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Post-operative albumin: Predictive bystander or a window into the clockwork?

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Long gone are the days when acute kidney injury (AKI) was considered a minor complication. A large body of evidence now supports the notion that the development of AKI predisposes to an increased risk of progression to chronic kidney disease and carries a substantial attributable risk of death(1). AKI accompanies a wide range of severity and settings of critical illness, and the context of orthotopic liver transplantation (OLT) is not the exception. AKI is frequent, occurring in 23% and 44% of patients undergoing living donor (LDLT) and cadaveric donor liver transplantation (CDLT) within the first 72 hours(2), respectively; and it is devastating, as increases the risk of progression to chronic kidney disease, is associated with early graft dysfunction(3) and increases the risk of death eight-fold(4). It is thus of clinical interest to understand the causes and risk factors leading to AKI, to identify early predictors and hopefully, to find effective preventive strategies.

Although desirable, understanding the landscape of AKI and its predisposing factors in diverse clinical scenarios like post-liver transplantation remains a daunting endeavor.

A major barrier in understanding AKI in this context has been the heterogeneity surrounding the very definition of AKI utilized in different trials, including the actual criteria, the timing of assessment, and the population evaluated (i.e. LDLT vs. CDLT, preoperative CKD vs. normal renal function). A key step forward has been the consolidation of definitions using the RIFLE or AKIN criteria, based on which, recent studies have reported less heterogeneous incidence rates in this population(2).

A second limitation is that most of the available studies are observational, and thus cannot provide further information about the governing mechanisms relating predisposing factors to the development of AKI. However, these same studies have helped building an important body of associative evidence that has exalted potential pre and perioperative risk factors for post-OLT AKI, including the Model for End-Stage Liver Disease – MELD score, diabetes,

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small for size graft, blood loss, overexposure to calcineurin inhibitors (5), transfusion of red blood cells and fresh frozen plasma (6), hypotension, and graft-reperfusion syndrome. Finally, in accordance with evidence in other patient populations(7), preoperative hypoalbuminemia below 3.2 (8) to 3.5 (9) g/dL has been consistently identified as an important risk factor for the development of post-OLT AKI and mortality.

It is in this context that Sang et al. report in this issue of Critical Care Medicine, the largest study to date on patients undergoing LDLT without prior renal dysfunction, with the aim of identifying if post-operative day 2 (POD 2) albumin levels are associated with the development of AKI.(10) Based on the performance of albumin levels as predictors of post-operative AKI, the authors divided the cohort in two groups, those with albumin of less than 3 g/dL (n=522) and those with 3 g/dL or more (n=476). The primary outcome of the study was the incidence of AKI assessed by RIFLE and AKIN criteria, assuming baseline creatinine as the last preoperative measurement. Secondary outcomes included hospital and ICU length of stay, major cardiovascular events, 30-day mortality, and overall survival (with median follow-up of 2.1 years). The authors used inverse probability of treatment weighting and propensity-score matching, a statistical methodology that attempts to match patients from two different groups (i.e. albumin < 3 vs. ≥ 3 g/dL) on the basis of their clinical characteristics, reducing thereby the impact of confounding variables and thus clarifying the effect of the variable of interest (hypoalbuminemia) on AKI. The authors found that the incidence of AKI and overall mortality were higher in patients with albumin below 3 g/dL. Importantly, by virtue of propensity matching, pre-operative albumin levels were identical between groups, suggesting that post-operative hypoalbuminemia was only indicative of the response of the patient to the perioperative insult. The authors concluded that POD 2 hypoalbuminemia is an independent risk factor for AKI.

Albumin is an interesting biomarker because it represents a convergence point for many key processes related to end stage liver disease, comorbid conditions and to the individual perioperative responses to injury, all of which may influence outcome. On the other hand, albumin offers possible beneficial effects; it is known to be a scavenger of radical oxygen species, has anticoagulant properties, limits tubular cell apoptosis, is intimately related to fluid movement across the endothelial barrier, and is central to maintain adequate microvascular blood flow (11, 12), which is crucial in the perioperative period.

Despite these potential benefits, the administration of albumin to maintain plasma concentrations above 3 g/dL showed no differences in the incidence of post-operative AKI in patients undergoing LDLT(13), suggesting that the protective effect associated with higher levels of post-operative albumin reported by Sang et al. may not be due to albumin itself, but rather to the underlying processes that prevented albumin from decreasing in the first place. On this point, recent data has suggested that the integrity of the glycocalyx, an albumin rich layer of hair-like projections made of glycosaminoglycans that covers the luminal endothelial surface, and that is essential to the endothelial barrier function and oncotic pressure gradient generation, may be compromised in patients undergoing liver transplantation, and particularly in those that develop AKI(14). In relation to hypoalbuminemia, damage of the glycocalyx layer may contribute to loss of oncotic

pressure gradients and barrier function, albumin and fluid leak into the interstitium (15), and microvascular flow alterations, all of which could potentially lead to tissue injury.

This is an important study for several reasons. First is the largest cohort of LDLT patients to date reporting outcomes on post-operative AKI. Second, it provides evidence of the utility of post-operative hypoalbuminemia as a predictor of early AKI and outcome. Third, it provides epidemiologic data on the development of AKI using standardized methods; and finally, because it lends a framework for comparison of different classification methods.

In summary, Sang et al. have demonstrated the utility of hypoalbuminemia as a post-operative marker of outcome and perhaps, of the early response of the patient to the surgical insult. However, an important knowledge gap remains, as the present data does not resolve if hypoalbuminemia is part of the mechanistic pathway leading to AKI and poor outcome, an indicator of the influence of underlying comorbid conditions or simply a serendipitously useful epiphenomenon; in moving forward, the mechanistic significance (or lack thereof) of this association will need to be clarified.

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