



The optimal timing of enteral nutrition and its effect on the prognosis of acute pancreatitis: A propensity score matched cohort study



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ABSTRACT

Background: Early enteral nutrition (EN) can improve the prognosis of acute pancreatitis (AP), but the optimal initiation time is unknown. In this study, the optimal time of early EN was analyzed to disclose the application of early EN in AP.

Methods: Data of 104 patients with AP were prospectively collected. With secondary infection (infected pancreatic necrosis and extrapancreatic infection) as the primary outcome variable, receiver operating characteristic (ROC) curve was used to calculate the optimal cut-off time of early EN. Propensity score matching was used to adjust for covariates. Secondary outcomes include acute gastrointestinal injury (AGI) grades, serum albumin level, and EN-related complications.

Results: The ROC curve analysis showed that the third day after hospital admission was the best cut-off time of early EN (with the area under the curve of 0.744). After PS matching, the proportion of secondary infection in the early EN group was significantly lower than the late EN group (8.6% vs. 36.5%, $P < 0.05$). Regression analysis showed that early EN was a protective factor against secondary infection (OR 0.161, 95%CI 0.036–0.718, $P < 0.05$). The AGI grades and serum albumin levels were better improved in the early EN group (AGI $F = 4.468$, $P < 0.05$; serum albumin $F = 3.794$, $P < 0.05$). The proportion of EN-related abdominal distension in the early EN group was significantly lower (8.8% vs. 38.5%, $P < 0.05$).

Conclusions: Early EN initiated within three days could reduce the risk of secondary infection and improve the nutritional status of patients with acute pancreatitis, with a better tolerance.

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Introduction

Acute pancreatitis (AP) is one of the most common clinical acute abdomen diseases. It can be complicated with pancreatic necrosis and multiple organ failure. The mortality rate of severe patients is as high as 20–25% [1].

Enteral nutrition (EN), as an economical and effective treatment regimen, has been widely recognized in the management of AP. Compared to total parenteral nutrition (TPN), EN could significantly decrease the mortality and reduce the risk of organ failure of patients with AP [2]. Furthermore, an early initiation of EN was more effective than delayed EN in reducing the risk of pancreatic

infection and mortality [3]. However, the current publications and consensus have inconsistent views for the timing of the early EN. The initiations of early EN were set at 24 h, 48 h, 48–72 h, 72 h and 96 h according to clinician's experience [4–11], which may cause bias.

The assumption of our study was that early initiation of EN improves the prognosis of acute pancreatitis and the state of nutrition. We performed this prospective cohort study to verify the efficiency of early EN in acute pancreatitis. Propensity score (PS) matching and receiver operating characteristic (ROC) curve analyze were used to explore the best initiation time of early EN.

Materials and methods

Study subjects

From October 2013 to June 2016, 104 patients with moderate

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severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) who were treated at Peking Union Medical College Hospital in China were prospectively consecutively enrolled. The diagnostic criteria of MSAP and SAP [12] were according to the revised Atlanta classification [12]. The exclusion criteria were (1) patients with gastrointestinal bleeding or gastrointestinal obstruction; (2) patients allergic to the components of EN fluid; (3) patients with malignant tumors; (4) patients with multiple onsets; (5) patients not able to describe the subjective uncomfortable symptoms; and (6) pregnant patients.

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital.

Study procedures

The prospective open-study was performed in this study. Patients who met the diagnostic criteria for MSAP or SAP received treatments of rehydration, correction of electrolyte disorders and organ function support after hospital admission, in accordance with the 2013 American College of Gastroenterology guideline [5]. Starting EN was determined from the admission to hospital, and when patient was fully resuscitated and/or stable [13]. The EN starting time was defined from hospital admission, and was determined by the clinician. The X ray-guided placement of a nasojunal feeding tube was performed, and EN was initiated.

Peptide formulation was selected as the EN preparation. EN formulation was continuously input using an infusion pump following a strict volume regimen: 20 ml/h in the first 24 h, 40 ml/h between 24 and 48 h, 60–80 ml/h between 48 and 72 h, and reach a sufficient amount (25 kcal/kg/d, ideal weight) at 72 h and thereafter. Feeding intolerance was defined as the aggravation or new onset of vomiting, abdominal distention, abdominal discomfort, and diarrhea, which occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced. If the above feeding speed was not tolerated, it would be reduced to 50% and stepwise rebuilt gradually until tolerated. If after two of such attempts, full nutrition could not be attained, PN will be started to reach the required energy target. The EN-related side effects were observed and recorded, including (1) mechanical side effects, such as catheter obstruction; (2) aspiration pneumonia; (3) EN associated diarrhea: occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced; and (4) EN associated abdominal distension: occurred after the start or an increase of EN infusion speed, and alleviated when the EN was stopped or the infusion speed was reduced.

Data collection

Patients' gender, age, etiology, and BMI were recorded; the clinical manifestations and the laboratory and imaging data of the patients at hospital admission and on the 7th and 14th days after the hospital admission, as well as the length of hospital stay and cost, were collected. The acute gastrointestinal injury (AGI) was defined as the malfunctioning of the gastrointestinal tract in critically ill patients. According to the 2012 recommendations of the ESICM [14], AGI can be distinguished into four grades: Grade I = risk of developing gastrointestinal dysfunction or failure (a self-limiting condition); Grade II = gastrointestinal dysfunction (a condition that requires intervention); Grade III = gastrointestinal failure (gastrointestinal function cannot be restored with interventions); Grade IV = severe impact on distant organ function (a condition that in immediately life-threatening). The AGI ratings were performed for all of the patients at admission, and were reevaluated on a daily basis.

The primary outcome variables were secondary infection and death during hospitalization. Secondary infection included infected pancreatic necrosis and extrapancreatic infection (bacteremia, pneumonia and urinary tract infection) occurred during hospitalization [12,15]. The diagnosis of infected pancreatic necrosis was presumed when there was extraluminal gas in the pancreatic and/or peripancreatic tissues on computed tomography or when fine-needle aspiration was positive for pathogen culture [12]. The diagnosis of extrapancreatic infection was defined as positive pathogen culture obtained from blood, sputum or urine samples [15]. The secondary outcomes were defined as the need for percutaneous, endoscopy or surgical intervention, local complications (acute necrotic collection, walled-off necrosis) [12], admission to the ICU, the length of hospital stay, and cost.

Statistical analysis

The statistical analysis of the data was performed using SPSS 23.0 software. The counting data were represented as the percentage, with the χ^2 test; the measurement data were represented as the mean \pm standard deviation, with a *t*-test for the normally distributed variables and a non-parametric test for the non-normally distributed variables.

The PS is the probability that a patient would receive the treatment of interest, based on characteristics of the patient, treating clinician, and clinical environment, estimated by multi-variable statistical methods. The PS matching involves assembling 2 groups of study participants, while matching individuals with similar or identical PSs. The analysis of a PS-matched sample can approximate that of a randomized trial by directly comparing outcomes between different groups. In this study, the PS matching was performed as 1:2 match of the early and late EN groups through nearest-neighborhood method, with a caliper width of 0.25 times the SD of the logit of propensity scores. Age, sex, etiology, disease severity, abdominal pain, visual analogue scale of abdominal pain, abdominal distension, AGI grade and serum albumin level at admission were included for PS matching. After PS matching, all cases were equally matched for relevant confounders.

An ROC curve was used to determine the optimal EN starting time. A logistic regression was used to analyze the effect of early EN on secondary infection. The data of repeated measurements were analyzed using an analysis of variance (ANOVA) for repeated measures. $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of study population

During the study period, a total of 135 patients admitted meeting the inclusion criteria. Thirty-one were excluded, including gastrointestinal bleeding ($n = 1$), multiple onsets ($n = 11$), pregnant ($n = 7$). During assessment, 12 patients were excluded for missing data. (Fig. 1)

As a result, 104 patients were eligible for final analysis. Among them, 68 were male (65.4%) and 36 were female (34.6%), with a mean age of 43.12 ± 15.13 years. There were 56 cases of MSAP (53.8%) and 48 cases of SAP (46.2%). All patients with SAP presented with local complications. The frequency distribution of EN initiation time was showed in Fig. 2. The average starting time of enteral nutrition was 5.7 ± 4.2 days, with a range of 1–20 days after admission.

Optimal EN starting time

With secondary infection as the outcome variable, the ROC

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