Early enteral nutrition versus delayed enteral nutrition in acute pancreatitis
A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Whether early enteral nutrition (EEN) administration is more beneficial than delayed enteral nutrition (DEN) for patients with acute pancreatitis remains controversial.

Methods: This meta-analysis aimed to pool all relevant articles to evaluate the effects of EEN within 48 hours versus DEN beyond 48 hours on the clinical outcomes of patients with acute pancreatitis. We searched PubMed, Scopus, Embase, and Web of Science for all relevant studies and extracted the data concerning basic characteristics, complications, and mortality. We calculated the pooled risk ratio (RR), weighted mean difference, and the corresponding 95% confidential interval (95% CI) using STATA 12.0.

Results: For complications, the pooled analysis showed that EEN was related to a reduced risk of multiple organ failure (RR = 0.67, 95% CI 0.46–0.99, P = .04), but not for necrotizing pancreatitis (RR = 0.95, 95% CI 0.81–1.12, P = .57). There was a tendency for decreased systemic inflammatory response syndrome in the EEN group, but the trend was not significant (RR = 0.85, 95% CI 0.71–1.02, P = .09). For mortality, no significant difference was found between the EEN and DEN groups (RR = 0.78, 95% CI 0.27–2.24, P = .64).

Conclusion: EEN within 48 hours is superior to DEN beyond 48 hours for patients with acute pancreatitis; however, more studies are required to verify this conclusion.

Abbreviations: CI = confidential interval, CRP = C-reactive protein, DEN = delayed enteral nutrition, EEN = early enteral nutrition, RCT = randomized comparative trial, RR = risk ratio, SIRS = systemic inflammatory response syndrome.

Keywords: acute pancreatitis, enteral nutrition, meta-analysis, multiple organ failure

1. Introduction

Acute pancreatitis is one of the most common diseases leading to hospital or intensive care unit (ICU) admission because of the risk of increased systemic inflammatory response syndrome (SIRS), multiple organ failure, septic organ dysfunction, local complications, and other ailments.\(^1\)\(^{-}\)\(^3\)

Nutritional support is very important for patients with acute pancreatitis, especially for those with severe acute pancreatitis.\(^4\)\(^{-}\)\(^6\) Infected pancreatic necrosis is associated with a mortality of 15%. Damage to the gut barrier in the early phase of acute pancreatitis accounts for the initiation of SIRS, sepsis, and infected pancreatic necrosis.\(^7\)\(^{-}\)\(^6\) Thirty-three percent of pancreas infections take place in the first 24 hours and 75% between 48 and 96 hours.\(^7\) Therefore, not only the gut barrier but also nutrition timing is crucial for patients with acute pancreatitis. Many trials have found that enteral nutrition was better at maintaining the gut barrier and decreasing bacterial translocation.\(^8\)\(^{-}\)\(^10\) Recently, a series of clinical trials stressed the importance of early enteral nutrition (EEN) compared with delayed enteral nutrition (DEN).\(^9\)\(^\)\(^11\) In a meta-analysis including 11 studies, although EEN was associated with a lower rate of pancreatic infection, mortality, and organ failure than total parenteral nutrition (TPN) and DEN, there is still no sufficient and direct proof to support EEN being preferable to DEN for patients with acute pancreatitis.\(^11\)\(^{-}\)\(^13\) That meta-analysis only performed comparative analyses between the EEN group and DEN plus PN groups; however, there was no separate comparison between the EEN group and DEN group.\(^11\)

To explore whether EEN is more beneficial to patients with acute pancreatitis than DEN, we searched for eligible studies that reported the clinical outcomes of EEN and DEN groups and performed aggregating analyses.

2. Patients and methods

2.1. Search strategies

We searched for relevant studies concerning early EN in PubMed, Web of Science, Embase, and Scopus from inception to August 2016. The following terms and strategies were used to search in the databases: “Enteral nutrition OR tube feeding OR nasogastric OR nasojejunal” and “Randomized controlled trial OR RCT OR clinical trial OR trial” and “Pancreatitis.” During the search, no language limits were set. To avoid missing qualified trials, we
also scrutinized the reference lists of relevant meta-analyses and reviews. All analyses were based on previous published studies and no ethical approval and patient consent were required.

2.2. Selection criteria

Studies included in this meta-analysis had to fulfill the following criteria:

1. Randomized comparative trials (RCTs) or retrospective trials with available information;
2. Consecutive patients with acute pancreatitis;
3. Early enteral nutrition (EEN) within 48 hours and delayed enteral nutrition (DEN) beyond 48 hours.

Studies were excluded if they were

1. Duplicate publications;
2. Case reports, reviews, meta-analyses, or guidelines;
3. Contained no available data for this meta-analysis.

2.3. Data extraction and management

The following information was extracted from the included trials: first author, year of publication, start time and route of EN administration, severity of acute pancreatitis, number of participants. Basic data about gender, age, APACHE II score, and C-reactive protein (CRP, mg/L) were extracted and analyzed. To compare the clinical outcomes of the EEN and DEN groups, data on SIRS, multiple organ failure, and mortality were extracted. We used a formula adopted by previous studies to acquire the mean and standard deviation.[12,13]

2.4. Quality assessment and bias assessment

The quality of the included RCTs was assessed according to the methodological criteria of the Cochrane Handbook for Systematic Reviews of Interventions, and the quality of retrospective researches was assessed by the Newcastle–Ottawa Scale (NOS). Begg test was used to assess the publication bias, which was based on the risk ratios (RRs) of mortality and necrotizing pancreatitis.

2.5. Statistical analysis

All analyses were performed using STATA 12.0 (Stata Corporation, College Station, Texas). Data of binary outcomes extracted from original studies were pooled to estimate the RRs and corresponding 95% confidence intervals (CIs), and continuous outcomes were pooled to estimate overall weighted mean difference and corresponding 95% CIs. The $I^2$ test and $Q$ test were used to measure statistical heterogeneity among the included studies and $P < 0.1$ or $I^2 > 50\%$ indicated significant heterogeneity. A random-effect model was used for statistics with heterogeneity, otherwise a fixed-effect model was applied. A $P < 0.05$ in the $Z$ test was considered as a significant difference for the pooled estimates. The potential publication bias was assessed by Begg test and a $P < 0.05$ was considered as a statistically significant publication bias.

3. Results

3.1. Included trials characteristics and quality assessment

A total of 1424 articles were obtained from PubMed, Scopus, Embase, and Web of Science. The flow diagram for searching and screening of eligible studies is shown in Fig. 1. Finally, 6 articles including enrolled 1007 patients were included in this meta-analysis, comprising 2 retrospective studies and 4 RCTs.[9,10,14–17] The characteristics of the included studies are illustrated in Table 1. The quality of the included RCTs, as assessed by the Cochrane Handbook for Systematic Reviews of Interventions, is displayed in Table 2, and quality assessment of the included retrospective trials, as assessed by the Newcastle–Ottawa Scale, is summarized in Table 3.

![Figure 1. PRISMA flow diagram of the article screening process for the meta-analysis.](image-url)
3.2. Basic characteristics comparison between EEN and DEN

To explore whether the baseline characteristics were similar, we aggregated the available data on age, gender, APACHE II score, and CRP (mg/L). Our results showed no differences between the EEN and DEN groups in terms of these characteristics (Figs. 2 and 3).

3.3. Effect of EEN on complications and mortality

Acute pancreatitis can bring about many nonpancreatic complications, such as SIRS, multiple organ failure, and necrotizing pancreatitis. After aggregating the data, we found that EEN was associated with a significant reduction in the rate of multiple organ failure (RR = 0.67, 95% CI 0.46–0.99, P = .04,

Table 1

Included studies comparing EEN with DEN.

| Ref.   | Year | EEN timing | DEN timing | Case | EEN group | DEN group | Setting          | EN route         |
|--------|------|------------|------------|------|-----------|-----------|------------------|------------------|
| Bakker et al[14] | 2009 | Within 48 h | Beyond 48 h | 296  | 184       | 112       | Retrospect       | Nasojejunal tube |
| Urszula[17]     | 2013 | Within 48 h | Beyond 72 h | 197  | 97        | 100       | Retrospect       | Nasojejunal tube |
| Sun et al[10]   | 2013 | Within 48 h | beyond 8 d  | 60   | 30        | 30        | RCT              | Nasojejunal tube |
| Petrov et al[15] | 2013 | Within 24 h | Beyond 72 h | 35   | 17        | 18        | RCT              | Nasogastric tube |
| Bakker et al[9] | 2014 | Within 24 h | Beyond 72 h | 205  | 101       | 104       | RCT              | Nasoenteric tube or oral |
| Stimac et al[16] | 2017 | Within 24 h | Beyond 72 h | 214  | 107       | 107       | RCT              | Nasojejunal tube |

Table 2

Quality assessment of included studies: quality of the included RCTs.

| Study            | Adequate sequence generation | Adequate allocation concealment | Blinding | Incomplete outcome data adequately addressed | Free of selective reporting | Free of other bias |
|------------------|-------------------------------|---------------------------------|----------|---------------------------------------------|-----------------------------|-------------------|
| Sun et al[14]    | Yes                           | Yes                             | Unclear  | No                                           | Yes                         | Unclear           |
| Bakker et al[9]  | Yes                           | Yes                             | Yes      | No                                           | Yes                         | Yes               |
| Petrov et al[15] | Yes                           | Yes                             | Yes      | No                                           | Yes                         | Unclear           |
| Stimac et al[16] | Yes                           | Yes                             | Unclear  | Yes                                          | Yes                         | No                |

Table 3

Quality assessment of included studies: quality of the included retrospective studies.

| Ref.            | Representativeness of treated arm | Selection of the comparative treatment arm (s) | Ascertainment of the treatment regimen | Demonstration of outcome of interest was not present at star of study | Comparability between patients in different treatment arms: main factor | Comparability between patients in different treatment arms: secondary factor | Assessment of outcome with independency | Adequacy of follow-up length (to assess outcome) | Lost to follow-up acceptable (less than 10% and reported) |
|-----------------|-----------------------------------|-----------------------------------------------|--------------------------------------|---------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Urszula 2013[17] | Yes                               | Yes                                           | Yes                                  | Yes                             | Yes                                             | No                              | No                              | Yes                             | Yes                             |
| Bakker et al[14] | Yes                               | Yes                                           | Yes                                  | Yes                             | Yes                                             | No                              | No                              | Yes                             | Yes                             |

Figure 2. Gender of the patients at baseline (fixed-effect model).
Fig. 4), but not for necrotizing pancreatitis (RR = 0.95, 95% CI 0.81–1.12, P = .57, Fig. 5). There was a tendency of decreased SIRS in EEN, but the difference was not significant (RR = 0.85, 95% CI 0.71–1.02, P = .09, Fig. 6).

3.4. Effect of EEN on mortality

Four studies presented data on the incidence of mortality of EEN and DEN. There was no significant reduction in mortality when comparing the EEN group with the DEN group (RR = 0.78, 95% CI 0.27–2.24, P = .64, Fig. 7).

3.5. Publication bias

In this part of the study, 4 RCTs and 2 retrospective trials were included. The funnel plots of the RRs for mortality and necrotizing pancreatitis were used to assess publication bias. Begg test results showed Pr > |z| = 1.00 and Pr > |z| = 0.09,
respectively (Figs. 8 and 9). Therefore, we believe that the risk of publication bias is low in this meta-analysis.

4. Discussion
Acute pancreatitis can lead to serious local and systemic complications, such as pancreatic necrosis, pancreatic infection, multiple organ failure, and SIRS. Many studies on nutrition have supported a shift from TPN to enteral nutrition for patients with pancreatitis because of fewer complications and lower mortality.[18] Moreover, some studies also indicated that the timing of EN should start as early as possible compared with conventional parenteral nutrition.[19,20] However, whether early EN is better than delayed EN in acute pancreatitis remains controversial. In this meta-analysis, we included 6 studies that satisfied our criteria and aggregated the data for clinical outcomes. We found that EEN was associated with a significant decrease in the incidence of multiple organ failure, but was not significant for other complications and mortality.

This meta-analysis was designed to compare the effect of early EN and delayed EN in acute pancreatitis. We set “beyond 48 hours” as the delayed EN, as in previous studies.[11] Our results showed that EEN could help to reduce the rate of multiple organ
failure. Intestinal permeability caused by pancreatitis leads to increased serum endotoxin and cytokine levels, resulting in SIRS, which is involved in organ failure. Gut function damage in the course of acute pancreatitis can occur as early as 48 to 72 hours after onset. EEN may help to sustain gut permeability and prevent bacterial translocation. Second, the starting time of EN in the included articles varied between 24 or 48 hours. Some studies set an optimal time of 24 hours, while others used 48 hours, or even 72 hours. Therefore, early enteral feeding would help stabilize the integrity of the gut mucosa and enhance recovery from acute pancreatitis; however, the optimal time of administration remains controversial.

Some limitations of our study need to be discussed. First, not all included studies were RCTs; however, a sensitivity analysis was performed to assess the publication bias. Only 1 item among these studies showed significant heterogeneity. When the heterogeneity was over 50%, the random model was used. Second, because of the different feeding routes and timing, it was hard to avoid these slight differences. In this meta-analysis, we only focused the distinction between EEN and DEN and the time point of their administration was set as 48 hours after disease diagnosis, as described in a previous study. Therefore, in this meta-analysis, we aimed to provide some general conclusions about the superiority of EEN over DEN for patients with acute pancreatitis. Finally, not every included study reported every item, such as mortality and multiple organ failure, even upon request.

Our results indicated that EEN should be recommended as the preferred nutrition routine in acute pancreatitis; however, more multicenter, randomized clinical trials are warranted to verify these findings.

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