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Critical Care Nutrition

Nutrition Information Byte (NIBBLE)

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The North American vs. European Controversy Continues: The timing of supplementary parenteral nutrition in the critically ill

Background: There has been considerable controversy regarding the timing of supplemental parenteral nutrition (PN) in the critical care setting. Guideline recommendations range from continued underfeeding with EN alone for up to 7-10 days (American guidelines)[1] to the addition of supplemental PN (European) within 24-48 hours in patients who are expected to be intolerant to EN within 72 hours of admission.[2] The Canadians conclude there are insufficient data to warrant a clinical recommendation and suggest that efforts to maximize the benefits of EN (small bowel feeding tubes and motility agents) are used prior to starting PN.[3] Proponents of the use of early supplemental PN have focused on data demonstrating that the cumulative energy deficit or caloric debt is associated with adverse clinical outcomes in critically ill patients.[4] Opponents cite the literature demonstrating increased adverse events in patients who receive PN during their ICU stay.[4,5] Data from existing randomized trials are inconclusive.[6] Recent large-scale multicenter observational studies fail to confirm a benefit from early PN.[7,8] The recent publication entitled "**Early versus late parenteral nutrition in critically ill adults**", published by Michael Casaer, Greet Van den Berghe and colleagues, is a large scale randomized trial that contributes to resolving this controversy.[9] **Or does it?**

The Study: In this **unblinded**, **multicenter trial**, Casaer and colleagues **randomized 4640 patients** to receive early initiation of PN or late PN. Both groups received a standard enteral nutrition protocol. The early PN group received intravenous dextrose (20% solution) on ICU days 1 and 2; investigators initiated EN on day 2, and added PN on day 3 as needed to reach daily caloric targets. The late PN group received intravenous dextrose (5% solution) on day 1 and EN on day 2; PN was initiated on day 8 where necessary to reach caloric goals.

What they Found: There were no significant differences between groups in terms of baseline illness severity, sepsis, measures of nutritional risk, age, sex, or other factors that might have influenced outcomes. Length of ICU stay, the primary outcome, was about a **day shorter in the late PN group** (median 3 vs. 4 days). Patients in the late PN group overall were 6.3% **more likely to be discharged earlier** from the ICU than patients in the early PN group. **Infections developed in 22.8% of patients in the late PN group, compared with 26.2% of early PN recipients (p=0.008). Mortality rates were similar** in the early vs. late PN patients during their ICU stay (6.3% vs. 6.1%) or at 90 days (11.2% in both groups).

How Do These Results Apply? There are specific aspects of this study that influence the degree to which results can be applied to patient care in the ICU. All patients in the **early PN group received a large parenteral glucose load** (1200 kcal I.V. from a 20% glucose solution) over the first 48 hours following randomization. This is **not usual practice** in the critical care setting. Moreover, all patients in both groups were managed by **tight glucose control**, per the protocol based on the 2001 Van den Berghe study.[10] This concept of tight glucose control has subsequently been shown to be ineffective and potentially harmful.[11] In addition, almost ninety percent of the patient population were **surgery patients** (mostly cardiac), the majority of whom (58.5%) appeared to be admitted electively. Study patients remained in the ICU for a fairly short time, with over 70% of subjects averaging only a 3-4 day length of stay. These patients were only moderately severely ill, with an 8% ICU mortality (and 11% hospital mortality). Almost 75% of study patients had a normal or slightly high BMI between 20 and 30. Thus, it is not clear the degree to which all of these patients needed supplemental PN. **Most practitioners would not consider there to be a role for early PN in low mortality risk patients with short ICU stays and a normal BMI. Finally, it is hard to attribute the adverse events seen in this study to early PN, when the majority of study patients received very little exposure to early PN.** The details provided in Figure 2 of the manuscript show that a large portion (58%) of the patients in the early PN group were exposed only to 1 to 2 days of PN. PN was initiated on day 8 in the late PN group and as a result only a small portion of the late PN patients (approximately 25%) ever received PN.

It is plausible that the increase in adverse events seen in this study in the early PN group were due to the delivery of a large glucose load in the first 48 hours in the ICU. This may be related to increased insulin resistance in the early phase of acute illness.

While early PN in low risk patients is clearly harmful, **it is not clear whether supplemental PN added to insufficient EN early in the course of high risk patients would also be harmful.** Fortunately, ongoing trials are addressing this important question including the TOP UP Study being conducted in North America and Europe and a Swiss study that was recently presented at the European Nutrition meeting (stay tuned for more!).[12,13]

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