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BRIEF REPORT

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Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence

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Abstract *Objective:* A combination of enteral (EN) and parenteral nutrition (PN) is often used as a strategy to optimize nutritional intake in critically ill patients; however, the effects of this intervention on clinically important outcomes have not been widely studied. This paper systematically reviewed studies that compare EN + PN to enteral nutrition (EN) alone in critically ill patients. *Methods:* We searched bibliographic databases, personal files, and relevant reference lists to identify randomized controlled trials that compared combination EN + PN to EN alone. *Results:* Only five studies met the inclusion criteria. In all these studies PN was started at the same time as EN in the experimental group. When the results of these trials were aggregated, EN + PN had no significant effect on mortality. There was no difference between the two groups in rates of infectious complications, length of hospital stay, or ventilator days. *Conclusions:* In critically ill patients who are not malnourished and have an intact gastrointestinal tract, starting PN at the same time as EN provides no benefit in clinical outcomes over EN alone. More research is needed to determine the effects of combination EN + PN on clinical outcomes in critically ill patients who are poorly intolerant to EN.

Keywords Enteral nutrition · Parenteral nutrition · Critical illness · Meta-analysis · Randomized trials · Nutrition support

Introduction

While enteral nutrition (EN) is the preferred method of providing nutrition support, it is often interrupted in critically ill patients due to various reasons and often falls short of meeting nutrient needs. Suboptimal nutrition in critically ill patients is well documented [1, 2, 3, 4]. A recent survey of Canadian ICUs shows that patients on EN received on average less than 60% of prescribed calories and protein [5]. When EN fails to meet the prescribed rate of nutrition, practitioners often prescribe parenteral nutrition (PN) in combination with EN to achieve the estimated nutrient needs and to avoid nutritional deficits. There is great variation in practice among ICUs, ranging from only 4% of patients on combination EN + PN [3] to as high as 60–80% of patients, as seen in some European centers [4, 6]. However, the use of parenteral nutrition is not without its risks in critically ill

patients [7]. When randomized trials comparing EN to PN were reviewed, EN was associated with significantly fewer infectious complications [relative risk (RR) 0.61, 95% confidence intervals (CI) 0.44, 0.84, p=0.003] than PN [8]. In recently developed Clinical Practice Guidelines for Nutrition Support, the use of EN over PN is strongly recommended in patients with an intact gastrointestinal tract [9].

The benefits of any nutrition intervention must be balanced with the potential risks and complications of that intervention. The purpose of this study was to systematically review and statistically aggregate those studies using combination EN + PN to those using EN alone in critically ill patients.

Methods

Four bibliographic databases (Medline, Embase, CINAHL, and the Cochrane Library) were searched from 1980 to 2003. Studies were selected for inclusion in the review if they were: randomized clinical trials in critically ill patients (defined as those cared for in an ICU environment who had urgent or life threatening complications) and compared combination EN + PN to EN alone. We assessed the methodological quality of all selected articles in duplicate, independently, using a scoring system we have used previously [7] (Table 1).

The primary outcomes of interest were mortality rate (ICU and hospital) and number of patients who developed infectious complications. Secondary endpoints included measures of nutritional intake. We combined data from all studies to estimate the common risk ratio and associated 95% confidence intervals for death and infectious complications. The common risk ratios and their confidence intervals were estimated using the random effects model of DerSimonian and Laird [10] as implemented in RevMan4.1 [11]. For evaluation of the treatment effect we considered p<0.10 to be supportive of a trend and p<0.05 to be statistically significant. For the test of heterogeneity we considered p<0.10 to be statistically significant.

Results

Study identification and selection

Of 11 studies identified [12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22] 5 met the inclusion criteria [13, 14, 15, 16, 17]. The details of the study design, population, methodological quality, and outcomes of the included studies are shown in Table 2. In all the studies patients had an intact gastrointestinal tract, and PN was started at the same time as EN; none of the studies evaluated outcomes of combination EN + PN in patients with feeding intolerance in whom PN was started subsequently. Other trials were excluded due to nonrandomization [18, 19, 20, 21, 22] and other interventions (i.e., compared EN + PN to PN, not to EN) [12].

Effect of combination EN + PN on mortality

In three studies the group receiving combination EN + PN had a higher mortality rate than the group receiving EN alone, but this reached statistical significance in only one study (63% in the EN + PN group vs. 26% in the EN alone group, p<0.05) [14]. The largest study showed no effect on ICU or day 90 mortality [17]. When all five studies were aggregated, the meta-analysis showed that the use of combination EN + PN had no effect on mortality (RR 1.27, 95% CI 0.82–1.94, p=0.3; see Fig. 1). The test for heterogeneity was not significant (p=0.26). A subgroup analysis was conducted to determine the confounding effects of nonisocaloric regimes in the trials and the possible relationship between "overfeeding" and the effect on mortality. There were no significant differences in mortality when trials in which the EN + PN group received more calories than the EN group [13, 14, 17] (RR=1.30 95% CI 0.78–2.16, p=0.3) were compared to trials in which the EN + PN group received similar calories to the EN group [15, 16] (RR=1.31, 95% CI 0.29–5.82, p=0.7, p value for differences between subgroups=0.94).

Table 1 Methodological quality assessment criteria

Criterion	Score 0	Score 1	Score 2
Randomization	Not applicable	Not concealed or not sure	Concealed randomization
Analysis	Other	Not applicable	Intention to treat
Blinding	Not blinded	Single blind	Double blind
Patient selection	Selected patients or unable to tell	Consecutive eligible patients	Not applicable
Comparability of groups at baseline	No or not sure	Yes	Not applicable
Extent of follow-up	<100%	100%	Not applicable
Treatment protocol	Poorly described	Reproducibly described	Not applicable
Cointerventions[a]	Not described	Described but not equal or not sure	Well described and all equal
Outcomes	Not described	Partially described	Objectively defined

[a] The extent to which antibiotics, nutritional support, ventilation, oxygen, and transfusions were applied equally across groups

Table 2 Randomized studies evaluating combined EN + PN in critically ill patients. Maximal score: 14 (for methodological quality assessment criteria see Table 1) (*EN* enteral nutrition, *PN* parenteral nutrition, *TBSA* total burn surface area)

	Herndon et al. [13]	Herndon et al. [14]	Dunham et al. [15]	Chiarelli et al. [16]	Bauer et al. [17]
Population	Burns >50% TBSA (*n*=28)	Burns >50% TBSA (*n*=39)	Blunt trauma (*n*=37)	ICU patients medical and surgical (*n*=24)	ICU patients (*n*=120)
Methods					
Concealed randomization	Not sure	Not sure	Not sure	Not sure	Not sure
Intent to treat	Yes	Yes	No	Yes	Yes
Blinding	No	No	No	No	Double
Score	6	7	8	8	12
Mortality					
EN + PN	8/13 (62%)	10/16 (63%)	3/10 (30%)	3/12 (25%)	17/60 (28%)
EN	8/15 (53%)	6/23 (26%)	1/12 (8%)	4/12 (33%)	18/60 (30%)
Infections[a]					
EN + PN	NA	NA	NA	6/12 (50%)	39/60 (65%)
EN	NA	NA	NA	3/12 (25%)	39/60 (65%)
Length of stay (days)					
EN + PN	NA	NA	NA	37±13 hospital	31.2±18.5 hospital; 16.9±11.8 ICU
EN	NA	NA	NA	41±23 hospital	33.7±27.7 hospital; 17.3±12.8 ICU

[a] Number of patients with infections

Effect of combination EN + PN on infectious complications, length of stay, ventilator days, and cost

In one trial of mixed ICU patients [16] a trend towards a higher incidence of bronchopneumonia was observed in the group receiving EN + PN vs. EN alone (6/12, 50%, vs. 3/12, 25%, p=0.085). There were no differences in infectious complications between the groups in a larger study in a similar population of ICU patients [17]. We aggregated these two studies and observed an overall estimate of RR 1.14 (95% confidence interval 0.66 – 1.96, p=0.6; see Fig. 2). Only two trials reported on length of stay and ventilator days [16, 17], and when these were aggregated, combination EN + PN had no effect. The cost of combination EN + PN was significantly higher than EN alone as demonstrated by Bauer et al. [17] (204±119 vs. 106±47 euros/patient per 7 days, p=0.0001) and Chiarelli et al. [16] (31 Italian lira per parenteral calorie vs. 19 per enteral calorie).

Effect of combination EN + PN on nutritional intake

Three of the four studies evaluating the effect of combination EN + PN on nutritional intake (see Table 3) reported that the combination group received significantly more calories than the group that received EN alone [13, 14, 17]. Improved visceral proteins were seen in patients receiving EN + PN compared to those receiving EN alone in two studies [16, 17].

Discussion

In many ICUs, particularly in Europe, up to 60% of patients [6] receive EN + PN in combination as a strategy to optimize nutrient delivery. In this review we found no supportive evidence for this practice with respect to improving clinical outcomes. This systematic review of all studies comparing EN + PN to EN in critically ill patients revealed that despite favorable effects on nutritional indices, when PN is started at the same time as EN, it has no beneficial effect on mortality, complications, or length of stay but does result in significant higher costs. It has been argued that the negative effects associated with combination EN + PN may be attributed to "overfeeding" when compared to EN alone, however, according to the subgroup analysis there were no differences in mortality that could be attributed to "overfeeding."

This review, which focuses on studies in critically ill patients only, has a comprehensive search strategy and robust methodology. The results of the studies are homogeneous, making the interpretation more valid. However, there are several limitations to the studies included in the review. First, one should be careful in extrapolating

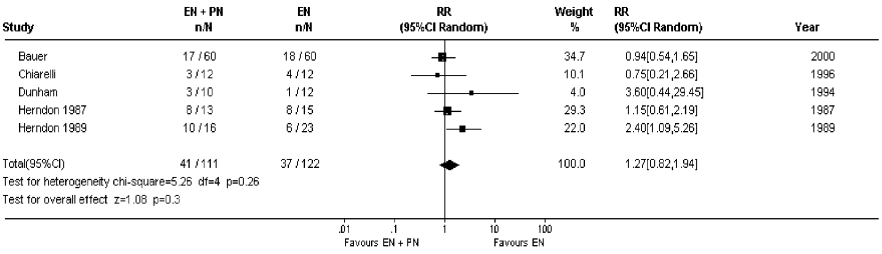

Fig. 1 Effect of combination EN + PN on mortality [13, 14, 15, 16, 17]. *EN* Enteral nutrition; *PN* parenteral nutrition; *EN + PN* combination enteral nutrition and parenteral nutrition; *n* number of persons who died in the group; *N* total number of persons in the group; *RR* relative risk; *CI* confidence intervals. (Reprinted with permission from the American Society for Parenteral and Enteral Nutrition from the *Journal of Parenteral and Enteral Nutrition*, *Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients, Vol. 27; no, 5, pp355-378, Fig. 8; Sept. 2003*; the American Society for Parenteral and Enteral Nutrition does not endorse the use of this material in any form other than its entirety

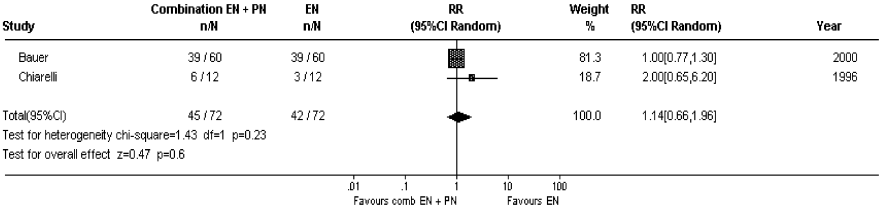

Fig. 2 Effect of combination EN + PN on infectious complications. *EN* Enteral nutrition; *PN* parenteral nutrition; *EN + PN* combination enteral nutrition and parenteral nutrition; *n* number of persons with infectious complications in the group; *N* total number of persons in the group; *RR* relative risk; *CI* confidence intervals

Table 3 Studies on the effect of combination EN + PN on nutritional intake (both interventions began at the same time) (*EN* enteral nutrition, *PN* parenteral nutrition, *BEE* basal energy expenditure, *GI* gastrointestinal)

	Herndon et al. [13]	Herndon et al. [14]	Dunham et al. [15]	Chiarelli et al. [16]	Bauer et al. [17]
Intervention					
Design	EN + PN vs. EN	EN + PN vs. EN	EN + PN vs. EN	EN + PN vs. EN	EN + PN vs. EN + placebo
Timing	Upon return of GI function	upon return of GI function	Within 24–48 h admission	Both groups received PN within 24–36 h of enrollment for 4 days before experimental group received EN	Within 24–48 h of admission
Duration	10 days	2 weeks	1 week	2 weeks	4–7 days
Calories					
Calories prescribed	25 kcal/kg per day +40 kcal/% TSBA	25 kcal/kg per day +40 kcal/% TSBA	1.3 ×BEE	Energy according to catabolic rate	25 kcal/kg per day
Calories received		N/A[a]			
EN + PN	3431±336 kcal/day[b] 3977±304 kcal/day[c]		1154±904 to 2218±335 kcal/day[d]	31±6 kcal/kg per day	24.6±4.9 kcal/kg per day
EN alone	2159±196 kcal/day[b] 3036±337 kcal/day[c]		1065±435 to 1931±353 kcal/day[d]	33±9 kcal/kg per day	14.2±6.5 kcal/kg per day
p	<0.05[b] <0.05[c]		NS	NS	<0.0001

[a] Calorie intake reported as survivors vs. nonsurvivors only; text reports EN + PN group received more calories than the EN group
[b] 0–3 days
[c] 4–7 days
[d] 1–7 days

the results to those populations of critically ill patients who are severely malnourished. In the largest study in this review [17] a majority of the ICU patients were well nourished (59%) and had a normal body mass index. In other studies, authors do not comment on the state of malnutrition. Second, there were only two trials that report infections, and given the paucity of data, only weak inferences can be made from the aggregated estimate. Third, the duration of the intervention in the trials varied from 4–7 days [17] to 2 weeks [14, 16]. Since the trials of longer duration reported a higher mortality in the EN + PN group than in the EN group [13, 14, 15], one could hypothesize that the longer exposure to PN resulted in higher mortality. Fourth, as illustrated in Table 2, the methodological quality of these studies varied significantly (range from 6–12, out of a maximum of 14 points). Furthermore, although two of the primary authors reported costs associated with the combined approach, we did not do a formal evaluation of the economic data in these primary trials. Hence the inferences from these costing data are limited.

It is also important to note that the studies included in this review did not address the effects of combination EN + PN in patients who were started on PN due to intolerance to EN or in those with a compromised gastrointestinal tract or who were malnourished. All the studies looked at the effects of starting PN with EN at the same time.

Our findings have many implications for future studies on combination EN + PN in critically ill patients. Well designed randomized trials in critically ill patients who are intolerant to enteral nutrition and/or have a compromised gastrointestinal tract and/or are malnourished need to be conducted to determine the effects of combined EN + PN on clinically important outcomes in these populations. The degree of malnutrition and weight loss also needs to be considered while conducting these studies to determine the effects of combination EN + PN on mortality and morbidity in malnourished patients. The optimal timing of PN in these patients and the effects of transitional feeding (i.e., weaning from parenteral nutrition to enteral nutrition) also need to be studied. Recent evidence from nonrandomized studies shows that the addition of "trickle feeds," i.e., small amounts of enteral nutrition added to parenteral nutrition reduces the complications associated with parenteral nutrition in ICU patients [20, 21].

In conclusion, in critically ill patients (with an intact gastrointestinal tract) who are not malnourished, starting PN at the same time as EN appears to have no added clinical benefit and is associated with higher costs than EN alone. Given the signals of potential harm from PN in critically ill patients from randomized trials and in the absence of data suggesting a benefit from using combination EN + PN, based on the evidence that we have presented, we recommend that PN not be started at the same time as enteral nutrition in critically ill patients. There are insufficient data on when to start PN in the patient who is not tolerating adequate amounts of EN. Practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis. We recommend that PN not be started until all strategies to maximize EN delivery (e.g., small bowel feeding tubes, motility agents) have been attempted.

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