (15% vs 3%; $P < 0.05$; Table 3). All patients admitted to the

TABLE 2. Assessment of SAP in Study Patients by Using Scoring Systems

	Group A Early Enteral Nutrition (n = 97)	Group B Delayed Enteral Nutrition (n = 100)	
Scoring System	**Median, IQR (min-max)**		***P***
BISAP	2.0 (1.0–3.0) (0–5)	2.0 (1.0–3.0) (0–5)	0.215
Panc 3	1.0 (0.0–1.0) (0–3)	1.0 (0.0–2.0) (0–3)	0.803
Ranson	2.0 (1.0–3.0) (0–8)	2.0 (1.0–4.0) (0–8)	0.314
APACHE II			
Day 1	4.0 (2.0–7.0) (0–17)	5.0 (2.0–7.5) (0–21)	0.279
Day 2	3.0 (2.0–6.0) (0–15)	5.0 (2.0–7.0) (0–24)	0.118
Day 3	3.0 (1.0–5.0) (0–12)	4.0 (2.0–6.0) (0–25)	0.097
Day 7	2.0 (0.0–5.0) (0–11)	3.0 (1.0–6.0) (0–22)	0.088
SOFA			
Day 1	1.0 (0.0–3.0) (0–8)	2.0 (0.0–3.0) (0–12)	0.272
Day 2	1.0 (0.0–2.0) (0–8)	1.0 (0.0–3.0) (0–12)	***0.032***
Day 3	0.0 (0.0–2.0) (0–8)	1.0 (0.0–3.0) (0–15)	***0.020***
Day 7	0.0 (0.0–1.0) (0–5)	0.0 (0.0–1.0) (0–19)	***0.001***
SIRS, n (%)			
Persistent >48 hours	45 (46.4)	53 (53)	0.3537

TABLE 3. Clinical Outcomes

Outcome	Group A (n = 97) Early Enteral Nutrition	Group B (n = 100) Delayed Enteral Nutrition	*P*
Hospitalization days, median (IQR)	18.0 (14.0–26.0)	18.5 (14.0–30.0)	0.459
Surgery, n (%)	7 (7.2)	11 (11.0)	0.357
Admission to ICU, n (%)	3 (3.1)	15 (15.0)	***0.019***
Mortality, n (%)	0	9 (9.0)	***0.007***
Local complications, n (%)			
Necrosis	30 (31.0)	34 (34.0)	0.645
Acute fluid collection	36 (37.0)	42 (42.0)	0.483
Infected necrosis/fluid collection	4 (4.1)	18 (18.0)	***0.002***
Pseudocyst	7 (7.2)	13 (13.0)	0.657
Venous thrombosis	7 (7.2)	1 (1.0)	0.064
Ascites	23 (23.7)	31(31.0)	0.106
Hemorrhage	3 (3.1)	6 (6.0)	0.683
Pancreatic fistula	0	2 (2.0)	
Systemic complications, n (%)			
Pulmonary	42 (43.3)	49 (49.0)	0.385
Pleural effusion	37 (38.1)	41 (41.0)	0.682
Atelectasis	24 (24.7)	32 (32.0)	0.259
Pneumonia	19 (19.6)	27 (27.0)	0.219
Respiratory failure	5 (5.2)	15 (15.0)	***0.022***
Acute renal failure	9 (9.3)	16 (16.0)	0.156
Shock	2 (2.1)	5 (5.0)	0.265
Sepsis	2 (2.1)	4 (4.0)	0.498
Hematological complications	26 (26.8)	28 (28.0)	0.851
MOF, n (%)	9 (9.3)	16 (16.0)	0.156
Urinary tract infection, n (%)	7 (7.2)	12 (12.0)	0.256

ICU required assisted ventilatory therapy for respiratory failure. The number of patients that needed additional PN was slightly but not significantly higher in group B than in group A (5% vs 13%; $P = 0.056$; Table 1). The overall inhospital mortality rate was 4.6% (9/197 patients). All reported deaths only occurred in patients with delayed EN ($P < 0.05$; Table 3). All patients who died were hospitalized in ICU because of MOF; four of them were operated on because of infected pancreatic necrosis, and 1 patient was operated on because of abdominal hemorrhage and ileal perforation. One patient died during the first week of hospitalization, 4 patients died during the next 3 weeks, and the last 4 patients died after 1 month of hospitalization.

Local Complications

Contrast-enhanced CT or magnetic resonance imaging scans showed more than 30% pancreatic and/or peripancreatic necrosis in 64 patients (32.5%): 30 (31%) in group A and 34 (34%) in group B ($P > 0.05$). Acute fluid collections occurred in 78 patients (39.4%): 36 in group A and 42 in group B. Pancreatic pseudocysts were reported in 20 patients (10%): 7 patients in group A and 13 patients in group B. There were also no differences between the study groups regarding pancreatic ascites, venous thrombosis, and hemorrhage because of vascular complications of AP. However, infected necrosis or fluid collections were statistically reported more frequently in the patients with delayed EN than in the patients with early EN (accordingly, 18.0% and 4.1%; $P < 0.05$; Table 3). Other rare complications included: pancreatic fistula in 2 cases (group B), ileal perforation in 1 case (group B), rupture of pseudocyst in 1 case (group A), focal splenic lesions on CT scan with characteristics typical of infarction in 3 cases (1 case in group A and 2 cases in group B; data not shown).

Systemic Complications

Overall, pulmonary complications occurred in 91 patients (46.2%): 42 patients (43.3%) in group A and 49 patients in group B (49%). When analyzing the occurrence of specific pulmonary complications according to the time of nutrition introduction, no statistically significant differences were found for pleural effusion, atelectasis, and infection; whereas respiratory failure occurred more often in patients with delayed EN than in the group with early EN (15.0% vs 5.2%; $P < 0.05$). No significant differences between the study groups were noted in the percentage of acute renal failure, shock, sepsis, and hematological complications (including disseminated intravascular coagulation, thrombocytopenia, high level of D-dimer, and prothrombin time elongation). Multiple-organ failure persisting for more than 48 hours was observed more frequently in group B than in group A (16 patients [16%] vs 9 patients [9.3%]), although the difference was not statistically significant.

Predictors of Infected Necrosis/Fluid Collections and Mortality

We next focused on the determination of predictive variables for infected necrosis/fluid collection. In the first step of regression analysis, the following were significant predictors of infected necrosis/fluid collection: the time of initiation of EN, Ranson score, the APACHE II score and SOFA scores at days 2, 3, and 7; the BISAP score; the PANC 3 score; persistence of SIRS after 48 hours; and the presence of MOF. The final model of the stepwise multivariable logistic regression for infected necrosis/fluid collection (logistic regression χ^2, 49.6; $P < 0.001$, pseudo R^2, 0.360; Nagelkerke R^2, 0.443) consisted of 3 variables: the time of initiation of EN, the APACHE II score at day

3, and persistence of SIRS after 48 hours (Table 4). All 3 coefficients were statistically significant. The patients who started EN later (after 48 hours) had almost 4 times increased probability of infected necrosis or fluid collection than the patients who started EN earlier (up to 48 hours). Calibration of the model determined quantitatively by measures as the Hosmer-Lemeshow (HL χ^2, 5.82; $P = 0.668$) and Pearson (χ^2, 38.01; $P = 0.961$) goodness-of-fit statistics confirmed that the model is able to assign appropriate risk among the patients whose experience the model simulates. As a result of discrimination evaluated using ROC, analysis values of sensitivity (31.82%), specificity (98.28%), positive predictive value (70.00%), and negative predictive value (91.94%) were obtained. Using the model, 90.82% of all observations were correctly classified, and the *c*-statistics was 0.8861.

The significant predictors of mortality in the first step of univariate regression analysis were the following: the Ranson score, the APACHE II score at days 1, 2, 3, and 7; the BISAP score; the PANC 3 score, the SOFA score at days 1, 2, and 7; LDH, creatinine, and urea levels on admission to hospital; respiratory failure; shock; infected necrosis/fluid collection; and MOF. The final model for mortality (logistic regression χ^2, 39.03; $P < 0.001$; pseudo R^2, 0.663; and Nagelkerke R^2, 0.700) consists of 3 variables: the APACHE II score at day 3, the SOFA score at day 3, and LDH level on admission, in which only one coefficient was statistically significant (LDH). Calibration of the model determined quantitatively by measures as the Hosmer-Lemeshow (LH χ^2, 2.57, $P = 0.959$) and Pearson (χ^2, 40.45; $P = 1.000$) goodness-of-fit statistics confirm that the model is able to assign appropriate risk among the patients whose experience the model simulates. As a result of discrimination evaluated using ROC analysis values of sensitivity (71.43%), specificity (99.41%), positive predictive value (83.33%), and negative predictive value (98.82%) were obtained. Using the model, 98.30% of all observations were correctly classified, and the *c*-statistics was 0.9856.

DISCUSSION

In the current study, we have demonstrated the advantages of early EN initiated within the first 48 hours after admission to hospital in patients with AP. Early EN, as opposed to delayed EN started after 48 hours (range, 3–7 days), significantly reduced the incidence of infection of pancreatic necrosis and/or fluid collection, mortality, respiratory failure, and the need for hospitalization in ICU. Moreover, the time to initiate EN was a predictor of infected necrosis/and fluid collection.

The fact that the EN is beneficial in AP is supported by a large body of experimental and clinical data. Several randomized controlled studies and meta-analysis showed the superiority of enteral feeding over PN. Enteral nutrition significantly reduced mortality, systemic infections, MOF, and the need for operative intervention compared to TPN.[10–20]

To date, the precise time for initiating enteral support has not been well studied in patients with AP. However, the role of early EN has been studied in critically ill patients hospitalized in ICUs. Enteral nutrition administrated before 48 hours from admission has been associated with a significant 24% reduction of infectious complications and a 32% reduction in mortality compared with delayed nutrition started after that point in time.[23,31] In another meta-analysis of 11 randomized controlled studies of any type of enteral feeding initiated early—within 24 hours of gastrointestinal surgery compared to delayed (started after 24 hours) enteral feeding—the authors demonstrated a reduced risk of infectious complications and reduced hospitalization stay with the use of early enteral feeding.[32] In recently published meta-analysis with 2 additional studies, the reduced mortality was shown in the group with early enteral feeding started within 24 hours after gastrointestinal surgery.[33] An important finding in our study is that delayed EN is associated with an increased incidence of infection of necrosis and/or fluid collection, which occurred in 18 patients compared to 4 patients with an early start of EN. Moreover, we found 3 main predictors of infectious complications: delayed nutrition, persistence of SIRS for more than 48 hours, and the APACHE II score at day 3. Furthermore, all 9 deaths occurred in the group with delayed nutrition, introduced after 48 hours (range in days, 3–7). All patients who died were hospitalized in ICU because of MOF; four of them were operated on because of infected necrosis, and 1 patient was operated on because of abdominal hemorrhage and ileal fistula. In our study, we did not show the differences in the duration of hospitalization regarding the time of EN. However, this might be associated with the differences in the mortality between the groups.

The results of the present study are in concordance with some data from the study of Petrov at al.[19] In this systematic review of 11 randomized controlled studies on the effect of EN versus TPN in patients with AP, the authors noted the significant benefits of EN over TEN including decreased risk of MOF development, pancreatic infectious complications, and mortality. However, these benefits were observed only if EN was started within the first 48 hours of admission, whereas there were no significant differences when nutrition support was started after that time.

TABLE 4. Prognostic Variables of Infected Necrosis/Fluid Collection and Mortality

	Infected Necrosis or Infected Fluid Collection				
Variable	**Coefficient Expressed in Logits**	**Standard Error**	***P***	**Odds Ratio**	**95% Confidence Interval**
Time to start EN	1.410	0.640	0.028	4.094	1.169–14.343
APACHE II score at day 3	0.329	0.087	<0.001	1.389	1.173–1.646
Persistence of SIRS after 48 hours	1.147	0.562	0.041	3.150	1.048–9.471
Constant	−7.946	1.600	<0.001		
	Mortality				
	Coefficient expressed in Logits	**Standard Error**	***P***	**Odds ratio**	**95% Confidence Interval**
APACHE II score at day 3	1.818	0.147	0.215	1.199	0.899–1.598
SOFA score at day 3	0.404	0.207	0.051	1.498	0.999–2.247
LDH on admission to hospital	0.001	0.001	0.028	1.001	1.000–1.002
Constant	−7.882	1.772	<0.001	−7.882	1.772

Our results may be partly explained by the fact that prolonged fasting can potentially lead to bacterial translocation across the gut barrier and complications. The protective role of EN in maintaining the integrity of the gut barrier has been demonstrated in a rate model of AP. The group with EN had significantly less bacterial translocation and a lower endotoxin level than the group with TPN.[21] Intestinal mucosa dysfunction is injured in the early phase of AP, especially in patients with organ dysfunction, which may be a stimulus for the development of organ failure, and correlate with bad outcomes in patients with AP.[34] Moreover, Besselink et al[24] demonstrated that bacteremia in AP can be detected as early as day 7 and is associated with an increased risk of infected necrosis and higher mortality. In addition, bacteremia, infected necrosis, organ failure, and mortality are all associated with intestinal barrier dysfunction early in the course of AP. In a randomized trial of a specific probiotic composition and intestinal barrier dysfunction in AP, it was demonstrated that the excretion of intestinal fatty acid–binding protein (a parameter for enterocyte damage) in the first 72 hours was higher in patients who developed bacteremia and organ failure or who died.[35] According to the aforementioned studies of Besselink at al, prophylactic strategies in AP should focus on early intervention.[24,35] Therefore, EN started early may be beneficial. The findings of our study support the benefits of the use of early enteral feeding in patients with AP, which include lower incidence of necrosis infection or fluid collection infection and mortality. Overall, 19 (9.6%) of the 197 patients underwent surgical treatment in our study. However, we have not demonstrated the significant differences in the number of patients who needed surgical intervention regarding the time of initiating the nutrition.

In addition, we have demonstrated the higher incidence of respiratory failure in the patients with delayed EN than in the patients with early administration of EN. Moreover, the number of patients who needed hospitalization in the ICU was higher in the group with delayed EN than in the group with early EN. All 18 (9%) of the 197 patients (18 patients admitted to the ICU required assisted ventilatory therapy for respiratory failure. In this regard, a recent study has shown that the use of mechanical ventilation is an independent predictor of the outcome in patients with AP admitted to the ICU.[36] In addition, we observed a tendency of more frequently used additional PN in patients with delayed EN compared to patients with early EN.

Moreover, we observed that the delayed EN was associated with a trend toward increased incidence of MOF and all other complications shown in Table 3. The differences in the incidence of complications (except infected necrosis/fluid collection and respiratory failure) between the study groups did not reach significance level, probably because of the small sample size. Multiple organ failure was observed in 9 patients (9.3%) in the group with early EN and in 16 patients (16%) in the group with delayed EN. These observations are in agreement with another study finding: the differences in the SOFA score between study groups over consecutive days. The mean SOFA score was similar on admission to hospital in both groups; but after 48 hours, we noted significant differences between the groups. The mean score was higher in the group with delayed nutrition on days 2, 3, and 7 than in the group with early EN. Among all scoring systems of the severity of AP, the SOFA score has additional advantages of easy applicability and timely assessment.[27,36–38] Sequential Organ Failure Assessment–based models for organ failure assessment seem to have a comparable performance with other organ failure scores. The combination of sequential SOFA derivatives with APACHE II/III and Simplified Acute Physiology Score II models clearly improved prognostic performance of either model alone for predicting mortality in patients hospitalized in the ICU.[38]

This study has some limitations, mainly due to the retrospective nature of the analysis. Therefore, it may be biased because of difficulties with the assessment of the onset of symptoms before admission to hospital that has resulted in including, for the purposes of this analysis, the patients at different points in the development of the disease. However, we considered for the final analysis those patients with the onset of symptoms no more than 72 hours before hospitalization, and we also included patients transferred from other hospitals. We think that the observed slightly significant differences in sex between the 2 study arms may rather reflect the not significant differences in gallstone etiology between the arms but not the study results. We believe it rather resulted in the early use of endoscopic retrograde cholangiopancreatography on patients with choledocholithiasis but did not influence the severity of the disease. In addition, we think the higher levels of CRP observed in group B partly depend on cholangitis. However, the differences in the CRP levels were not significant. Moreover, there were not any significant differences between the study groups in the severity scores and laboratory tests analyzed on admission to hospital, which may indicate that in the first hours, the severity of AP in both study arms was comparable.

We did not focus on prophylactic antibiotic use in our patients. However, to date, there is no evidence that supports the survival benefits of the routine use of the antibiotic prophylaxis in patients with severe AP.[39–41] The use of the prophylactic broad-spectrum antibiotic may reduce the infection rates in CT-proven necrotizing pancreatitis but may not improve a patient's survival. We should also point out that in all studies, meta-analysis investigating the role of the antibiotic prophylaxis in AP has several limitations. To date, the data are mixed and difficult to interpret, and different recommendations have been made.[1–3,22,30] In addition, in our study, most of the patients (90%) received the antibiotic prophylaxis. Moreover, there were no statistical differences between the study groups in the number of patients who received or did not receive prophylactic antibiotics; and therefore, we believe that the antibiotic prophylaxis did not influence the results of the study. It should be pointed out that we excluded from the final analysis of clinical outcomes in AP those patients with severe AP who died early in the course of the disease and who had not received EN or who had received total PN alone.

In summary, the present study shows that in patients with AP, early EN initiated within the first 48 hours of admission to hospital significantly reduced infection of pancreatic necrosis or fluid collection, respiratory failure, mortality, and the need for ICU hospitalization compared to delayed EN started after 48 hours. Enteral nutrition should be started as soon as possible, no later than 48 hours after admission to hospital.

Our findings warrant further adequately powered prospective randomized studies on early versus delayed EN in severe AP. The timing of the initiation of EN must be investigated. Currently, a randomized controlled parallel-group multicenter PHYTON trial is ongoing that has been designated to investigate whether the start of EN within 24 hours after admission to hospital reduces infections and mortality in predicted severe AP compared to the start of EN after 72 hours. This trial may give a more definitive answer.[42]

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