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Meta-Analysis of Early Enteral Nutrition Provided Within 24 Hours of Admission on Clinical Outcomes in Acute Pancreatitis

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Abstract

Background: Enteral nutrition (EN) is more beneficial than parenteral nutrition (PN) in reducing organ failure, infectious complications, and mortality of acute pancreatitis (AP), but its timing is controversial. We attempted to evaluate the safety and clinical outcomes of early EN within 24 hours of admission in patients with AP, especially in predicted severe or severe acute pancreatitis (SAP). *Methods:* We searched PubMed, EMBASE Databases, Web of Science, and the Cochrane Library for relevant articles before June 2016 using RevMan 5.2 software. *Results:* Eight studies containing 727 patients with AP were analyzed in the meta-analysis. Comparing early EN to late EN or total parental nutrition in AP, the odds ratios (OR) were 0.56 (95% CI 0.23 –1.34) for the risk of mortality, 0.40 (95% CI 0.20–0.79) for multiple organ failure, 0.57 (95% CI 0.23–1.42) for infectious complications, 0.45 (95% CI 0.17–1.21) for adverse events, and 0.83 (95% CI 0.59–1.18) for pancreatic-related infections. Furthermore, subgroup analysis for early EN in predicted severe or SAP showed a significant reduction in multiple organ failure (OR 0.30; 95% CI 0.09–0.96) and pancreatic-related infections (OR 0.51, 95% CI 0.29–0.88). Early EN provided no benefits for mild to moderate AP. *Conclusion:* Early EN within 24 hours of admission is safe and provides benefits for predicted severe or SAP, but not for mild to moderate pancreatitis. (*JPEN J Parenter Enteral Nutr.* 2018;42:1139–1147)

Keywords

acute pancreatitis; early enteral nutrition; meta-analysis; timing

Clinical Relevancy Statement

The optimal timing of enteral nutrition in acute pancreatitis is uncertain. Our article describes the benefits for early EN within 24 hours of admission in predicted severe or severe acute pancreatitis. Therefore, our findings are both essential and clinically relevant to provide patients with acute pancreatitis to receive enteral nutrition.

Background

Sequential systemic infections and multiple organ failure are major risk factors for mortality of severe acute pancreatitis (SAP).[1,2] Most patients with acute pancreatitis (AP) can recovery uneventfully after a few days. Approximately 20% of patients have infectious complications, and they account for a mortality of 15%.

AP is the most common gastrointestinal and hypermetabolic disease that leads to increased risk of infectious complications due to damage of the gut barrier. Previous studies have revealed that the increased intestinal permeability is a pivotal initiated factor for bacterial overgrowth and translocation in the gut, resulting in bacterial infection and higher mortality among patients with AP.[3,4] Nevertheless, enteral nutrition (EN) for SAP patients stimulates metabolic activity of the gut to help maintain the integrity of the intestinal mucosa, preserve protein metabolism of internal organs to reduce the acute phase response, and down-regulate the cytokine response.[5,6]

Guidelines have recommended the importance of EN within 24–48 hours of intensive care unit (ICU) admission;[7,8] however, almost 60% of critically ill patients are not fed for 48 hours or longer during their ICU stay.[9]

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It is possible the optimal timing to initiate early EN is still an unresolved issue, and the appropriate time needs to be supported by sufficient convincing evidence. Some systematic reviews have confirmed that compared with parenteral nutrition (PN), a significantly reduced mortality in patients with AP within 24–48 hours admission of ICU compared with patients who received EN.[10-14] However, the aforementioned studies were not stratified according to the severity of disease,[14] which may mislead to a diagnosis of mild AP with a much lower rate of complications, thereby potentially causing selection bias. To address this problem in the management of AP, we explored the benefits of early EN (starting within the first 24 hours of admission) in predicted severe acute pancreatitis (pSAP) or SAP and mild to moderate AP patients.

Materials and Methods

Search Strategy

We independently searched PubMed, EMBASE Databases, Web of Science, and the Cochrane library for relevant studies about early EN in any language published from 1965 to June 2016 using the Medical Subject Heading (Mesh) headings or key words as: (acute pancreatitis) AND (enteral nutrition) OR (nasojejunal) OR (jejunal) OR (nasogastric) OR (tube feeding) OR (jejunostomy) OR (ileostomy) OR (gastrostomy). No language restrictions were implemented.

Inclusion criteria

Studies that were included in this systematic review fulfilled the following criteria: (1) randomized clinical trials (RCT) irrespective of publication status, language, or blinding; (2) patients diagnosed with AP; and (3) any type of EN initiated within 24 hours of admission controlled with PN or EN outside 24 hours.

Exclusion criteria

Exclusion criteria were: (1) duplicate publications; (2) not RCT; (3) patients <18 years of age; (4) undefined timing of EN initiated within 24 hours of admission; and (5) not reporting clinically relevant outcomes.

Types of outcome measures

Primary outcomes are: (1) mortality; (2) multiple organ failure; and (3) adverse events, including nausea, vomiting, bloating, diarrhea, pain relapse, hyperglycemia. Secondary outcomes are: (1) all the infections as a whole, and (2) pancreatic infection.

Data extraction

Two review authors (MP, BY) independently retrieved and validated data from all studies using data extraction forms. We extracted the following information from the included studies: first author, year of publication, country of origin, trial design, starting time of EN, severity of AP, number of participants, participant characteristics, EN route, and primary and secondary outcomes of trials at the latest available follow-up of both the early EN group and the control group.

Assessment of risk of bias in included studies

Two authors (MP, BY) evaluated the risk of bias independently in the included studies according to the Cochrane guidelines. We assessed risk of bias using the domains allocation sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, management of incomplete outcome data, selective outcome reporting, and other potential sources of bias.

Statistical analysis

We performed statistical analyses using RevMan Software (version 5.3, Cochrane Collaboration, Oxford, UK) and STATA software (version 12.0, StataCorp, College Station, TX). The odds ratio (OR) and dichotomous data outcomes are given 95% CI. We tested heterogeneity between trials with χ^2 tests, with $P \leq 0.05$ indicating significant heterogeneity. If $P \leq 0.05$ revealed significant heterogeneity, the pooled OR was obtained using a random-effects model. Otherwise, a fixed-effects model was used. We also quantified the heterogeneity by I^2 metric where $I^2 < 25\%$, $25\% \leq I^2 \geq 50\%$, and $I^2 > 50\%$ represent low, moderate, and extreme heterogeneity, respectively.[15] Sensitivity analysis was tested using the "metaninf" STATA command. Visual inspection of funnel plots, Begg's test, and Egger's asymmetry tests were used to assess publication bias ($P \leq 0.05$ was considered statistically significant).

Results

Overall, we identified 3977 studies from PubMed, EMBASE, Web of Science, and the Cochrane Library. After duplicates were identified, 1479 references were found. According to initial eligibility screening, we then excluded 699 references on the basis of title and abstract alone. Finally, 73 clinical trials were closely reviewed, and we excluded 65 trials. Among them, 61 trials were excluded because they did not fully meet the including criteria, 2 trials failed to report any related clinical outcomes,[16,17] and 2 trials were based on early EN with symbiotic or n-3 polyunsaturated fatty acids.[18,19]

Finally, 8 trials qualified for inclusion in the primary analysis (Table 1). Among them, 7 were available as full-text papers, and 1 was made available in abstract form only.[20-26] A total of 727 participants were enrolled in the 8 studies contained in the meta-analysis(Figure 1).

Table 1. Study Characteristics.

Study (Year)	Study Design	Severity of AP	Feeding Routes		Patients, n	Feeding Start, hours
			Early	Delayed		
Olah (2002)	RCT	AP	Nasogastric	PN	89	<24
Gupta (2003)	RCT	pSAP	Nasojejunal	PN	17	<6
Petrov (2006)	RCT	pSAP	Nasojejunal	PN	69	<24
Eckerwall (2006)	RCT	SAP	Nasogastric	PN	47	<24
Kumar (2010)	RCT	SAP	Not stated	PN	50	<24
Petrov (2013)	RCT	Mild to moderateAP	Nasogastric	nil per os	35	<24
Bakker (2014)	RCT	pSAP	Nasoenteric	Oral diet initiated 72 hours	205	<24
Stimac (2016)	RCT	Moderate AP	Nasojejunal	nil by mouth	214	<24

AP, acute pancreatitis; PN, parenteral nutrition; pSAP, predicted severe acute pancreatitis; RCT, randomized controlled trial; SAP, severe acute pancreatitis.

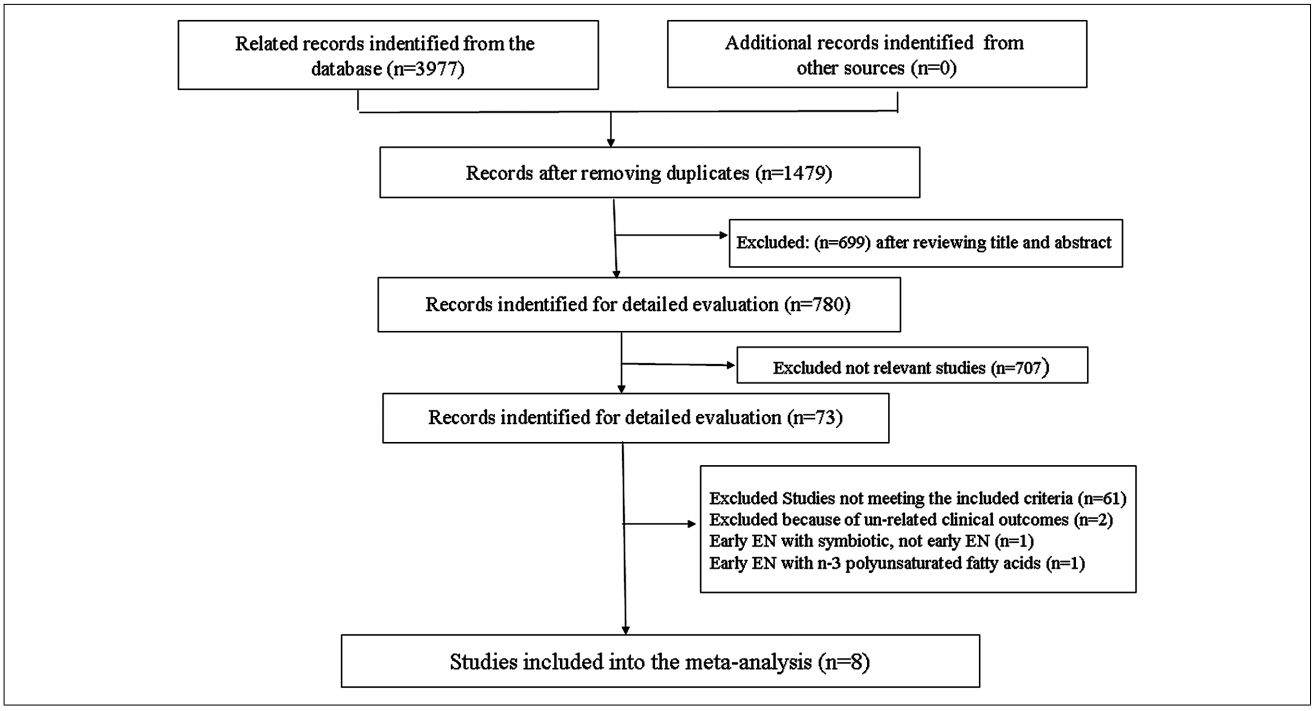

Figure 1. Process of study selection of randomized controlled trials. EN, enteral nutrition.

Risk of bias in included studies. Risk of bias was assessed according to 7 domains, including allocation sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, management of incomplete outcome data, selective outcome reporting, and other potential sources of bias. Among 8 included RCTs, 6 studies provided allocation sequence generation. In Olah et al., randomization was performed by birth dates and inadequately concealed allocation.[23] Eckerwall et al. did not describe the method of allocation concealment used.[20] Allocation concealment was unclear in 4 trials.[22,23,25,26] None of the studies provided enough information regarding the blinding method used (Figure 2).

Main Results of Meta-Analysis

Mortality. This is the only outcome reported in all 8 studies with a total of 727 patients. We obtained data on all causes of mortality from 8 studies. The studies were heterogeneous, and a random-effects model was used. There were no death cases reported in 2 studies.[21,24] We observed that the early EN group had a decreasing trend in all-cause mortality

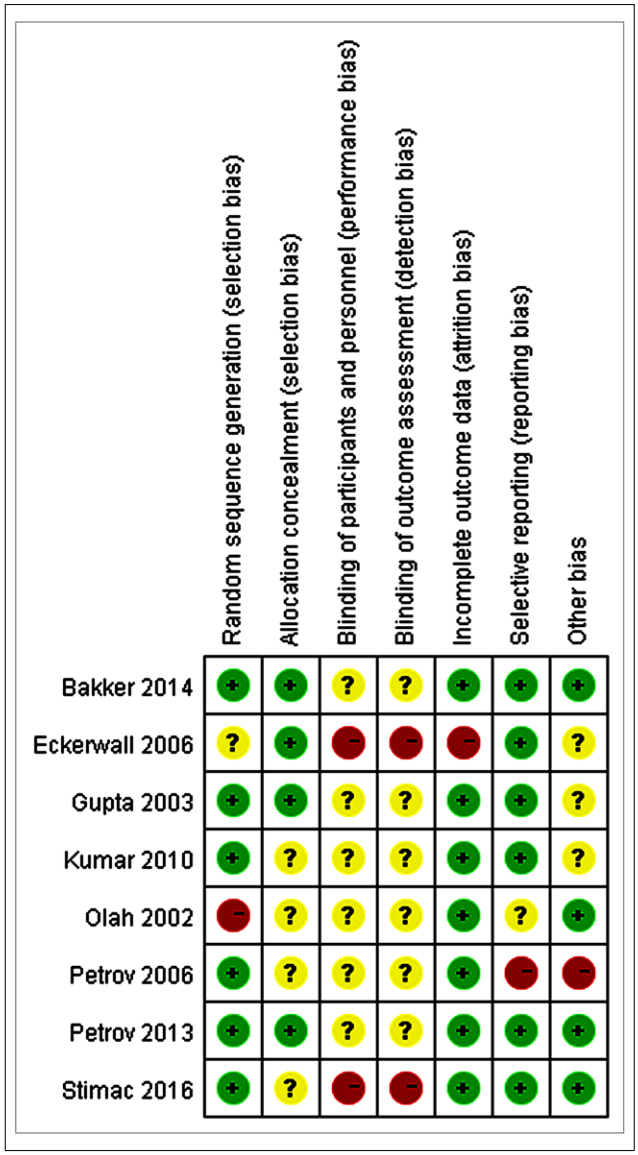

Figure 2. Methodologic quality summary. Our judgments about each methodologic quality item for each included study. "+" is "Yes"; "−" is "No"; "?" is "uncertain".

compared with the late EN or PN group (OR 0.56, 95% CI 0.23–1.34, $P = 0.19$) (Figure 3).

PSAP in included studies was defined as an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 8 or more and/or a C-reactive protein (CRP) level in excess of 150 mg/L, except 2 RCTs[21,25] defined as APACHE II score of 6. Among the 8 studies, 5 studies included patients with pSAP or SAP, showing a reduction of mortality in early EN compared with the late EN or PN group (OR 0.63, 95% CI 0.33–1.23) (Figure 3), but no statistically significant relationship ($P = 0.18$) with significant heterogeneity was detected ($I^2 = 70\%$, $P = 0.02$); 3 included patients with mild to moderate AP, showed an OR of 0.55 (95% CI 0.26–1.16). There was no significant subgroup difference between pSAP or SAP subgroup and mild to moderate subgroup ($I^2 = 0\%$, $P = 0.78$).

Multiple organ failure. Seven studies with 691 participants provided incidence of multiple organ failure,[20-23,25-27] and showed an OR of 0.40 (95% CI 0.20–0.79, $P = 0.008$) (Figure 4). There was heterogeneity across all the studies and a random-effects model was used.

Subgroup analysis of 5 trials with pSAP or SAP showed a significant reduction of multiple organ failure in the early EN group, with an OR of 0.30 (95% CI 0.09–0.96, $P = 0.04$) (Figure 4). However, there was no significant reduction in the 2 trials with mild to moderate AP (OR 0.60, 95% CI 0.36–1.04, $P = 0.06$) (Figure 4), and no subgroup difference between pSAP or SAP subgroups and mild to moderate subgroups ($P = 0.28$).

Infections. In total, 6 trials reported on the incidence of infections in the meta-analysis. Infections recorded included pneumonia, sepsis, pancreatic-related infection, and non-pancreatic-related infection. Overall, the OR was 0.57 (95% CI 0.23–1.42) (Figure 5), but there was no statistically significant relationship ($P = 0.23$).

In the stratified study, 5 articles were included in the pSAP or SAP subgroups, and the OR was 0.61 (95% CI 0.19–1.97) (Figure 5) with no significant reduction. One trial with mild to moderate AP, showed an OR of 0.46 (95% CI 0.20–1.08). There was no significant heterogeneity across all the studies (($I^2 = 0\%$, $P = 0.71$).

The incidence of adverse events. Adverse events were reported by 7 studies. Reported adverse events included nausea, vomiting, bloating, diarrhea, pain relapse, and hyperglycemia. Bakker reported 72 adverse events, including nausea, vomiting, and diarrhea, in the early EN group and 92 in the control group.[27] The number of participants experiencing adverse events showed a reduction in the early EN group compared with the late EN or PN groups (OR 0.45, 95% CI 0.17–1.21) (Figure 6), but there was no statistically significant relationship ($P = 0.12$).

Five trials were stratified into pSAP or SAP subgroups. No significant reduction was observed with an OR of 0.44 (95% CI 0.16–1.21) (Figure 6) in pSAP or SAP, as well as in mild to moderate AP. No significant subgroup difference was found between pSAP or SAP subgroups and mild to moderate subgroups ($I^2 = 0\%$, $P = 0.78$).

Pancreatic infections. Pancreatic infections, the most severe complication of AP, were reported by 6 studies. The studies were homogenous and a fixed-effects model was used ($I^2 = 55\%$, $P = 0.08$). No significant difference was observed in the occurrence of pancreatic infections when comparing early EN with late EN or PN (OR 0.83, 95% CI 0.59–

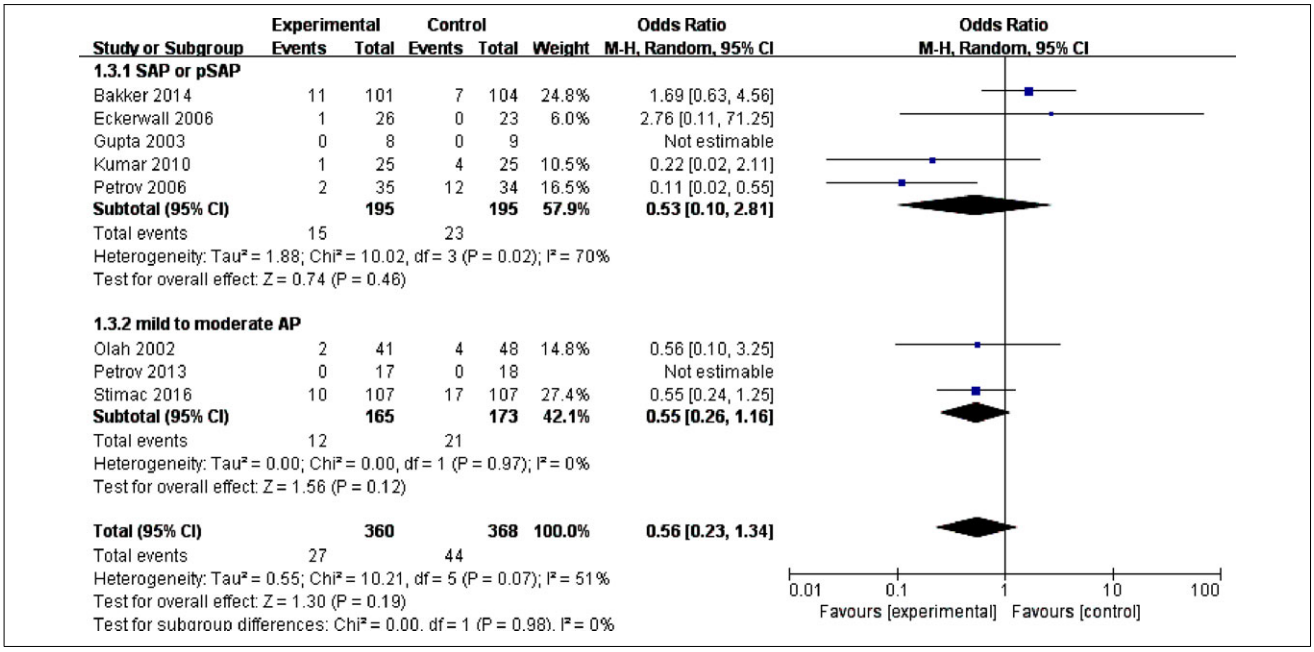

Figure 3. Forest plot of the meta-analysis of early EN on mortality stratified by severity of AP. AP, acute pancreatitis; EN, enteral nutrition; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis; M-H, Mantel Haenszel test.

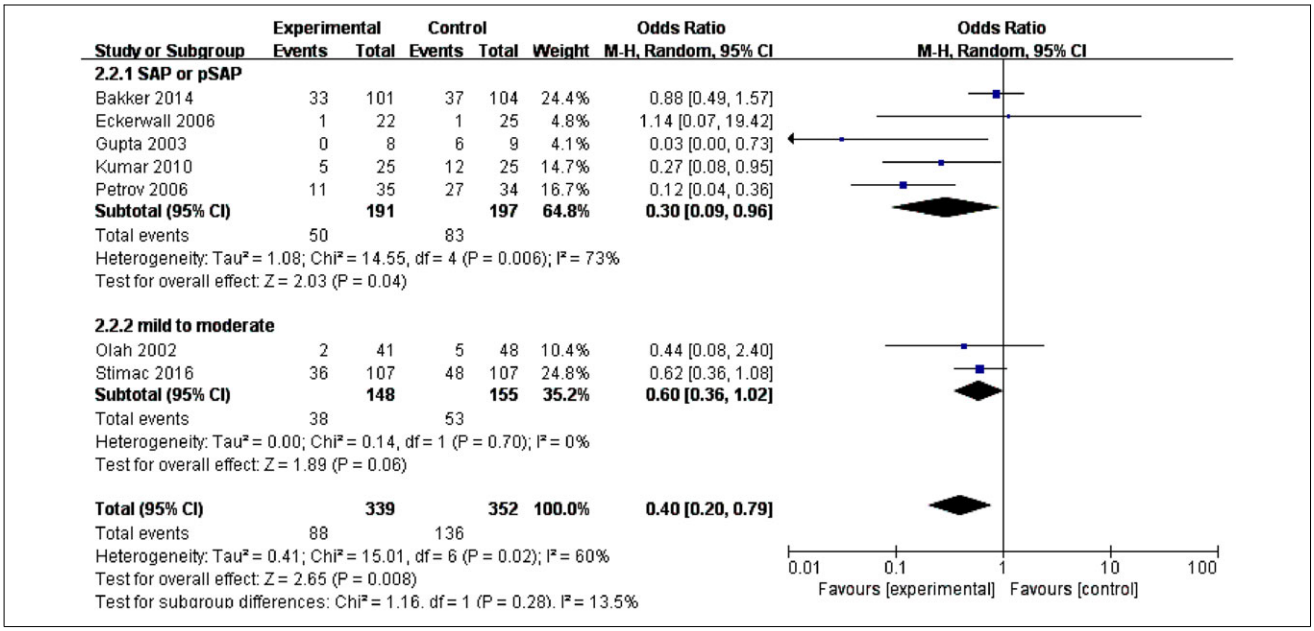

Figure 4. Forest plot of the meta-analysis of early EN on multiple organ failure stratified by severity of AP. AP, acute pancreatitis; EN, enteral nutrition; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis; M-H, Mantel Haenszel test.

1.18) (Figure 7), and there was no statistically significant relationship ($P = 0.30$).

Four of the 6 trials were stratified into pSAP or SAP subgroups, and a significant reduction in the risk of pancreatic infections was shown in the early EN group with a OR of 0.51 (95% CI 0.29–0.88, $P = 0.02$) (Figure 7). Two trials with mild to moderate AP showed an OR of 1.19 (95% CI 0.75–1.88). There was no significant subgroup difference ($I^2 = 62\%$, $P = 0.10$).

Sensitivity Analysis and Publication Bias

The results of the sensitivity analysis are shown in Figure 8. When each individual study was sequentially

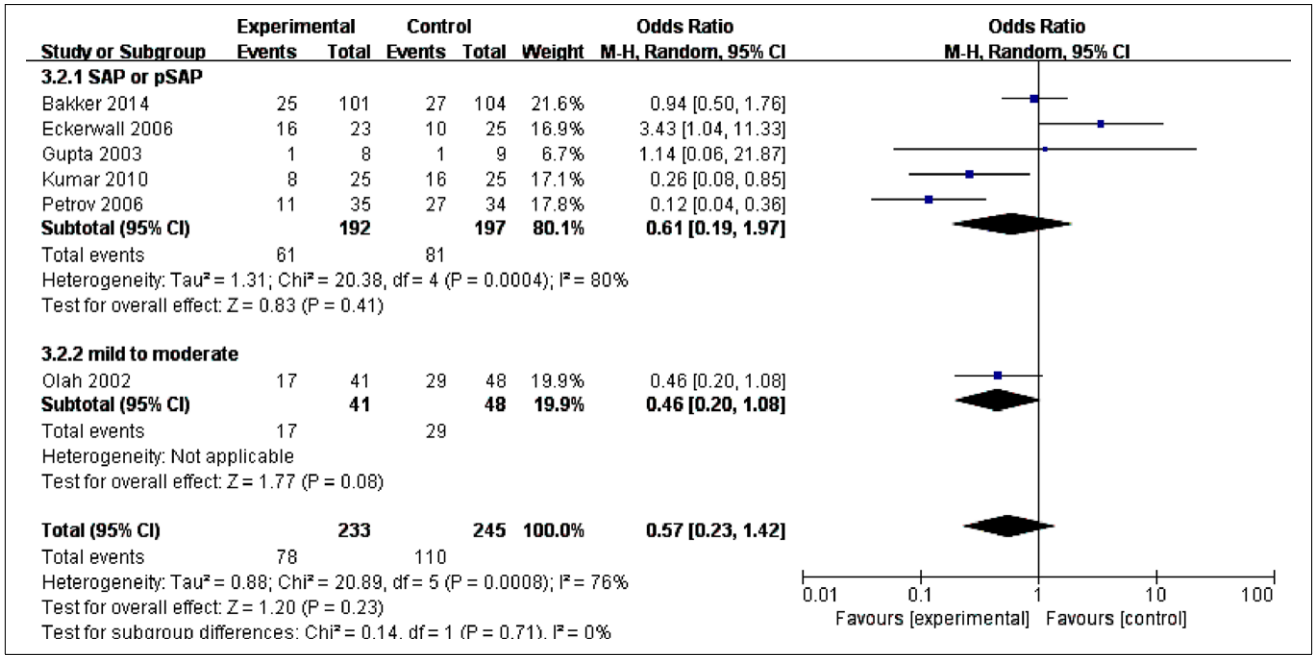

Figure 5. Forest plot of the meta-analysis of early EN on infections as a whole stratified by severity of AP. EN, enteral nutrition; AP acute pancreatitis; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis; M-H, Mantel Haenszel test.

excluded, the combined 95% CI of the remaining 7 studies did not exceed the 95% CI of the pooled HR of 8 studies, indicating that no individual study dominated the results. No obvious publication bias was revealed by Egger's test and Begg's test (Table 2).

Discussion

The main risk factors for mortality in SAP are the secondary to systemic infections and multiple organ failure. We conducted this study to assess the effectiveness of early standard EN in AP, and 8 clinical trials fulfilled our selection criteria. Meta-analysis of these trials showed significant benefits in AP patients upon early EN vs late EN or PN by reducing multiple organ failure. Moreover, a decreasing trend was also found in mortality, infections, adverse events, and pancreatic-related infections. The benefits were especially pronounced in pSAP or SAP patients, and significant reductions were shown in multiple organ failure and pancreatic-related infections, which are the main concerns about the risk of mortality in SAP.

It is proposed that the gut may be a "motor" in the progression of multiple organ failure and infectious complications in AP, and the prevention of gut dysfunction plays a major role in reducing mortality in AP.[28,29] The reasons early standard EN could decrease the infectious complications and mortality may include (1) preservation of the gut-associated lymphoid tissue, (2) stability of the gut barrier function, and (3) detoxification of lipopolysaccharides and reduction of bacterial translocation.[30,31]

It has been proved that patients with SAP have higher serum endotoxin levels, cytokine levels, and intestinal permeability, and the optimal time of EN plays an important role in its prognosis. The timing of early EN has been promoted by the American Society for Parenteral and Enteral Nutrition.[7] Initiating early EN therapy within 24–48 hours of admission can decrease the incidence of complications in the early phase of SAP and can reduce the risk of mortality. Failure to initiate EN therapy for >72–96 hours in SAP patients may deteriorate the nutrition status and enhance the incidence of complications. However, there were no recommended guidelines for EN in mild to moderate AP. The reasons were as follows: (1) patients with mild AP have a much lower rate of complications (6%) than patients with more severe disease; (2) patients have close to 0% mortality rate in mild AP and 10% in moderate AP; and (3) patients have an 81% chance of advancing to oral diet within 7 days.

We wanted to understand the benefit of early EN according to the severity of AP, and we undertook subgroup analysis of trials where patients were classified as pSAP or SAP and mild to moderate AP. Interestingly, our stratified analysis based on the severity of AP reported the early EN of pSAP or SAP within 24 hours of admission had a significant decrease only in multiple organ failure and pancreatitis-related infections. The reductions in mortality, infectious complications, and adverse events were also mentioned, but they were not statistically significant. These

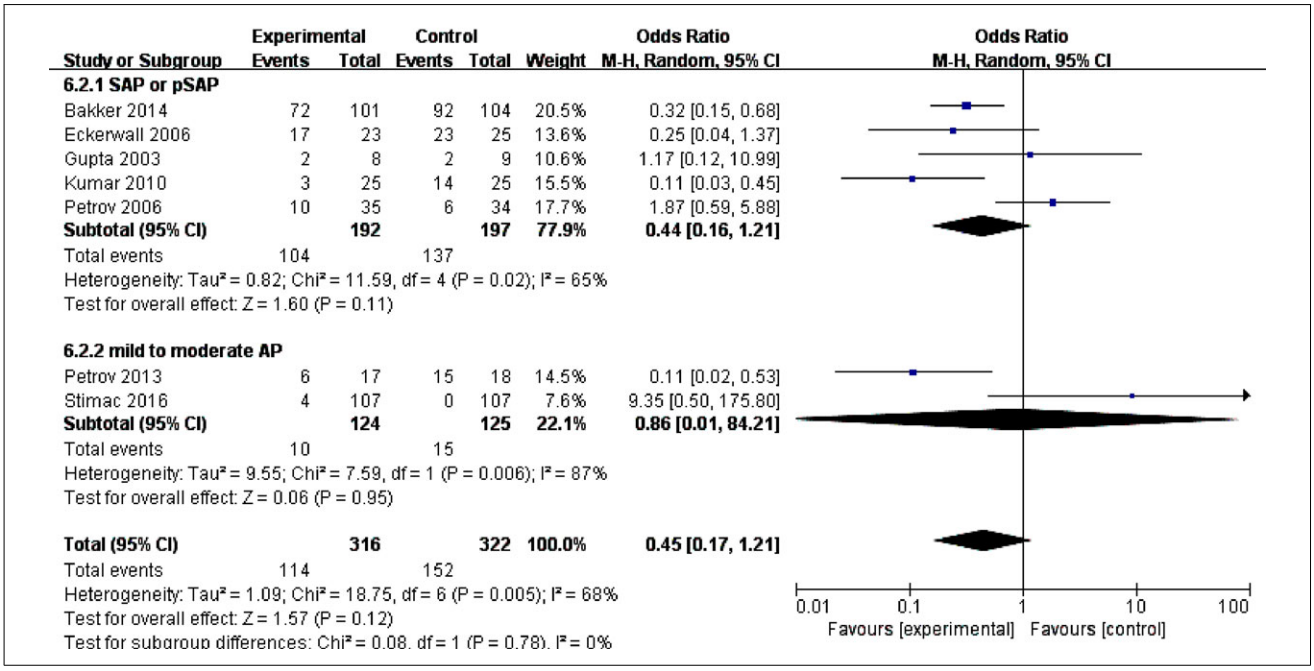

Figure 6. Forest plot of the meta-analysis of early EN on adverse events stratified by severity of AP. AP, acute pancreatitis; EN, enteral nutrition; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis ; M-H, Mantel Haenszel test.

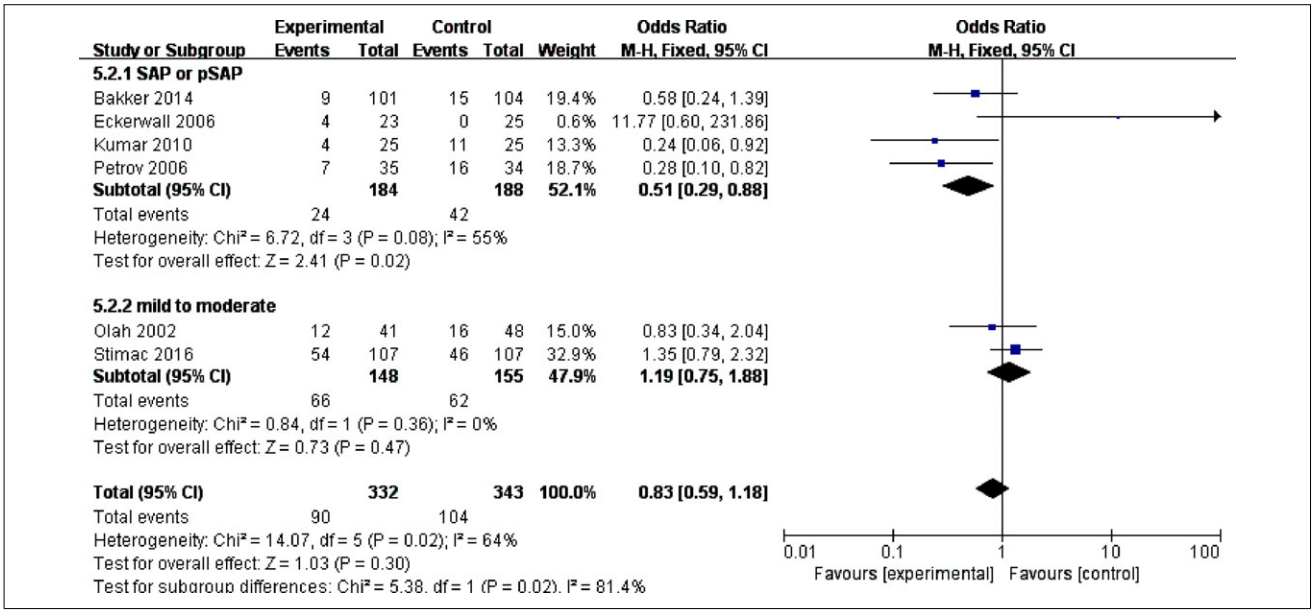

Figure 7. Forest plot of the meta-analysis of early EN on pancreatic-related infections stratified by severity of AP. AP, acute pancreatitis; EN, enteral nutrition; pSAP, predicted severe acute pancreatitis; SAP, severe acute pancreatitis; M-H, Mantel Haenszel test.

data are somewhat inconsistent with previous findings.[14] The conclusions of the previous meta-analysis might cause deviation for not stratifying the included studies. Nevertheless, our study is stronger than the only other published meta-analysis[14] in its adherence to strict methodologic criteria. Early EN feeding within 24 hours of admission in SAP was clearly beneficial and decreased the risk for multiple organ failure and pancreatitis-related infections, and there was a beneficial tendency for risk of mortality, infections, and related adverse events. As predicted, there

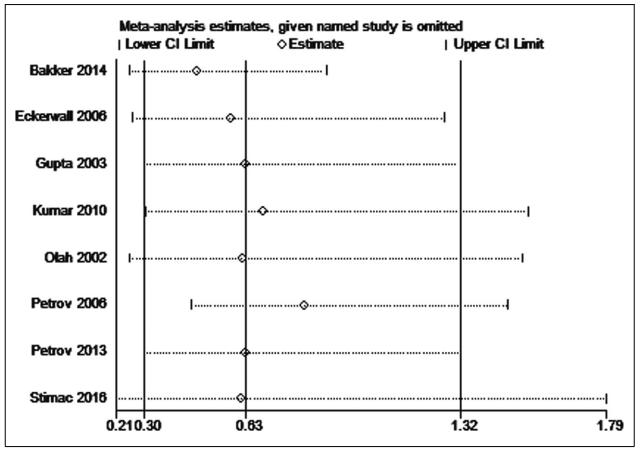

Figure 8. Effect of individual studies on the pooled odds ratio (OR) for the effect of early EN on mortality. The horizontal axis number 0.63 represents the overall OR, and 0.30 and 1.32 represent the 95% CI. EN, enteral nutrition.

were no trials sufficient to analyze EN in mild to moderate AP. The data showed no significant difference between early EN and late EN or PN in mild to moderate AP. The implication of the results may be related; mild to moderate AP is not typically a cause of nutrition status deterioration and early nutrition treatment may not be needed. Most cases of AP are mild and self-limiting; therefore, specific nutrition intervention is not required. Patients with mild AP who are unable to resume oral feeding after 48 hours of conservative therapy should initiate early EN. Well-nourished patients who resume oral intake within a few days may not benefit from early EN.

A meta-analysis[32] containing 7 trials with mild to moderate pancreatitis and 4 with pSAP showed early EN within 48 hours after hospitalization seemed not to increase adverse events. However, Vaughn et al[32] mainly focused on mild to moderate AP with limited data of pSAP. Another meta-analysis in 2013, including 11 trials with early EN (within 48 hours of admission) vs delayed EN (48 hours after admission) or PN, reported a significantly decreased risk of mortality and total infectious complications and a reduced length of hospitalization.[13] Whether it is prudent for pSAP with early EN (within 24 hours of admission) needs to be clarified. The present analysis proves definitely that EN in the very early phase of AP without "gut rest" is superior to PN which makes the gut totally rest. Nevertheless, compared with delayed EN or PN at the same time point, it seems that EN initiated within 24 hours of admission for patients with AP provided fewer benefits to EN started within 48 hours of admission. Its explanation may be related to the duration of nutrition. The observed increasing beneficial effect of EN with time may be due to the length of time of intestine rest. The early fluid resuscitation may also involve the benefit of very early EN.

Table 2. Publication Bias on the Association of Each Clinical Outcome and Early EN.

Clinical Outcome	Begg's test (*P*)	Egger's test (*P*)
Mortality	1.000	0.513
Multiple organ failure	0.881	0.281
Infection complications	0.851	0.851
Adverse events	0.453	0.245
Pancreatic infections	0.174	0.223

EN, enteral nutrition.

The present systematic review contains a number of limitations. First, 6 of the included RCTs were small and of poor quality. None of the RCTs was blinded. Four studies with inadequate concealment of allocation may have overestimated the intervention effect. However, none of the RCTs included in our analysis had methodologic flaws, and the funnel plot revealed no obvious evidence of a negative publication bias. Second, the included trials seemed to be clinically heterogeneous. The difference in severity of the disease may explain this heterogeneity. Thus, we stratified the patients in trials according to the severity of disease, and there was no significant heterogeneity between the groups. Third, different feeding routes of EN and control groups in the trials may influence the data correction, and only 3 trials controlled with late EN. However, previous RCT studies showed no significant differences comparing gastric with jejunal feeding in SAP.[33-35] Also, a meta-analysis claimed no difference in pain sensation, diarrhea, or energy balance. It indicates that different feeding routes of EN play no influence in our analysis. Fourth, the different definition of pSAP in APACHE II scores may result in some bias for our data. Included patients with pSAP in 2 RCTs may be diagnosed as moderate AP in other trials.[21,25] However, bias may not play the pivotal role for the definition of pSAP containing 3 parts, namely, an acute physiology, APACHE II score, and CRP level in excess of 150 mg/L. Nevertheless, within the constraints of small sample size and different control interventions in some of the included trials, the present study suggests that early EN within 24 hours of admission in pSAP or SAP patients may be beneficial for the clinical outcome. This hypothesis should be corroborated by a subsequent multicenter clinical trial.

Conclusions

The American Society for Parenteral and Enteral Nutrition recommends to initiate early EN therapy within 24–48 hours of admission. The present analysis shows a significant reduction in multiple organ failure with early EN initiated within 24 hours of admission in AP. Early EN seems to be beneficial in pSAP or SAP by significantly decreasing the risk of multiple organ failure and pancreatic infections; this effect does not apply to mild to moderate AP.

Statement of Authorship

Milin Peng contributed to the conception and design of the research; Desheng Qi, Bo Yu, and Milin Peng equally contributed to the acquisition and analysis of the data; Bo Yu, Jia Huang, and Milin Peng contributed to the interpretation of the data; and Milin Peng and Desheng Qi drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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