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BEST EVIDENCE IN CRITICAL CARE MEDICINE

Early versus late parenteral nutrition in the adult ICU: feeding the patient or our conscience?

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Article appraised

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Structured abstract

Background: Critical illness increases the risk of malnutrition, which can increase infections, prolong mechanical ventilation, delay recovery, and increase mortality. While enteral nutrition (EN) is considered optimal, this is not always an option. Furthermore, algorithms for parenteral nutrition (PN) vary significantly, and it is unclear whether early initiation or delay of parenteral feeding is preferable.

Objective: This study compares intensive care unit (ICU) duration of stay in adults randomized to early initiation of PN (within 48 hr of ICU admission) *vs* delayed (at eight days or later after ICU admission), as consistent with European and North American guidelines, respectively.

Design and setting: This multicentre parallel-group randomized controlled trial was carried out from August 2007 to November 2010 and involved seven Belgian ICUs. The trial was powered at $> 80\%$ to detect a one-day between-group change of stay in the ICU and powered at 70% to detect a 3% change in mortality. The study was supported by an unrestricted and unconditional grant from Baxter Healthcare.

Patients: Inclusion criteria included patients older than 18 yr who were admitted to the ICU and had a nutritional risk screening (NRS) score of ≥ 3 (scale of 1-7; where ≥ 3 indicates nutritional risk). Exclusion criteria included patients with a *do not resuscitate* order, short bowel syndrome, absence of central venous access, a body mass index (BMI) < 17, the ability to tolerate oral nutrition or a predetermined nutritional regimen, and those with lung ventilation at home; patients in a diabetic coma or enrolled in other studies were also excluded.

Intervention: Eight thousand, seven hundred three patients were screened, and 4,640 of those were randomized in blocks of ten via sequentially numbered envelopes. Two thousand three hundred twelve patients were assigned to early PN initiation, and 2,328 patients were assigned to late PN initiation. Patients received enteral feeding by unit protocol, if appropriate. In addition, early PN patients received an intravenous solution of 20% glucose to achieve 400 $kCal \cdot day^{-1}$ on day one, 800 $kCal \cdot day^{-1}$ on day two, and 100% of the caloric goal by day three. Patients were weaned from PN when enteral nutrition met $> 80\%$ of caloric goals. The late PN initiation group received an intravenous solution of 5% glucose (equal in volume to the early initiation group and adequate to maintain hydration). If EN did not meet caloric goals by day seven, then PN was initiated on day eight. Both groups were maintained semi-recumbant (unless contraindicated); they received prokinetic agents, had duodenal feeding tubes, and received early parenteral trace elements, minerals, and vitamins.

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Measurements: The primary outcome was the number of days in the ICU, and secondary end points were new infections, the infection site (airway, lungs, blood, urinary tract, or wounds), inflammation (as measured by plasma C-reactive protein), time to ventilator weaning, rate of tracheostomy, rate of acute kidney injury (defined by RIFLE criteria), rate and duration of ICU renal replacement therapy (RRT), duration of hemodynamic support, rate of liver dysfunction, duration of hospital stay, functional status prior to discharge (measured by the distance walked in six minutes), and the proportion of patients performing independent everyday activities at discharge. Cost-benefit analysis was used to compare the two groups in terms of the total incremental healthcare cost from randomization to discharge. The two groups were also compared in relation to safety outcomes, specifically, mortality (in ICU, in hospital, and at 90 days) and the number of hypoglycemia episodes and nutrition-related complications.

Main results: The median [interquartile range] ICU stay was one day shorter in the late than in the early PN group (3 [2-7] *vs* 4 [2-9] days, respectively; $P = 0.02$). More late than early PN initiation patients were discharged alive from the ICU within eight days (75.2 *vs* 71.2%, respectively; $P = 0.007$), although mortality in the ICU, in the hospital, and at 90 days was not statistically different. Fewer late than early PN initiation patients acquired a new infection (22.8% *vs* 26.2%, respectively; $P = 0.008$) or cholestasis ($P < 0.001$). Late PN initiation was also associated with statistically shorter mechanical ventilation, RRT, and median duration of hospitalization than early PN initiation (14 days *vs* 16 days, respectively; $P = 0.004$). In contrast, late PN initiation was associated with a more pronounced inflammatory response, based on median C-reactive protein, than early PN initiation (190.6 $mg{\cdot}L^{-1}$ *vs* 159.7 $mg{\cdot}L^{-1}$, respectively; $P < 0.001$) and more episodes of hypoglycemia (3.5% *vs* 1.9%, respectively; $P = 0.001$). However, there were no statistical differences in nutrition-related complications. There was also no significant difference in functional status at discharge or incidence of acute kidney injury requiring RRT. Late initiation was associated with a small reduction in total incremental healthcare cost. Subgroup analysis yielded no differences in primary or safety outcomes. Where EN was surgically contraindicated [517 patients; APACHE 27 (11)], the infection rate in the late *vs* the early initiation group was 29.9% *vs* 40.2%, respectively; $P = 0.01$. Further, this late initiation subgroup had a relative increase of 20% in the likelihood of earlier discharge alive from the ICU (hazard ratio 1.20; 95% confidence interval 1.00 to 1.44; $P = 0.05$).

Conclusions: While ICU and 90-day survival were not significantly different, patients in the late PN group were discharged earlier from both the ICU and the hospital. Late PN initiation was also associated with fewer infections, shorter mechanical ventilation time, shorter RRT time, and lower overall healthcare costs. While there were more episodes of hypoglycemia and more inflammation in the late PN group, there was no apparent clinical consequence. No primary or secondary end points showed that early PN was superior.

Commentary

Current state of the literature and study relevance

Many patients are admitted to the ICU with poor nutrition. Moreover, critical illness and prolonged hospitalization can further worsen nutritional status due to increased catabolism, increased pro-inflammatory cytokines, increased counter-regulatory hormones (e.g., cortisol, catecholamines, and glucagon), and increased resistance to endogenous anabolic hormones (e.g. insulin and insulin-like growth factor 1).[1] Accordingly, over 40% of patients in the ICU may be clinically malnourished.[2] This condition can be associated with increased mortality and greater morbidity (more infections, impaired wound healing, and prolonged ventilation), longer ICU stay, and higher costs.[3] For these reasons, intensivists may be tempted to start some form of supplemental nutrition at the earliest opportunity. However, the data are incomplete.

In an excellent review of 111 trials in 2005, Doig *et al.* found that nutritional studies were generally small; they did not use randomization or concealed allocation adequately; they had excessive loss to follow-up; or they did not use intention-to-treat analysis appropriately.[3] Despite these limitations, studies *have* shown benefits associated with early EN in many ICU populations, including patients with trauma, burns, head injury, major surgery, and acute pancreatitis. These benefits have included lower mortality, reduced infection rates, decreased ventilator time, and shorter ICU stay.[2,4-7] In contrast, the use and optimal timing for initiation of PN remains less well defined. While no clear difference in mortality has been shown when EN and PN are compared, there is evidence that EN is associated with less morbidity and lower cost.[8,9]

Use of PN as an adjunct to EN is even less well defined, and European and North American guidelines differ substantially. While EN is the recommended route on both continents, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends that PN be initiated for all patients within 24-48 hr of admission whenever EN fails to meet caloric goals.[10] In contrast, the American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine generally suggest use of PN after ICU day seven.[9] Regardless, the dearth of randomized trials means that many recommendations are Grade C or lower.[11] In short, more evidence is needed to tackle a substantial issue and to facilitate evidence-based practice.

Analysis of methodology

We commend the authors for performing a large multicentred prospective randomized trial which included a variety of medical and surgical populations and predefined subgroups and also adhered to the CONSORT recommendations for clinical trial reporting.[12] The investigators also identified populations at risk for malnutrition (using the NRS); however, they did exclude those considered severely malnourished (BMI < 17), a population not unfamiliar in critical care. Groups were well-matched according to demographics, illness severity, diagnosis, and NRS scores, and the investigators included clinically relevant secondary end points. Patients were analyzed using intention-to-treat analysis, and all were included in the analysis except for 15 of the late intervention group (due to protocol violations). Patients received not only standard early EN but also standard early intravenous micronutrients. This approach should control for (and limit) micronutrient depletion and re-feeding effects such that the only differences between study arms were macronutrients, such as parenteral amino acids and lipids. Although the objective of the study was to compare the two protocols, many patients may not have met the ESPEN guidelines for early PN. For example, the guidelines recommend PN in patients where EN is contraindicated, not tolerated, or insufficient to meet caloric needs for three days[10]; however, half of the subjects' tracheas were extubated by day two, they were discharged from the ICU by day four, and they were already receiving a majority of their caloric needs from oral feeding. This information raises the concern as to whether the study design targeted the appropriate patients.

A major limitation is the lack of blinding, and another limitation may be the high percentage of cardiac patients enrolled (see discussion below). In addition, the doses of amino acid were lower than recommended by current guidelines.[10] The authors acknowledge that their standard PN formulas had a low protein-to-energy ratio and no glutamine or other immunomodulatory additives. However, these compounds are not without controversy, and they also vary in utilization.[13] As such, their exclusion is considered acceptable. It is also noteworthy that nutritional requirements were calculated without determining energy expenditure via indirect calorimetry, as current recommendations do caution that equations may be inaccurate, particularly in the obese.[9] It is also unclear how lipid calories from propofol were taken into account, as this may have influenced both total caloric intake and hepatic function (a secondary end point). With regard to cost, while a small reduction in healthcare cost was observed, this calculation was made using invoices billed to the patient or government. As the Belgian government awards a flat intravenous administration fee, which includes PN, the reported values did not deduct true PN costs in the late initiation group. As a result, these savings are difficult to generalize to other jurisdictions.

Relevance to clinical practice (strengths/weaknesses/external validity)

As outlined, evidence surrounding ICU nutrition has been deficient due to small and inadequate studies.[4] Casaer *et al.* undertook a large well-designed study to answer an important question, and they found that late PN initiation was associated with statistically significant and clinically relevant improvements in morbidity and resource utilization. If newer PN formulas—specifically those which include immunomodulatory compounds—in randomized trials are shown to be associated with improvements in morbidity, and especially infection rates, then the inferences from these data may be less clear. However, this study may represent a new benchmark due to the large number and broad set of patients examined. As such, these data could influence clinical practice and guidelines.

The extent of that influence, however, is limited by important caveats. First, as referred to above, cardiac surgery patients made up > 60% of each study arm. Cardiac surgical ICU patients have specific risks (i.e., higher rates of atrial fibrillation and ventricular dysrhythmias) as well as a shorter average ICU stay compared with general ICU patients.[14,15] Short stays and increased tolerance of EN should mean that PN is required less often for cardiac surgical patients. A sufficiently powered subgroup analysis — to examine early *vs* late PN in non-cardiac surgical ICU patients — could help answer how generalizable these data are to general ICU patients. Second, patients with a low BMI (< 17) were excluded; however, it is not uncommon for ICU patients with a low BMI to be malnourished. Since this condition could be associated with worse outcome, this patient population is therefore an important group to study.[1,2,5] Later, Casaer justified their exclusion by stating that "available data suggested not providing PN to such patients was unethical".[16] However, a large meta-analysis has suggested that patients with protein-energy malnutrition do better with EN *vs* PN, and they also have better outcomes with PN compared with standard care (oral diet with intravenous dextrose).[17] This would have made them reasonable candidates for a study which provided EN where appropriate. Third, this study was carried out prior to publication of the NICE-SUGAR trial, which found increased mortality and more hypoglycemia in patients managed with intensive insulin therapy.[18] Accordingly, updated guidelines favour a blood sugar of 6-10 $mmol \cdot L^{-1}$ (80-180 $mg \cdot dL^{-1}$) compared with the older target of 4.4-6.1 $mmol \cdot L^{-1}$ (80-100 $mg \cdot dL^{-1}$) which was used by Casaer *et al.* In addition, Casaer *et al.* also used a 20% glucose solution in the early PN group *vs* 5% in the late PN

group. This would have increased insulin requirements, especially with their low glycemic target. As would be predicted by NICE-SUGAR, there was a higher rate of hypoglycemia in Caesar's late initiation arm, which should also have an adverse effect on outcome.[18] Regardless, this confounds the data and raises doubts as to generalizability, particularly now that a higher blood sugar target is used.

It is also noteworthy that differences were seen in morbidity and secondary outcomes (i.e., in those that survived). However, rates of withdrawal of life-support were not provided for the two arms. While the multicentre nature of the study should mitigate this omission, it would be useful to learn if a difference in withdrawal rates existed in order to suggest any effect on outcome.

Clinical perspective

The data suggest no evidence of obvious harm by withholding PN (including in those unable to take EN). They also suggest no obvious clinical benefit from early PN. Moreover, there may be harm associated with early PN, a finding that is consistent with recent work by Kutsogiannis *et al*.[19] In contrast, delaying PN was associated with many better secondary outcomes. In fact, Casaer's work provokes an intriguing question: Why was mortality not improved with late PN despite improvements in so many secondary outcomes? Regardless, using PN during the first week to supplement insufficient EN in ICU patients at risk of malnutrition appears inferior to withholding PN. The clinical caveat is that we should probably provide vitamins, trace elements, and minerals.

The erstwhile instinct to meet caloric goals early on (despite little evidence) probably originates with the assumption that catabolic patients need calories. Alternatively, it may reside in our desire to do *something* rather than to do *nothing*, i.e., our conscience is fed even if the patient is not. Perhaps this is most often observed when a dextrose drip is administered to the nil-by-mouth patient, despite providing only 170 $kCal \cdot L^{-1}$.

The best studies challenge (or bolster) common sense, and therefore the work by Casaer *et al.* qualifies. However, many questions remain. For example, Casaer *et al*. excluded patients with BMI < 17 while other studies have shown an increase in ICU mortality in this population.[20] Another recent study found increased calories improved clinical outcomes in patients with BMI < 25 and > 35.[5] Taken together, this suggests more work is needed to evaluate the role of PN in these at-risk populations. There are additional unresolved questions: Is seven days (*vs*, for example, 14 days) an optimal delay or just an improvement on a one-day delay? Just how many calories are really needed? What is the optimal division of lipids and proteins? What is the best means to determine caloric requirements? What is the putative role of immunomodulatory micronutrients, and how does the specific composition of a diet mitigate or muddle healing?

Overall, no harm resulted from delaying PN for seven days in the nutritionally at-risk ICU population, and the delay was associated with improved morbidity, including ICU length of stay, hospital length of stay, duration of RRT, and duration of mechanical ventilation. Further, these outcomes were observed despite the use of blood sugar goals now shown to increase mortality and the use of nutritional formulas without *potentially* beneficial immunomodulatory agents. In summary, despite the abovementioned study limitations, no evidence was shown to promote early PN in critically ill patients started on early EN. There is a great deal yet to learn, especially in patients with a low BMI; however, this study offers a clinically important step forward.

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Conflicts of interest None declared.

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