Design of nutrition trials in critically ill patients: food for thought

Yaseen M. Arabi¹, Hasan M. Al-Dorzi¹, Lauralyn McIntyre², Sangeeta Mehta³

¹King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; ²Department of Medicine, Division of Critical Care Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Canada; ³Interdepartmental Division of Critical Care Medicine, Department of Medicine, Division of Respirology, University of Toronto, Mount Sinai Hospital, Toronto, Canada

Correspondence to: Yaseen M. Arabi, MD, FCCP, FCCM. Chairman, Intensive Care Department; Professor, College of Medicine, King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, ICU 1425, PO Box 22490, Intensive Care Department, MC 1425, Riyadh 11426, Saudi Arabia. Email: yaseenarabi@yahoo.com or arabi@ngha.med.sa.

Submitted Mar 25, 2016. Accepted for publication Mar 30, 2016. doi: 10.21037/atm.2016.05.02

We would like to thank Drs. Casaer and Van den Berghe for their thoughtful editorial on our article “Permissive underfeeding or standard enteral feeding in critically ill adults” published in the New England Journal of Medicine on June 18, 2015 (1,2). Over the last few years, several large clinical trials have added immensely to our knowledge regarding nutritional support of critically ill patients. Table 1 summarizes and contrasts eight recent multicenter trials which compared different doses of enteral nutrition (1,3-5), or enteral versus parenteral nutrition (6-9).

PermiT and other trials showed no difference in outcomes in patients receiving restricted versus full caloric intake. Drs. Casaer and Van den Berghe raise many important questions regarding these trials: Is mortality an appropriate primary endpoint for nutrition trials? Do we need larger trials to detect smaller treatment effect? Should we use different endpoints than mortality? How about biomarkers? How generalizable are the results of PermiT to normal weight or underweight patient populations? Are specific patient groups more likely to be nutrition-responsive?

Is mortality an appropriate primary endpoint for nutrition trials?

While early enteral feeding in critically ill patients has been shown in systematic reviews to reduce mortality (12), the association between caloric intake and mortality is less clear, with several observational studies reporting conflicting results (13-16). In a previous 2x2 factorial design trial of hypocaloric feeding and intensive insulin therapy, we demonstrated lower hospital mortality with hypocaloric intake, although this was a secondary endpoint (17). There is sufficient pathophysiological evidence to suggest that caloric intake may alter many important biological processes that may affect mortality. Caloric restriction has been shown to prolong life span in several species (18,19), promote mammalian cell survival (20) and improve biomarkers of longevity in humans (21). These effects may be mediated through the effect of caloric restriction on reducing metabolic rate, oxidative stress (22), and mitochondrial free radical generation (23) improving insulin sensitivity and myocardial ischemia tolerance (24) and modifying neuroendocrine and sympathetic nervous system function (19). These findings buttress the equipoise regarding the effect of caloric intake on mortality, which was the basis for PermiT and other trials. As reflected in Table 1, several trials used mortality (at 28- to 90-day) as the primary endpoint; others used intensive care unit (ICU) length of stay, ventilator free-days or nosocomial infections. Mortality is an objective outcome and less subject to bias than other outcomes such as infection; and therefore will likely remain a core outcome in critical care nutrition studies, particularly large pragmatic trials.

Do we need larger trials to detect smaller treatment effect?

The lack of benefit of increased caloric intake appears to be a consistent finding across the different studies. A recent meta-analysis of six trials and 2,517 patients demonstrated...
Table 1 Randomized trials of nutrition management in adult critically ill patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enteral nutrition trials</th>
<th>Enteral versus parenteral nutrition trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PermiT (1)</td>
<td>EPaNIC (6)</td>
</tr>
<tr>
<td>Intervention</td>
<td>Permissive underfeeding</td>
<td>Early versus late initiation of parenteral nutrition</td>
</tr>
<tr>
<td></td>
<td>versus target feeding</td>
<td>Early PN versus standard care</td>
</tr>
<tr>
<td>Population</td>
<td>General ICU patients</td>
<td>TPN versus enteral feeding</td>
</tr>
<tr>
<td></td>
<td>Patients with acute lung injury</td>
<td>General ICU patients</td>
</tr>
<tr>
<td></td>
<td>Patients with acute respiratory failure</td>
<td>General ICU patients</td>
</tr>
<tr>
<td>BMI in kg/m² (intervention, control)</td>
<td>29, 30</td>
<td>6% with BMI less than 20</td>
</tr>
<tr>
<td>Duration of study treatment</td>
<td>14 days</td>
<td>ICU stay</td>
</tr>
<tr>
<td>Calculation of caloric intake includes protein calories</td>
<td>Yes</td>
<td>5 days</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>90-day mortality</td>
<td>Nosocomial infections after day 8 until day 28</td>
</tr>
<tr>
<td>Difference in primary outcome used for sample size calculation</td>
<td>Mortality ARR 8%</td>
<td>Mortality ARR 17%</td>
</tr>
<tr>
<td>Sample size</td>
<td>894</td>
<td>1,470</td>
</tr>
<tr>
<td>Functional outcomes</td>
<td>No</td>
<td>2,400</td>
</tr>
<tr>
<td>Difference in caloric intake</td>
<td>Yes</td>
<td>305</td>
</tr>
<tr>
<td>Difference in protein intake</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

EDEN, early versus delayed enteral feeding to treat people with acute lung injury or acute respiratory distress syndrome; EPaNIC, the early parenteral nutrition completing enteral nutrition in adult critically ill patients; ICU, intensive care unit; BMI, body mass index in kg/m²; ARR, absolute risk reduction.
no difference in the risk of hospital-acquired infections, hospital mortality, ICU length of stay or ventilator-free days between patients receiving intentional hypocaloric versus normocaloric nutritional goals (25). Thus, current data demonstrate that in general, restricted compared to full caloric intake during the acute phase of critical illness does not affect mortality. However, we believe that there is a need to better assess who may or may not benefit from nutritional interventions; and a need for further adequately powered trial in these target groups.

Should we use different endpoints than mortality? How about biomarkers?

We believe the response to both of these questions is ‘Yes’. In particular, the effect of nutritional support on functional outcomes and quality of life should be systematically studied. These patient-centered outcomes have been incorporated in several recent trials as secondary endpoints or in a subset of patients (Table 1). The role of an integrated intervention that includes nutrition and mobilization needs further study; and functional outcomes will be essential to measure the effect of such intervention. Another important endpoint in nutrition studies is kidney function. In post-hoc analysis of the PermiT trial, need for renal replacement was lower in the permissive underfeeding group. As pointed out by Drs. Casaer and Van den Berghe, this is consistent with the findings of the EPaNIC trial which demonstrated longer median duration of renal-replacement therapy in the early parental nutrition group (6,26). It is also consistent with the Nephroprotective trial which found a trend towards increased renal replacement in patients receiving amino acid therapy compared to standard therapy (27). Animal studies have also shown beneficial effects of short-term calorie restriction on renal and vascular ischemia-reperfusion injury (28,29). Therefore, renal function should be an a priori outcome in nutrition trials in critically ill patients. Incorporating biomarkers in nutrition studies is important to better understand the underlying pathophysiologic effects. The PermiT Trial demonstrated that increasing caloric intake did not affect parameters of protein metabolism, as reflected by prealbumin, transferrin and nitrogen balance (1). Further work is underway to examine the effects of caloric dose on inflammation and oxidative stress in patients enrolled in the PermiT trial. While biomarkers are important, they will not replace important patient-centered outcomes, but will provide additional information about mechanisms.

Are specific patient groups more likely to be nutrition-responsive?

As indicated by Drs. Casaer and Van den Berghe, the patients enrolled in the PermiT trial were those considered most likely to be affected by nutritional interventions (predominantly non-surgical, many suffering from sepsis at inclusion, with a median ICU stay of about 13 days). Yet, permissive underfeeding compared to standard feeding did not affect the outcomes of such patients. Drs. Casaer and Van den Berghe noted that patients with hyperglycemia (>9.2 mmol/L) at randomization may be a subgroup that may benefit from permissive underfeeding compared with standard feeding (relative risk, 0.83; 95% confidence interval, 0.63–1.1, P=0.19) (1). Further work is needed to identify subsets of patients who may benefit from feeding below energy targets.

How generalizable are the results of PermiT to normal weight or underweight patient populations? Are there specific groups more likely to be nutrition-responsive?

These important questions are relevant to most of the recent trials, given that the majority of patients had an average body mass index (BMI) of 25–30, including a trial of patients with refeeding syndrome (5) (Table 1). This is a reflection of the BMI in the general population (for example, the age-adjusted average BMI in the United States is 29) (30). There is a need for studies evaluating patients with different BMI groups, however as indicated by Drs. Casaer and Van den Berghe, studies have shown that the nutritional effect may not be differ among different BMI groups, as BMI may not be the best measure for underlying nutritional status. While alternative approaches to assess nutritional status such as the Nutrition Risk in Critically ill (NUTRIC) score have been proposed (31), their ability to discriminate nutrition-responsive patients needs further evaluation.

We fully agree that the next pressing question is the effect of protein intake on critically ill patients. Recent trials have used different strategies for protein intake. It remains unclear whether more protein is associated with better outcomes through preservation of muscle mass (32), or with worse outcomes through inhibition of autophagy as suggested by Drs. Casaer and Van den Berghe.

Recent trials such as PermiT have helped paved the path on our journey to better understanding of the effect...
of nutrition on the outcome of critically ill patients. This journey is far from over, and is certain to be an exciting one.

Acknowledgements

This work is supported by King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


Cite this article as: Arabi YM, Al-Dorzi HM, McIntyre L, Mehta S. Design of nutrition trials in critically ill patients: food for thought. Ann Transl Med 2016;4(9):186. doi: 10.21037/atm.2016.05.02