Major confounders may influence multivariate analysis in a single-center observational study

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Society of Parenteral and Enteral Nutrition 2013, increased protein intake up to the recommended 2 g/kg/d provoked no clinical benefit and increased the need for renal replacement therapy in the first adequately powered RCT studying different protein doses in critical illness (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12609001015235).

The hypothetical potential for improved tissue repair and immunological response with enhanced protein intake early in critical illness is refuted by clinical results. First, early PN provoked increased incidence and delayed recovery of ICU-acquired muscle weakness, studied in 600 awake EPaNIC patients (7). Furthermore, microscopically, quadriceps muscle biopsy analysis indicated that the muscle weakness was not explained by muscle fiber size but by suppressed autophagy. Autophagy, a catabolic cellular household mechanism crucial for clearing of cellular damage and malfunctioning organelles, was clearly enhanced by late PN (7).

Second, none of the RCTs mentioned earlier (2–5) showed reduced incidence of new infections with enhanced feeding in the first week of critical illness. Even more, in EPaNIC, early PN provoked a dramatic increase in wound infections, air way infections, and septicemia (2). Whether this should be attributed to glucose rather than protein, lipids, or total energy dose remains speculative. Nevertheless, administered macronutrient doses and obtained blood concentrations are more likely to be important than the osmolarity in the IV bag prior to infusion.

In conclusion, the results of recent clinical, body composition and cell metabolism investigations all consistently question the paradigm of improving outcome in ICU through attenuation of early catabolism.

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Major Confounders May Influence Multivariate Analysis in a Single-Center Observational Study

To the Editor:

In a recent issue of *Critical Care Medicine*, we read with great interest the article by Bayer et al (1) on the effect of volume replacement using hydroxyethyl starch (HES), gelatin, and Ringer's acetate in cardiac surgical patients. Although the number of patients being analyzed is highly impressive, there are several substantial limitations which need to be addressed.

First, Bayer et al (1) need to be congratulated that they realized to start this sequential prospective analysis in 2004. This was 2 years before the data of the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial (2) were unblinded. In contrast, it is difficult to understand, why patients had to be retrospectively identified in the Patient Data Monitoring System in their prospective observational trial.

Collecting data over many years at a single center inevitably results in serious confounders. Between 2004 and 2010, perioperative management in cardiac surgical patients developed substantially, especially management of blood transfusion changed from liberal to a restrictive strategy based on the findings by Murphy et al (3) that there is a significant transfusion-related mortality in transfused patients. Interestingly, according to the data presented, there was no change in RBC transfusion over time. Additionally, management of coagulation changed from a fresh frozen plasma-based regimen to a point-of-care-based, goal-directed therapy, including more clotting factors and fibrinogen. Last but not least, operating techniques in cardiac surgery went from invasive to minimal invasive and patients being operated presented in a higher age group with a more comorbidities, and progressively more valve surgery was performed over the three study periods.

In addition, there were four different heads of department in cardiac surgery at the University Hospital in Jena between 2004 and 2010 including different teams and techniques, as well as three different interim heads of department. Therefore, a total of seven different cardiac surgical teams were active during the study period, which was not mentioned in the article as a major confounding point.

None of the above factors, such as type of surgery, surgeon, perioperative management, coagulation management, and

transfusion of blood products were not included in the multivariate analysis. Clearly, these factors need to be included and the multivariate analysis needs to be repeated. The negative result on the use of gelatin was not present after the univariate but only after the incomplete multivariate analysis.

Apart from the lack of correction for the inevitable confounders, there are obvious inconsistencies in the data: first, 500 mL of HES was used as cardiopulmonary bypass priming in the HES and gelatin periods. Therefore, a 7 mL/kg (ideal) body weight dose of HES in the gelatin period appears reasonable. However, in the crystalloid period, 1,000 mL of HES was used as cardiopulmonary bypass priming. Despite identical body mass indices, the median dose of HES administrated was reported to be 8 mL/kg (ideal) body weight. This obvious discrepancy needs explanation. Second, in Table 3 in the article by Bayer et al (1), the different fluids administered are listed. It is very difficult to understand how a total of 16 (8–29) mL/kg (ideal) body weight of gelatin was administered in the gelatin period when at the day of surgery 0 (0–8) and on postoperative days 1–3, each day another 0 (0–7 to 0–0) mL/kg (ideal) body weight of gelatin was administered. This simply does not add up and thus needs explanation or recalculation of the data.

In summary, there is insufficient evidence presented in this single-center trial justifying the authors' conclusion. In contrast to the findings of this trial, in a well-performed recent meta-analysis by Saw et al (4) based on 30 trials and more than 2,700 patients, it was demonstrated that the use of gelatin was associated with a lower prevalence of acute renal failure when compared with HES and a comparable risk when compared with crystalloids in critically ill patients.

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