CRITICAL CARE

COMMENTARY

Early vs late start of dialysis: it's all about timing

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See related research by Shiao *et al.*, http://ccforum.com/content/13/5/R171

Abstract

Acute kidney injury (AKI) is now well recognized as an independent risk factor for increased morbidity and mortality, particularly when dialysis is needed. The wide variation in dialysis utilization contributes to a lack of consensus on what parameters should guide the decision to start dialysis. While the association of early initiation of dialysis with survival benefit was first demonstrated four decades ago, few studies in the modern era of dialysis have addressed time of dialysis initiation. Though listed as one of the top priorities in research on AKI, timing of dialysis initiation has not been included as a factor in any of the large, randomized controlled trials in this area.

Whether or not to provide dialytic support and when to start are two dilemmas for clinicians managing patients with a sudden decline in renal function. Earlier initiation is thought to be associated with better control of uremia, acidemia, electrolyte imbalances, and volume accumulation. However, the appreciation of the effect of time of initiation depends on what is considered early versus late. Various studies have considered early versus late time of dialysis initiation based on arbitrary thresholds of traditional serum biomarkers or time from intensive care unit (ICU) admission or from the diagnosis of acute kidney injury (AKI). The study by Shiao and colleagues [1] in a recent issue of *Critical Care* provides support that early start may be beneficial and offers an additional approach to identifying a starting point for dialysis.

Although a recent meta-analysis that included four randomized controlled trials and 19 observational studies conducted over four decades suggested that early dialysis initiation may have a beneficial effect on survival [2], what constitutes early versus late has yet to be defined. Two main approaches have been used for stratifying early and late. In most studies, levels of solutes (blood urea nitrogen [BUN] and serum creatinine) have been used to define cutoffs for early and late dialysis initiation, showing variable results on different patient populations. In post-traumatic patients, BUN levels of less than 60 mg/dL at dialysis initiation were associated with a 20% absolute reduction in mortality [3]. Wu and colleagues [4] found a BUN level of less than 80 mg/dL to be predictive of mortality in patients requiring dialysis for acute liver failure after surgery. In the general ICU population, a large observational study (Program to Improve Care in Acute Renal Disease, or PICARD) showed an increased risk of mortality in patients with higher BUN concentrations (>76 mg/dL) [5]. However, a recent randomized single-center clinical trial in 106 critically ill patients with oliguric AKI [6] demonstrated that despite early dialysis at a BUN level of less than 48 mg/dL in comparison with 105 mg/dL for late dialysis, there was no difference in outcomes. These findings suggest that BUN levels are relatively insensitive as a target criterion for starting dialysis.

A second approach was used in the beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) study, in which investigators included in the analysis a stratification of early or late based on time to initiate dialysis from ICU admission, besides the absolute urea and creatinine, and relative change in urea and creatinine [7]. Although absolute or delta BUN levels were insensitive in predicting mortality, the analysis by time from ICU admission showed a more than twofold increase in the odds of hospital mortality. However, in two recent, large, randomized controlled trials of dialysis dose, time to initiate dialysis was assessed from ICU admission and was not associated with outcomes [8,9].

Though using heterogeneous definitions of early initiation, these large observational cohorts and small randomized trials suggest that there may be a survival advantage to an early start for dialysis. They also highlight the need for better parameters to define the need for dialysis and the delineation of what is early and late. In the postoperative setting, the timing and type of renal

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insult are more homogenous, providing an opportunity to ascertain the benefits of earlier dialysis initiation when the event associated with AKI is known. Two cardiac surgery studies demonstrated a benefit in earlier initiation [10,11]. In these studies, urine output of less than 100 mL during the first 8 hours after bypass surgery was a criterion to initiate dialysis regardless of solute clearance. Mortality rates appeared to be dramatically reduced in both studies in the early dialysis groups. Similar findings were seen in a small study of 21 patients treated with prophylactic perioperative hemodialysis [12].

In the study of Shiao and colleagues [1], 98 patients who required dialysis in the postoperative period of abdominal surgery were categorized as early or late dialysis initiation based on the estimated glomerular filtration rate criteria of the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) classification (simplified RIFLE, or sRIFLE). The earlier initiation group had lower ICU and hospital mortality rates than the late initiation group. These results suggest that the severity of renal injury may provide a better parameter than arbitrary values of traditional serum biomarkers (BUN and serum creatinine) for initiating dialysis. However, several questions still need to be answered. The RIFLE and Acute Kidney Injury Network classification systems are validated criteria for the severity of AKI but may not be the ideal parameters of early or late, as previously pointed out by Bellomo and colleagues [13]. The relationship of RIFLE classes at initiation and outcomes is subject to other influences that need to be considered. For instance, in the cohort of Shiao and colleagues, cardiac failure was an independent risk factor for in-hospital mortality. By their definition of cardiac failure (low cardiac output with a central venous pressure of greater than 12 mm Hg and a dopamine equivalent of greater than 5 μg/kg per minute), it is reasonable to assume that cardiac failure was a surrogate marker of fluid overload. This finding corroborates studies finding an inverse relationship between fluid accumulation and survival [14,15]. Additionally, other factors influence recognition of the severity of AKI. Shiao and colleagues found a lower prevalence of chronic kidney disease (CKD) in the late dialysis group, confirming data showing that an earlier identification of AKI among patients with prior CKD could modify the process of care delivered to these patients [16]. Thus, the time to recognize AKI, the severity and response to injury, and the contribution of non-renal factors may all influence the timing of initiation.

Timing of dialysis initiation is a potentially modifiable factor that may play an important role in determining patient outcomes. Based on current knowledge, we would recommend assessing patients for changes in renal function and using dialysis to support organ function and prevent complications rather than waiting for complete renal shutdown prior to renal replacement [17]. Future research in this field is desperately needed and should include a combination of clinical and emerging biomarkers to inform these decisions. We look forward to doing away with comparisons of early versus late dialysis and focusing on improving outcomes with timely interventions of renal support individualized to patient need.

Abbreviations

AKI = acute kidney injury; BUN = blood urea nitrogen; CKD = chronic kidney disease; ICU = intensive care unit; RIFLE = Risk, Injury, Failure, Loss, and End-stage kidney disease.

Competing interests

The authors declare that they have no competing interests.

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