Original Article

Early parenteral nutrition alone or accompanying enteral nutrition in critically ill patients: a systematic review and meta-analysis

Xiao Wan BS[1], Xuejin Gao BS[1,2], Feng Tian BS[1], Chao Wu BS[1], Xinying Wang MD[1]

[1]*Department of General Surgery, Jinling Hospital, School of Medical, Nanjing University, Nanjing, Jiangsu Province, China*
[2]*Clinical College of South Medical University, Guangdong Province, China*

Background: Although several large-scale clinical trials shave examined the relationship between early parenteral nutrition (ePN) and critically ill patients, a consensus has not been reached. In addition, no meta-analysis in this area has yet been published. The objective of this meta-analysis was to examine the effect of ePN, alone or accompanying enteral nutrition, in critically ill patients. **Methods**: A meta-analysis was performed to evaluate risk ratios (RR) and mean differences with 95% confidence intervals (CIs) between the ePN and control groups. Subgroup analyses were conducted to evaluate combinations of early enteral nutrition (eEN). **Results**: Five randomized control trials (RCTs) were included. Compared with controls, ePN had no effect on mortality (RR: 1.05, 95% CI: 0.96, 1.16). Secondary outcomes were variable: compared with the control group, the ePN group required fewer days of ventilation (p=0.007, RR: -0.95, 95% CI: -1.64, -0.27), but a longer hospital stay (p<0.001, RR: 3.76, 95% CI: 2.25, 5.28). **Conclusion**: Overall, this meta-analysis from RCTs indicates that provision of ePN within 24-48 hours has no benefit on the survival rate in critically ill patients. Thus, provision of ePN in patients is not needed in those who have contraindications to enteral nutrition or can tolerate a low volume of enteral nutrition.

Key Words: early, parenteral nutrition, critically ill, enteral nutrition, mortality

INTRODUCTION

Parenteral nutrition (PN) has been widely used since 1968, and it is accepted as the standard care for patients with a non-functioning gastrointestinal tract, as it can decrease mortality.[1] However, early and adequate initiation of PN for critical illness is under debate.

In the past decades, enteral nutrition (EN) has been preferred over total PN due to several advantages, including decreased mortality, infective morbidity, and length of hospital stay.[2,3] It has been shown that nutrition support improves clinical outcomes when started within 10 days after hospital admission or surgery in patients who are unable to eat.[4,5]

In 2011, 4,640 critically ill patients were enrolled in the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study to investigate the effects of early PN in patients in whom EN could not meet the daily caloric demand.[6] To our disappointment, this survey did not reveal any clinical benefits of PN. Because most of the enrolled patients had undergone cardiothoracic surgeries, the conclusions of this study have limitations and remain under fierce debate.

Meanwhile, a new question was raised regarding whether early PN could be used in patients with relative contraindications to early EN. A meta-analysis compared critically ill patients using PN within 24 hours (hrs) with those who were unfed for 2-5 days and reported that, PN reduced mortality and increased infection morbidity.[7] Because of the small size of clinical trials involved in the systematic review, many investigators had different views and started further clinical trials.[8] In 2011 and 2013, two large-scale randomized trials were performed in patients with short relative contraindications to EN, but their conclusions were different.[9,10]

At present, there are two groups of critically ill patients that maybe considered for early PN.[11,12] The first includes patients who can tolerate a low volume of provisional EN, but in whom PN cannot meet the daily caloric requirements; the second includes patients with contraindications to EN. Clinically, the boundary between these patients is unclear, and most patients in both groups have a low caloric intake. The time at which PN should be started needs to be carefully evaluated.

Considering the advantages and disadvantages of early PN, several randomized controlled trials (RCTs) have been undertaken to examine the effect on morbidity and

Corresponding Author: Dr Xinying Wang, Department of General Surgery, Jinling Hospital, No.305, Zhongshan Road, Nanjing, Jiangsu Province, China.
Tel: +86 139 1302 8866; Fax: +86 025 8086 3736
Email: wxinying@263.net
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some other clinical indexes, but the results are variable. The aim of this study was to further evaluate the efficacy of early PN using data from several of the most recent RCTs, with a focus on patients with a contraindication to early EN or on those who could only tolerate a low volume of EN, so that the results obtained could be a guide for the use of PN.

METHODS

Data collection

We searched PubMed, EMBASE, and the Cochrane Library from 1980 to December 2013 using the key words "early parenteral nutrition," "critically ill," and their analogs. Potentially relevant studies and references listed in the identified reports were also searched. Studies were selected for analysis if they met the following inclusion criteria: 1) the research design included fully reported RCTs and had detailed information; 2) populations included adult critically ill patients or adult patients who had stayed for more than 48 hrs in an intensive care unit; 3) intervention included PN alone within 48 hrs or combined with hypocaloric EN and was compared with another treatment; and 4) the primary clinical outcome of interest was mortality rate, with secondary outcomes, including the time of invasive mechanical ventilation, the length of ICU stay (LOS-ICU), and length of hospital stay (LOS-H). Exclusion criteria included 1) control groups in which PN was started within 48 hrs; 2) outcomes after PN alone within 48 hrs were compared with those after EN within 48 hrs; 3) nutrition support was not given or delayed for up to 10 days in the control groups; 4) neonatal or pediatric patients; and 5) references were not in English.

Most trials evaluated the impact of early PN alone or combined with early EN on patients' clinical outcomes. We defined critically ill patients as those who were routinely admitted in the intensive care unit. Studies that evaluated the effect of PN or EN on nutritional outcomes (i.e., nitrogen balance, amino acid profile) were not included in this review.

Quality assessment and statistical analysis

The quality of the reported methods was assessed by a Jadad score,[13] and each study was independently appraised by two of the reviewers (Xiao Wan and Feng Tian). The quality of clinical trials was considered at a "low level" if they had a score of 1-2, while that of trials was considered "high level" if they had a score of 3-5. Any disagreement was resolved by consensus between the two reviewers. If data were missing, unclear, or not reported on a per-patient basis, we attempted to contact the primary investigator and request further information. As shown in Table 1, two RCTs had a Jadad score of 2, three had a score of 3, and one had a score of 5.

All data was retrieved and entered into Review Manager (Version 5.2 for Windows, Cochrane Collaboration, Oxford, UK). As a portion was abnormally distributed, data were transferred to represent the mean ± standard deviation (SD).[14] If hospital mortality rates were not reported, we used 60- or 90-day mortality instead. As some enrolled patients were not discharged within 60 days, the LOS-H for those patients was considered 60 days for a primary analysis and was excluded from a subsequent reanalysis. Data from all relevant studies were combined to estimate the common risk ratio (RR) or mean difference (MD) with accompanying 95% confidence intervals (95% CIs). Statistical heterogeneity among RCTs was assessed by I^2 statistics. If statistical heterogeneity was absent, a fixed-effect model was used; otherwise, a random-effect model was used. As a reanalysis was performed after removing any influential factors, we also conducted a subgroup analysis to determine the effect of early EN (PN alone vs PN with EN, across groups) because we considered that the combination of EN might influence the effect of early PN. Both analyses should be relatively consistent before considering statistical significance.

RESULTS

A total of 285 trials were retrieved; the process of selecting relevant trials is described in Figure 1. Of the 285 potentially relevant studies, 250 were not RCTs, and 30 were RCTs with excludable criteria or related to repeated trials. The final analysis consisted of five RCTs enrolling 9,746 patients;[6,9-12] the general information of these trials is shown in Table 2.

The results of the meta-analysis are shown in Figures 2-5. The nature of clinical outcomes varied with the particular patient population. Statistical heterogeneity existed in these groups of clinical trials, except for the analysis of mortality.

A forest plot demonstrated that early PN had no effect on mortality (RR: 1.05, 95% CI: 0.96, 1.16). Intervention with early EN showed no effect (difference between groups: p=0.93, I^2=0%).

Secondary outcomes showed variable results. For instance, early PN groups required fewer days of ventilation (p=0.007, RR: -0.95, 95% CI: -1.64, -0.27), but a longer LOS-H (p<0.001, RR: 3.76, 95% CI: 2.25, 5.28). As both results had significant heterogeneity, we focused on the subgroup analyses. The statistical results showed no difference in the need for ventilation between groups, and

Table 1. Jadad score of the studies include

Study	Randomisation	Blinding	Withdrawals and dropouts	Jadad score
Doig GS[10]	A central randomization web server	None	Yes	3
Cahill NE[9]	Not stated	None	Yes	2
Kutsogiannis[11]	Not stated	None	Yes	2
Bauer[12]	Not stated	Double-blind	Yes	3
Casaer[6]	Sequentially numbered, sealed, opaque envelopes	Double-blind	Yes	5

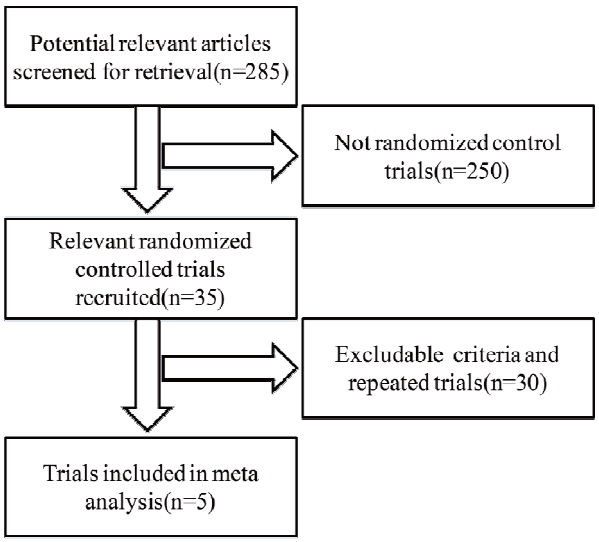

Figure 1. The study on the selection process

each subgroup was less significant. However, with the combined larger sample size and a greater possibility to detect smaller effects, the results approached significance, indicating a meaningful beneficial trend for early PN.

As some enrolled patients were not discharged within 60 days, we excluded these data on reanalysis (Figure 6). However, we found similar results, that early PN was associated with a longer LOS-H (p<0.001, RR: 1.06, 95% CI: 0.30, 1.81).

There was no effect on LOS-ICU (p=0.71, RR: -0.29, 95% CI: -1.39, 0.81). The information on subgroups was insufficient, except for the similar trend between the two subgroups.

DISCUSSION

The summaries of the five RCTs indicated that early PN did not improve clinical outcomes in critically ill patients, with no statistical difference in morbidity rates. Early PN therapy was associated with fewer days on ventilation and a longer LOS-H. There was no significant difference in LOS-ICU. Furthermore, the subgroup comparison demonstrated that early EN had no additional effects on the efficacy of early PN.

Various statements from international societies recommend adequate nutrition therapy for critically ill patients.[15-18] In 2010, an international survey from 514 respondents worldwide found that early special nutritional support can be well accepted, and more than 90% approved initial nutrition within 24-48 hrs after admission.[19] Providing nutrients via the gut with adequate calorie intake may reduce mortality, particularly in malnourished patients. However, many critically ill patients are unable to tolerate this because of relative contraindication to EN, including ileus or hypotension. Many guidelines are unclear about nutrition for hemodynamically unstable patients, even though nutrition support for them is contraindicated. Although the prerequisite that patients should be adequately resuscitated and hemodynamically stable was removed from the 2013 Canadian Critical Care Practice Guidelines Committee, hypocaloric intake was not removed.[20] Therefore, the timing of initiation of PN alone or with hypocaloric EN is still under debate.[21]

In this context, two important guidelines indicate conflicting recommendations. The 2009 European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines recommend initiation of PN within 24-48 hrs after admission in all critically ill patients if EN is contraindicated; this was supported by a 2005 systematic review that reported benefits associated with early PN. The 2009 the American Society for Parenteral and Enteral Nutrition guidelines recommend that PN only be started after 7 to 14 days of starvation. The early use of PN may lead to a worse clinical outcome, causing more infection because of overfeeding.[22]

To investigate the effect of early PN, several RCTs were conducted. Literature regarding nutrition support in critically ill patients continues to grow; however, because of methodological limitations and the small size of many studies, making inferences and generalizing results from individual trials is problematic. Doig et al favoured early PN in critically ill patients with contraindication to early PN, as it can shorten the days on ventilation [6.24

Table 2. Demographic data of the studies include

Study	Year of publication	Reference	Patients	Description
Doig GS	2013	10	Early PN: 682 standard: 681	People in Early PN team begun a mean of 44 minutes after randomization, standard care patients remained unfed for a mean of 2.8 days after randomization
Cahill NE	2011	9	Early PN: 83 late PN: 79 late EN: 541	People in Early PN team would start PN in 48 hrs after entering ICU
Kutsogiannis	2011	11	Early PN + EN: 188 late PN + EN: 170 EN: 2.56×10^3	People in Early PN team would start PN in 48 hrs after entering ICU
Bauer	2002	12	Early PN+EN: 60 EN: 60	People would start nutrition support in 48 hrs after entering ICU
Casaer	2011	6	Early PN + early EN: 2.31×10^3 late PN + early EN: 2.33×10^3	In early group, parenteral nutrition was initiated within 48 hrs after ICU admission, whereas in late group, parenteral nutrition was not initiated before day 8

PN: parenteral nutrition; EN: enteral nutrition; ICU: intensive care units.

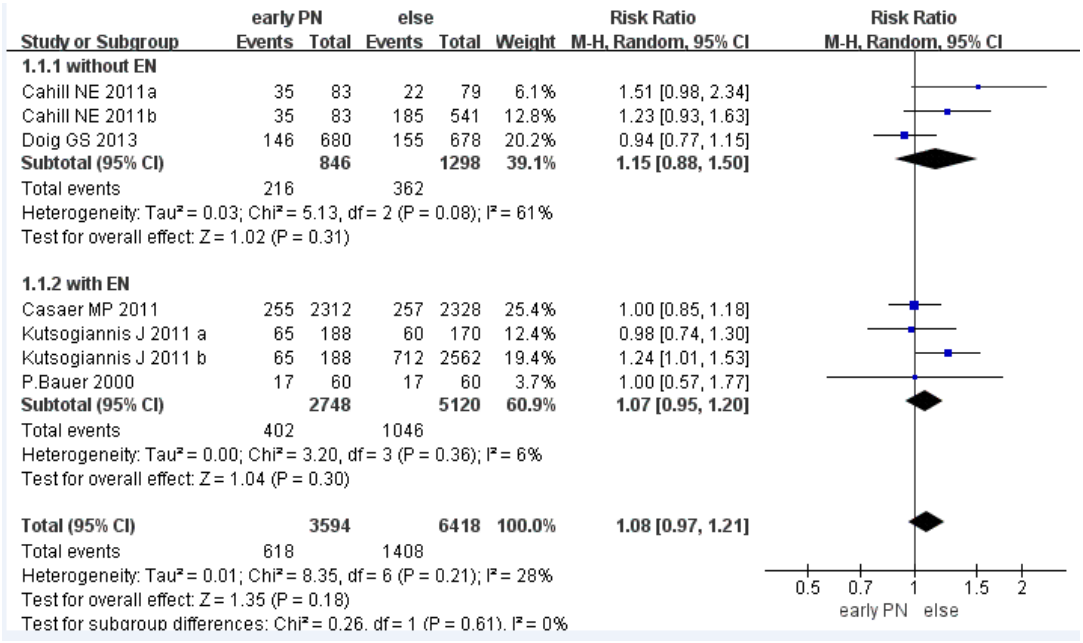

Figure 2. Forest plot for mortality. CI: confidence interval; PN: parenteral nutrition; EN: enteral nutrition.

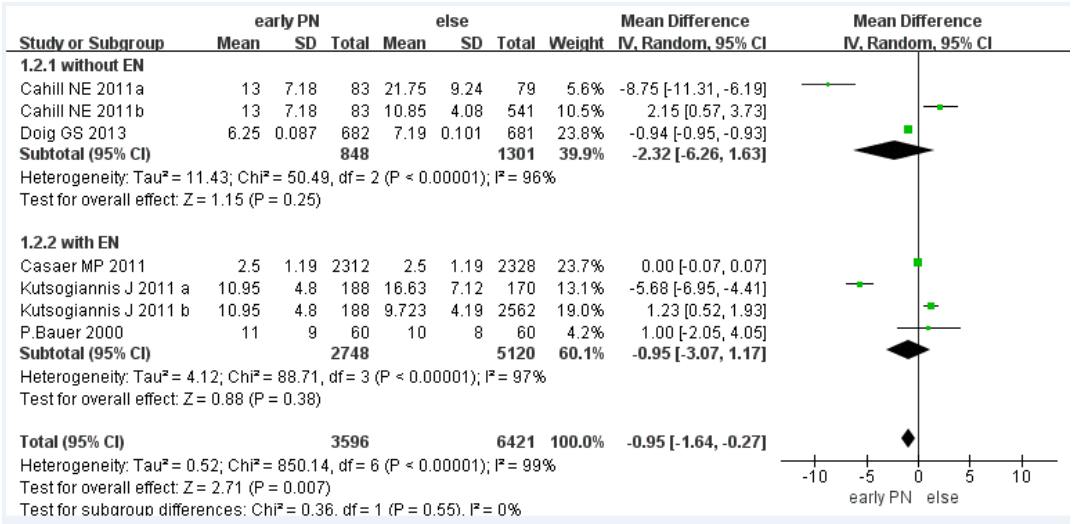

Figure 3. Forest plot for days of ventilation. CI: confidence interval; PN: parenteral nutrition; EN: enteral nutrition.

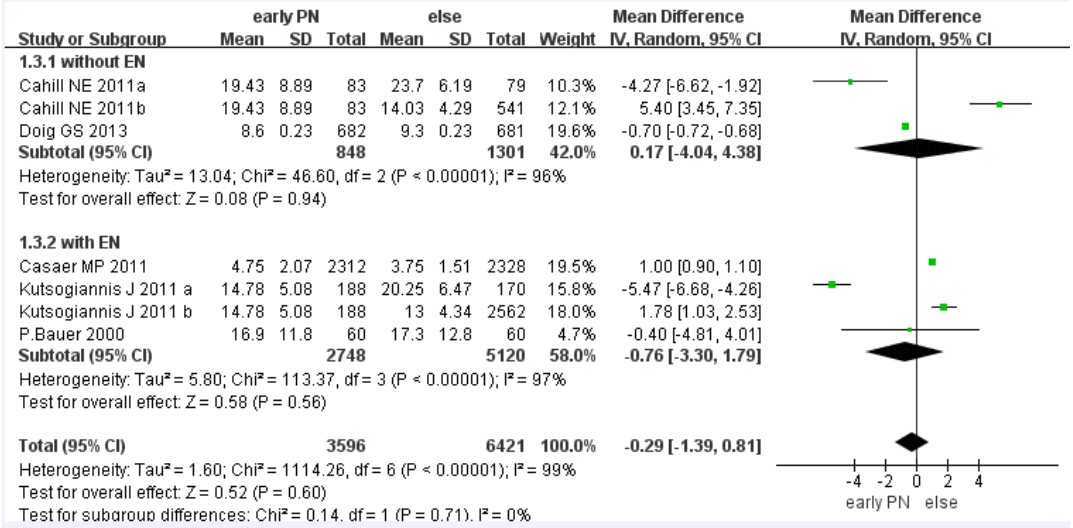

Figure 4. Forest plot for LOS-ICU. CI: confidence interval; PN: parenteral nutrition; EN: enteral nutrition.

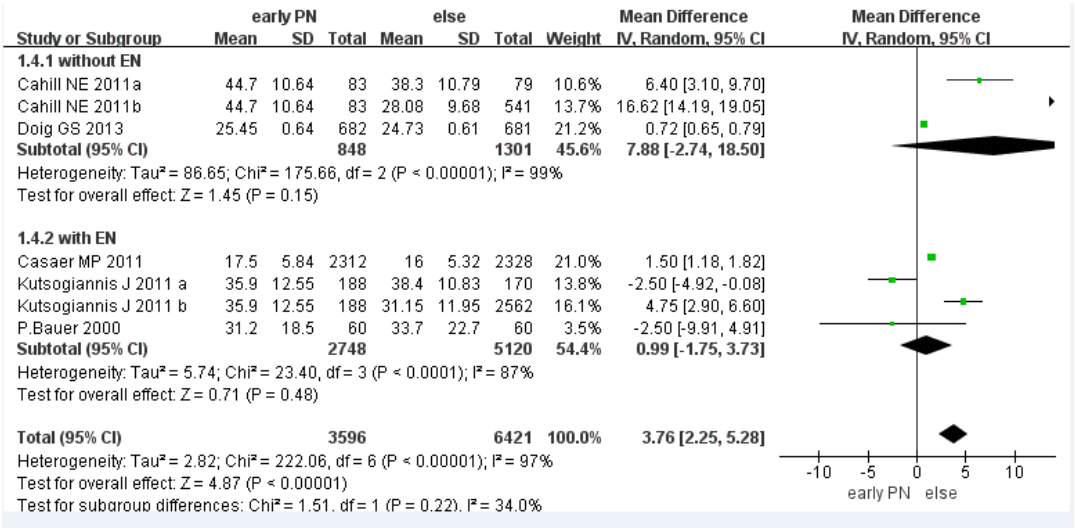

Figure 5. Forest plot for LOS-H. CI: confidence interval, PN: parenteral nutrition, EN: enteral nutrition.

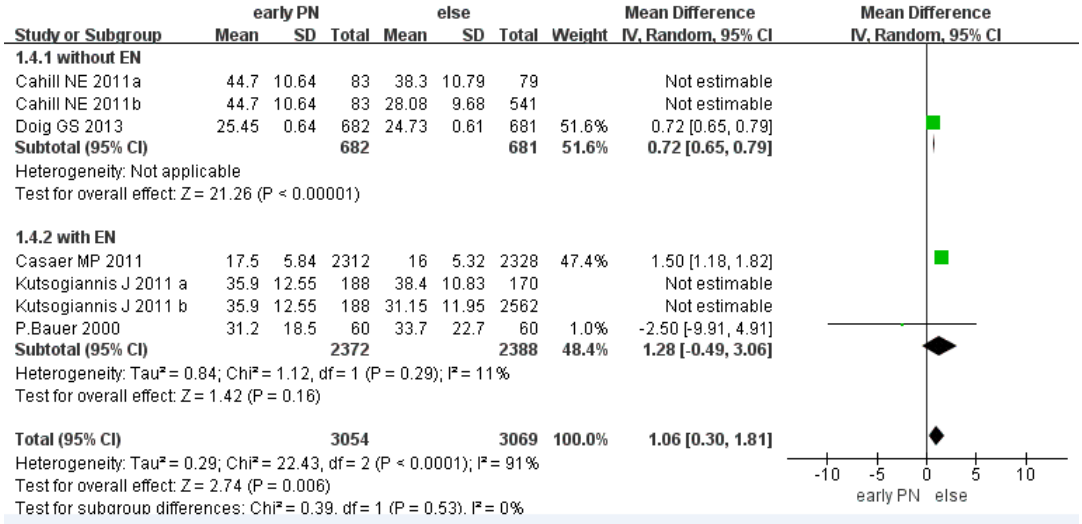

Figure 6. Forest plot for LOS-H after excluding some unreliable trial. CI: confidence interval, PN: parenteral nutrition, EN: enteral nutrition.

(6.1-6.4) vs 7.19 (7.02-7.37), p=0.01]. Conversely, the survey by Cahill et al found a negative result [8.8 (5.5-28.9) vs 9.3 (5.5-19.3), p>0.05]. Although a meta-analysis cannot replace a large, multicenter RCT, it does provide useful information and can provide guidance for designing a trial that specifically assesses the effect of early PN. In the current meta-analysis, our data cannot be judged as reliable because of heterogeneous data on the number of days on ventilation and LOS-H. Although we have investigated the potential source of heterogeneity, we have not been successful in ascertaining the reason for this difference. One reason may be the restrictions on RCT quality included in our study and the different interventions in the control group. The number of studies is also a limitation; this can be improved by additional research on early PN.

Despite the many shortcomings, the studies included in this meta-analysis strictly adhered to the decisive intervention of early PN within 48 hrs for the experimental group. Four of the five RCTs were large-scale clinical trials involving more than 9,000 patients in total, which ensures high reliability.[23] There were no obvious concerns with the methodology, and the secondary analysis increased the credibility of the conclusions.

Conclusion

Early PN within 24-48 hrs of admission had no benefit on the survival rate in critically ill patients. It reduced the duration of mechanical ventilation, but increased the total LOS-H. No significant effect was observed for LOS-ICU. The intervention of early EN showed no additional effect on early PN. Thus, early PN does not seem necessary in patients who have a contraindication to EN or in those who can only tolerate a low volume of EN.

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AUTHOR DISCLOSURES

None of the authors have any personal or financial conflicts of interest to declare.

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Original Article

Early parenteral nutrition alone or accompanying enteral nutrition in critically ill patients: a systematic review and meta-analysis

Xiao Wan BS[1], Xuejin Gao BS[1,2], Feng Tian BS[1], Chao Wu BS[1], Xinying Wang MD[1]

[1]*Department of General Surgery, Jinling Hospital, School of Medical, Nanjing University, Nanjing, Jiangsu Province, China*
[2]*Clinical College of South Medical University, Guangdong Province, China*

危重症患者行早期肠外营养治疗临床疗效的 meta 分析

背景：尽管一些大样本临床研究已经探究了早期肠外营养（early parenteral nutrition，ePN）在危重症患者的作用，但对于其疗效并没有达成共识，而且在这一领域也未见相关的 meta 分析报道。本研究的目的就是探究早期肠外营养在危重症患者中的治疗作用。**方法**：选取含有早期肠外营养的临床治疗的文献，对其数据进行 meta 分析，并根据患者是否合并使用早期肠内营养（early enteral nutrition，eEN）再进行亚组分析。**结果**：本研究总计纳入 5 篇随机对照研究（randomized control trials，RCTs）。结果显示，早期肠外营养组患者与对照组患者死亡率无明显差异(相对危险度：1.05, 95%置信区间：0.96, 1.16)。此外，与对照组相比，早期肠外营养组患者机械通气时间缩短（p=0.007，相对危险度：-0.95，95%置信区间：-1.64, -0.27），但是总住院时间延长（p<0.001，相对危险度：3.76，95%置信区间：2.25, 5.28）。**结论**：本 meta 分析表明，入院 24-48 小时以内的早期肠外营养并不会影响危重症患者死亡率。因此，肠内营养禁忌或者仅可使用低剂量肠内营养的患者无需使用早期肠外营养进行补充。

关键词：早期、肠外营养、危重、肠内营养、死亡率