Liberation From Continuous Renal Replacement Therapy: Does It Have an Impact on Short-term Outcomes?

Continuous renal replacement therapy (CRRT) is a rescue therapy for patients with life-threatening metabolic disturbances and uremia in severe acute kidney injury (AKI) and fluid overload. Despite the benefits of this lifesaving therapy, the risk of a major adverse kidney event (MAKE) remains high. Is the high rate of morbidity and mortality merely a marker of illness severity, or are these the systemic manifestations of AKI in which the nuanced patient-specific mechanistic complexities or metabolic derangements are incompletely understood?

In this issue of Mayo Clinic Proceedings, Liu et al report the results of a single-center retrospective study that sought to evaluate patient-centered outcomes with CRRT and the association of CRRT liberation with recovery, mortality, and MAKE-90 (death, RRT dependence, and persistent kidney dysfunction ≥200% of baseline). Only a fifth of the population was liberated from CRRT (>72 hours of no CRRT). Not surprisingly, those who had RRT reinstated had higher severity of illness scores, had lower urine output before RRT initiation, initiated RRT later in the intensive care unit course, and received a longer RRT treatment course before liberation was attempted. In the entire cohort, the overall mortality (intensive care unit, hospital, and 90-day) exceeded 60%. By 90-day follow-up, mortality in the liberated group approached that of the reinstituted group and was not significantly different. Strikingly, an association between successful liberation and lower MAKE-90 was not found after adjustment for confounders. Successful liberation was, however, associated with an increased probability of 90-day kidney recovery. But does recovery of kidney function really matter, even in the short term, when there continues to be a substantial mortality and the burden of forthcoming AKI-related complications is unknown? What if the survivors at 90 days were observed to 1 year? Would the rate of complication and attrition continue?

The authors suggest that in patients with dialysis requiring AKI, successful CRRT liberation does not causally contribute to survival and MAKE but is either a consequence of or marker of lower disease severity. Perhaps it is neither. Perhaps this is a consequence of the systemic manifestations of AKI that persist for a substantial yet unknown period beyond the initial AKI event. The concept that AKI is a systemic disease is not new. We now have better understanding of the nontraditional complications of AKI and the bidirectional complex interplay between the kidneys and many organ systems (AKI-induced distant organ crosstalk). This crosstalk may be mediated by disruption of immunologic balance, inflammatory mediators, apoptosis, and oxidative damage, among other mechanisms. Patients with AKI are at higher risk for acute lung injury and respiratory failure2 and often have longer duration of ventilation. Patients with AKI are also at a higher risk for infections,3 and the presence of AKI can lead to worse outcomes in patients with sepsis.

Continuous renal replacement therapy could theoretically improve outcomes in patients by avoiding or ameliorating fluid overload and acid-base and metabolic complications. However, there may be risks associated with it, and one wonders whether the theoretical benefits of CRRT are worth the risks. Moreover, do all patients who appear to require CRRT actually need CRRT? The STARRT-AKI trial (Standard
versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury) demonstrated that 40% of the patients who were randomized to the delayed group did not need CRRT and recovered. There is an incomplete understanding of the pathophysiologic mechanisms that may contribute to AKI-related adverse events, all of which may be independent of illness severity. In an animal model of ischemic AKI, metabolites were evaluated in the blood and cardiac tissue. There was evidence of amino acid depletion, increased oxidative stress, and alternative energy production with a shift to anaerobic energy production. These metabolic abnormalities are akin to direct myocardial ischemia. The next logical question is whether RRT removes remaining amino acids, electrolytes, and other important substrates that exacerbate cellular dysfunction and contribute to the associated morbidity and mortality.

How do we take the data from Liu et al and other studies to help move the needle in improving dialysis-requiring AKI—related outcomes? In recent years, various studies have looked at the impact of modifications in RRT timing, dose, dialytic membranes, and anticoagulation strategies on recovery of kidney function, and some answers are clearer than others. We now have clear evidence that increased dialysis dose does not lead to improved kidney recovery. The results from the STARRT-AKI trial support waiting to start RRT until it is absolutely indicated. Whereas some indications, like hyperkalemia, severe acidosis, and volume overload affecting oxygenation, are obvious, others, like severe AKI or oliguria, may be less so. In these situations, a combination of biomarkers can help identify those at greatest risk of progression and most likely to benefit from timely RRT initiation. Newer filters that provide immunomodulation or adsorb endotoxins and cytokines have shown some promise in small case series of patients with sepsis and AKI requiring CRRT. Although they are safe and have been shown to decrease cytokines and endotoxins, more data are needed to assess their impact on patient outcomes. As our understanding of the pathophysiologic process of AKI improves, we may be able to use predictive enrichment tools and targeted therapies to improve outcomes.

In summary, Liu et al highlight the associated morbidity and mortality of RRT, irrespective of whether a patient is liberated from this therapeutic modality. Whereas successful liberation reduces health care costs in the short term, medium and long-term complications may still exist. Until we can better characterize AKI-specific phenotypes that will allow us to personalize timing of CRRT initiation, filter type, and prescription based on the mechanistic interplay in kidney-organ crosstalk and the concurrent effect of dialysis, it is possible we will be unable to improve outcomes of AKI requiring dialysis.

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REFERENCES

