CRITICAL CARE

Does artificial nutrition improve outcome of critical illness?

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Abstract

Nutritional support is generally considered an essential component in the management of critically ill patients. The existing guidelines advocate early enteral nutrition, with the optimal timing for the addition of parenteral nutrition to insufficient enteral feeding being the subject of transatlantic controversy. The unphysiologic intervention of artificial nutrition in critically ill patients, however, may evoke complications and side effects. Besides the classically described complications, suppression of autophagy, potentially important for cellular repair and organ recovery, was elucidated only recently. The question whether artificial nutrition in critical illness improves or worsens outcome as compared with starvation has so far not been adequately addressed. This paper provides a critical analysis of the existing literature on ICU nutrition, highlighting important methodological shortcomings of many trials and meta-analyses and underlining the urgent need for high-quality research in this field. Recent adequately designed randomized controlled trials suggest that trophic enteral feeding during the first week of critical illness is as good as full enteral feeding and that early addition of parenteral nutrition to insufficient enteral nutrition does not provide any benefit and worsens morbidity.

Introduction

Admission to the ICU is usually necessary for acute diseases/injuries or for exacerbations/complications of chronic diseases. Both are associated with variable degrees of inflammation and result in reduced energy and protein intake, increased energy expenditure and protein catabolism [1]. As a result, ICU patients – even when not malnourished prior to admission – will inevitably develop a

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nutritional deficit during their ICU stay. Nutritional deficit is associated with adverse outcomes [2,3] and nutritional support is generally considered an essential part of managing ICU patients [4-6].

Existing guidelines recommend early enteral nutrition (EN) for patients who are hemodynamically stable and unable to consume a full oral diet within 3 days [4-6]. The optimal timing for adding parenteral nutrition (PN) in patients who cannot sufficiently be fed by the enteral route remains controversial, with European guidelines advocating an early start [6] whereas the American guidelines suggest postponing PN until day 7 to 10 in the absence of prior malnutrition [5]. Recommended protein requirements vary between 1.2 and 2 g/kg/day [5,6].

This paper aims to discuss the pros and cons of artificial nutrition in ICU patients and to assess the quality of the evidence for early full nutritional support in this population, with a focus on energy and protein delivery. For evaluation of evidence on micronutrients and immunonutrition, readers are referred to other recent reviews [7-11].

Pros and cons of nutritional support in the ICU

Without doubt, nutritional deficit in the ICU is associated with adverse outcomes (an association that may be causal or casual) and prolonged starvation ultimately leads to death. However, the key question is whether artificial nutrition, administered during critical illness, can prevent or correct this nutritional deficit and thereby also the associated adverse outcomes. Artificial nutrition in the critically ill is a medicine provided to anorectic patients, is unphysiologic and may evoke complications and unwanted side effects that should be weighed against any expected benefit.

Also without doubt, artificial nutrition improves energy and protein intake, but whether it also prevents accelerated muscle catabolism in immobilized critically ill patients with systemic inflammation remains unclear. The mechanisms underlying muscle atrophy and weakness in critical illness are extremely complex [12-14], and thus expecting the atrophy and weakness to be reversible by simply providing calories and protein is an oversimplification. Aggressive nutritional support in critically ill patients,

instead of preventing muscle loss or reducing proteolysis and gluconeogenesis, merely results in fat gain [15-19].

Complications of artificial nutrition include aspiration pneumonia, feeding tube dislocation, diarrhea, abdominal hypertension, intestinal ischemia, catheter sepsis, liver steatosis, hyperglycemia, dyslipidemia and refeeding syndrome [20-22]. Nutrition also suppresses autophagy, a survival mechanism serving to recycle intracellular nutrients and maintain energy homeostasis during nutrient deprivation. Recent evidence suggests that autophagy is essential for the immune response and for housekeeping functions such as removal of toxic protein aggregates and damaged organelles, and thus it could be critical for recovery from organ failure [22-24]. A recent study of critically ill rabbits showed that early PN, especially the provision of proteins and lipids, suppressed the ubiquitin–proteasome pathway, thereby contributing to the preservation of muscle mass, but also evoked a phenotype of autophagy deficiency in liver and skeletal muscle, suggesting that the maintenance of muscle mass might come at the price of accumulation of toxic protein aggregates, thus compromising function [25]. This same phenotype has also been found in the liver and muscle of fed critically ill patients [26] and was recently shown to contribute to vital organ failure in an animal model of critical illness [27]. Autophagy-deficient mice show muscle loss with accumulation of toxic proteins and dysfunctional organelles [28,29], suggesting that nutrition-induced suppression of autophagy might even have a negative impact on fat-free mass.

A direct link between nutrition and organ failure was also shown in a series of animal experiments evaluating the impact of different nutritional regimen on ischemia–reperfusion injury in the kidney. In these experiments, nutrition – more specifically protein rather than glucose – appears to increase the extent of kidney injury [30-32].

Given these pros and cons of artificial nutrition in critical illness, clinical trials should have clinical (morbidity, mortality, long-term functional outcome) and not nutritional or other surrogate endpoints. Also surprising is that the majority of the existing literature concentrates on when, how and what to feed, whereas the beneficial effect of feeding *per se* is rarely questioned.

What is the evidence that (more) nutrition improves outcome?
Observational trials
Several observational trials (OTs) suggest an association between caloric deficit and adverse outcomes. This caloric deficit mainly develops during the first days in the ICU, when EN is insufficient due to hemodynamic instability, slow progression to target, poor tolerance (gastric retention/vomiting) and interruptions for procedures [33,34]. In a large multinational prospective OT, an inverse relationship between caloric input and risk of mortality was only significant for patients with body mass index <25 or >35 kg/m^2 [35]. In another OT, proteins and energy were titrated separately for patients with an expected prolonged ICU stay. The authors concluded that achieving the energy/protein target is associated with lower 28-day mortality. However, ICU and hospital mortalities showed an opposite trend (surprisingly translated into a hazard ratio <1 in the unadjusted Cox proportional hazard analysis, suggesting erroneous censoring as discussed below). ICU and hospital stays and duration of mechanical ventilation were shortest for patients reaching neither the energy target nor the protein target [36]. In other OTs, higher caloric intake was associated with poorer outcomes, including mortality and infections [37,38].

Early initiation of (mainly enteral) nutrition was associated with a lower mortality in several OTs [39,40]. However the incidence of ventilator-associated pneumonia was lower and the ICU stay was shorter in the late initiation group [39]. Another OT found more gastrointestinal complications and a longer ICU stay with early initiation of EN in patients with high illness severity [41]. Early addition of PN to insufficient EN was not associated with shorter hospital stay in another large OT [42,43].

The evidence for the recommended amount of protein in artificial nutrition is limited. Four OTs using isotopes [44,45], nitrogen balances [46] or measurements of body composition [47] in an aggregate total of 90 septic, trauma or burn patients have shown that the net balance between protein synthesis and protein breakdown is improved with protein intakes up to 1 to 1.5 g/kg/day, whereas any further increase in protein intake is wasted in oxidative pathways. However, there are no randomized controlled trials (RCTs) showing any benefit of more protein intake on clinically relevant outcomes.

A major methodological problem with OTs investigating ICU nutrition is confounding by indication. Patients who receive less or later feeding also have an explanatory reason why feeding is inadequate or delayed, which is mainly related to illness severity. In addition, association is never proof of causality. True evidence for the optimal amount, route and timing of nutritional support in critically ill patients can hence only be provided by RCTs.

Another methodological (statistical) issue that often results in incorrect interpretation of clinical trials is inappropriate censoring [48,49] for any type of time-to-event survival analysis (for example, Kaplan–Meier statistics or Cox proportional hazards models) when the duration of follow-up is not identical for all subjects. To illustrate this problem we refer to the trial evaluating the impact of reaching nutritional targets on survival [36], where patients were followed-up throughout their hospital stay. Patients reaching the nutritional target had

longer ICU and hospital stays and also numerically higher ICU and hospital mortalities. However, uncorrected Cox proportional hazard analysis, censoring patients at last follow-up, suggested a lower mortality risk for patients reaching target. These data are internally inconsistent and can only be explained by inappropriate use of informative censoring.

Censoring is informative when the reason why a patient is censored (no longer included in the analysis) is not just by chance but in fact related to the outcome [48,49]. In the above-mentioned study, patients discharged earlier (and subsequently omitted from the analysis) do not have the same mortality risk as those who remain in the ICU or hospital [36]. The deletion/censoring of early discharge patients lowers the number of patients at risk (the denominator in the calculation) in the cohort not reaching nutritional target and, as a result, for a similar or lower numerical mortality, the proportion (altered by the lower denominator) of patients dying in that cohort seems higher (see illustration in Figure 1). This problem is preventable by obtaining landmark time-to-event analysis (for example, 90-day mortality) in *all* patients. Conversely, if the duration of stay in the ICU or hospital is the endpoint, patients dying before ICU/hospital discharge should be censored after the last patient has been discharged alive, to account for such competing risk between length of stay and mortality [50].

Meta-analyses of older randomized controlled trials

RCTs that compare any form or amount of (enteral or parenteral) nutrition with tolerating starvation (withholding/delaying nutritional support) in critically ill patients are non-existent [51]. Results from older (all largely underpowered) RCTs on other aspects of ICU nutrition have been summarized in meta-analyses, many of them including elective surgery patients. Two recent meta-analyses, limited to critically ill patients, showed a significant reduction of infections with early EN compared with late EN, whereas mortality reached significance in only one of the trials [52,53]. The quality of the included trials was poor, however, with high risk of bias [54-56]. Meta-analyses comparing EN with PN in critically ill patients suggested a reduction of infectious complications with EN but the mortality results were conflicting [57,58]. In many of the included RCTs, PN patients received more calories and had higher blood glucose levels than EN patients. Finally, two meta-analyses of trials comparing EN with a combination of PN and EN did not establish clinical benefit [58,59].

A common problem with all these meta-analyses is that they included small, old studies with high risk of bias (for example, lack of randomization concealment, no blinded outcome assessment, no intention-to-treat analysis). Other problems are the inclusion of different patient populations with variable illness severity and baseline nutritional status, variable nutritional formulations, inconsistent definitions of early, widely varying caloric input, and so forth. Better quality research on ICU nutrition is therefore urgently needed.

Recent randomized controlled trials

Two recent RCTs have compared different amounts of EN in ICU patients [60,61]. The first single-center trial compared the provision of 90 to 100% of the caloric goal with permissive underfeeding, defined as 60 to 70% of the target in 240 (of 1,587 screened) patients receiving EN and expected to remain in the ICU for at least 48 hours [60]. Permissive underfeeding significantly reduced the hospital mortality (risk ratio = 0.71; 95% confidence interval = 0.50 to 0.99) and tended to reduce 180-day mortality (risk ratio = 0.74; 95% confidence interval = 0.53 to 1.03). However, the actual energy delivery only differed by 10% (59% vs. 71% of target) [60]. The small number of patients, without a well-motivated sample size calculation to guarantee the required statistical power, makes this trial prone to observations evoked by chance.

The EDEN trial is a multicenter open-label RCT comparing trophic EN with full EN in 1,000 (of 7,968 screened) adult patients with acute lung injury requiring mechanical ventilation [61]. The sample size of this trial was determined by a well-rationalized calculation. In the full feeding group, EN was advanced to goal (25 to 30 kcal/kg ideal body weight/day of nonprotein calories) as quickly as possible. Patients in the trophic feeding group received 20 kcal/hour, and advanced to full feeding only if they were still on mechanical ventilation after 6 days. The actual caloric intake was 400 kcal/day (25% of target) for trophic EN versus 1,300 kcal/day (80% of target) for full EN. The feeding protocol had no significant effect on ventilator-free days through 28 days (the primary endpoint), nor on infectious complications, ICU-free days, organ failure-free days or 60-day mortality. Patients in the full-feeding group had significantly more episodes of gastrointestinal intolerance, higher blood glucose levels and insulin requirement and a greater cumulative net fluid balance [61]. An important limitation of this trial is the high exclusion rate, mainly for high disease severity or important comorbidity, thus limiting the generalizability of its findings.

Taken together, these two RCTs suggest that limiting enteral caloric delivery during the first ICU days is not deleterious for clinical outcome. Potential limitations are the insufficient power to prove equivalence between the nutritional strategies, the absence of prior malnutrition in included patients and the lack of long-term functional outcomes [62].

Two other RCTs evaluated the concept of combined PN and EN to prevent the development of a caloric
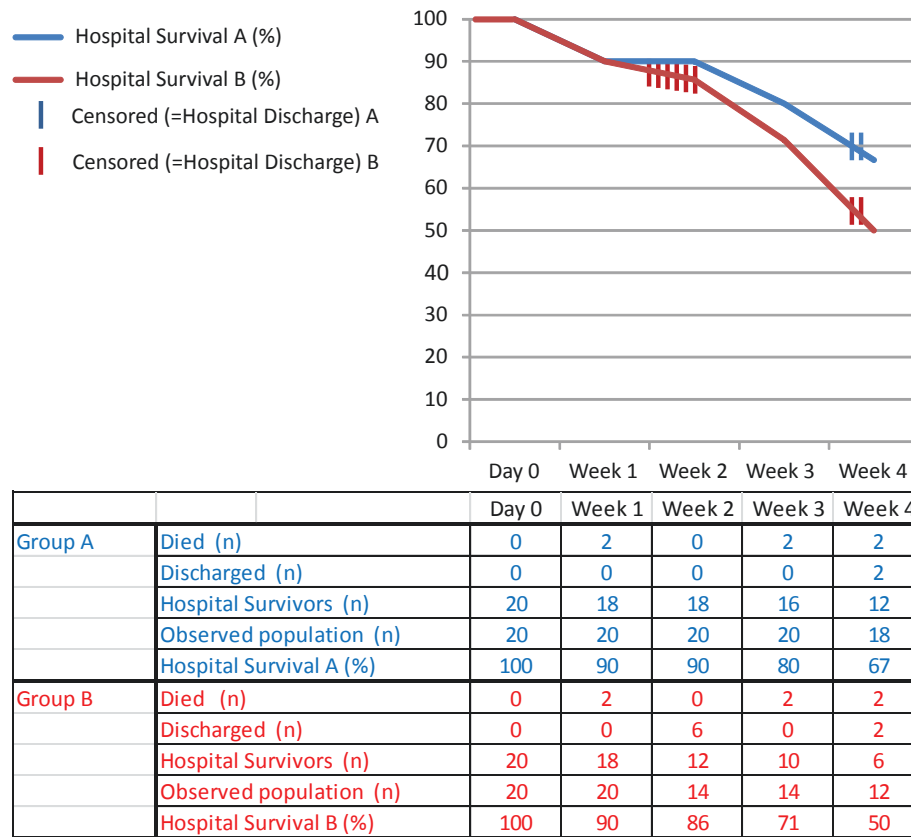
		Day 0	Week 1	Week 2	Week 3	Week 4
Group A	Died (n)	0	2	0	2	2
	Discharged (n)	0	0	0	0	2
	Hospital Survivors (n)	20	18	18	16	12
	Observed population (n)	20	20	20	20	18
	Hospital Survival A (%)	100	90	90	80	67
Group B	Died (n)	0	2	0	2	2
	Discharged (n)	0	0	6	0	2
	Hospital Survivors (n)	20	18	12	10	6
	Observed population (n)	20	20	14	14	12
	Hospital Survival B (%)	100	90	86	71	50

Figure 1. Informative censoring in two patient groups with identical hospital mortality but different hospital stay duration. Group A and B have identical hospital mortalities (6/20) but hospital stay in group B is shorter. Kaplan–Meier curves wrongly estimate a lower survival in group B; proportional hazard ratios will be affected likewise.

deficit [63,64]. The Tight Calorie Control Study (TICACOS) was conceived as a pilot trial and hence no sample size calculation was performed. This trial included 130 ICU (of 944 screened) patients on mechanical ventilation with an expected ICU stay ≥3 days [63]. Within 48 hours after admission, patients were randomized to the tight-calorie group, in which caloric intake was adjusted daily under supervision of a dietician guided by repeated indirect calorimetry, or a control group receiving a fixed 25 kcal/kg/day. If the caloric target could not be reached by EN alone, PN was added. In the tight-calorie group, the measured target varied significantly over time and caloric intake exceeded this target, resulting in a cumulative energy balance of 2,008 ± 2,177 kcal. Three patients received exclusive PN and 19 patients received combined PN and EN. In the control group, intake was consistently below the calculated target, resulting in a cumulative energy balance of −3,550 ± 4,591 kcal. Only one patient received exclusive PN and seven patients received combined EN and PN. The results for hospital mortality, the primary outcome, are only given for the per-protocol analysis (28.5% vs. 48.2%; P = 0.023 in favor of the tight-calorie group). The survival curve revealed a trend for decreased mortality in the intention-to-treat analysis and a significantly decreased mortality in the per-protocol analysis. However, both ICU and hospital stays were shorter in the tight-calorie group, clearly introducing the statistical problem of informative censoring/competing risk that we discussed earlier. In addition, not only the ICU stay but also the duration of mechanical ventilation was significantly longer in the tight-calorie group, which also revealed more infectious complications. The design of the study also does not allow distinguishing effects of indirect calorimetry guidance versus providing more nutrition [63]. A multicenter trial with similar design is currently ongoing (clinicaltrials.gov: NCT01479673).

The Early Parenteral Nutrition Completing Insufficient Enteral Nutrition in Adult ICU Patients (EPaNIC) trial is the largest RCT in the field of ICU nutrition. This trial randomized 4,640 ICU (of 8,703 screened) patients with nutritional risk score ≥3 to either early or late initiation of PN to complete insufficient EN [64]. Patients with severe prior malnutrition (body mass index <17 kg/m²; n = 106) were excluded. Patients in both groups received EN according to a standardized protocol. Calculations of

caloric target included protein energy and were based on age, gender and ideal body weight (25 to 35 kcal/kg/day). On days 1 and 2, the early PN group received 20% glucose to reach the caloric goal of 400 and 800 kcal/day, respectively. Mixed PN was started on day 3 and was continued until 80% of the caloric target was met by EN or the restart of oral feeding. The late PN group received glucose 5% in addition to EN for the first week in the ICU. If EN was insufficient after day 7, PN was added to achieve the target. Trace elements, minerals and micro-nutrients were given to both groups from day 3 onwards until full EN was reached. The EN amount did not differ between groups and reached ±50% of target at day 7. The early PN group received significantly more calories and proteins during the first 7 days. The ICU, hospital and 90-day survival rates (safety outcomes) were comparable. The ICU stay (primary outcome) was significantly shorter in the late PN group, reflected in a 6.3% increase in the likelihood of being discharged alive earlier from the ICU with a hazard ratio of 1.06 (95% confidence interval 1.0 to 1.13). The late PN group also had a shorter hospital stay, fewer new infections (22.8% vs. 26.2%) and a shorter duration of mechanical ventilation. Functional status at hospital discharge (evaluated in ±2,000 patients) was not affected by randomization. Late PN reduced total billed healthcare costs by €1,110/patient.

Of particular interest was the subgroup of 517 patients with contraindications for EN. In this subgroup the beneficial effect of withholding early PN, and thus tolerating virtual fasting for 1 week, was even more pronounced. Whether this reflects benefit of withholding any nutrition, irrespective of the route, or more deleterious effects of more PN remains to be studied [64]. The EPaNIC trial is unique by its power, preplanned analysis of hard clinical endpoints and blinding of outcome assessors. Formulated criticisms include the inclusion of a large postcardiac surgery cohort, although showing a similar outcome, and the use of tight glycemic control. Tolerating more PN-induced hyperglycemia, however, is very unlikely to improve outcome with early PN.

In summary, both the TICACOS trial and the EPaNIC trial show a beneficial effect of reduced energy intake on morbidity. The difference with regard to survival outcome in these trials with markedly different inclusion criteria (the TICACOS trial only included a small and specific subset of ICU patients, whereas the EPaNIC trial included a very representative sample of all-comers in the ICU) requires further investigation.

Conclusion
The provision of artificial nutrition to critically ill patients is largely based on association between malnutrition and poor outcome. Whether and to what extent artificial nutrition can prevent/attenuate muscle wasting/weakness or accelerate recovery, however, remains unclear. In addition, artificial nutrition during critical illness has deleterious effects that should be weighed against any presumed benefit. Future clinical trials should include hard clinical endpoints.

The available evidence suggests that, in patients without severe prior malnutrition, early trophic enteral feeding is at least as good as full EN and that early addition of PN to insufficient EN does not provide any benefit and worsens morbidity. How long critically ill patients can be nutrient restricted or how to determine at which time point the benefits of artificial nutrition start to outweigh the risks remains to be determined.

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