ICU MANAGEMENT & PRACTICE

ELAIN Trial for AKI: Significant Mortality Reduction in Early RRT Group

Results of the Early vs Late Initiation of Renal Replacement Therapy in Critically Ill Patients With Acute Kidney Injury (ELAIN) Trial found a significant reduction in 90-day all-cause mortality in the early initiation group. The single-centre study, by Alexander Zarbock, MD, of University Hospital Munster, Germany, and colleagues, which is to be presented at the 53rd European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress in Vienna, is published online by *JAMA*.

The researchers randomly assigned 231 critically ill patients who met the criteria of stage 2 acute kidney injury (AKI) (according to Kidney Disease: Improving Global Outcomes guidelines) and had one other condition from among severe sepsis, use of vasopressors or catecholamines, refractory fluid overload, or development or progression of organ dysfunction in another (non-kidney) organ) and had a plasma concentration of 150 ng/mL of neutrophil gelatinase–associated lipocalin (NGAL). The groups were randomised either to early (within 8 hours of diagnosis of stage 2; n = 112) or delayed (within 12 hours of stage 3 AKI or no initiation; n = 119) initiation of RRT.

See Also: Optimal Timing of Renal Replacement Therapy 'Elusive'

All patients in the early group and 108 of 119 patients (91 percent) in the delayed group received RRT. The researchers found that early initiation of RRT significantly reduced 90-day mortality compared with delayed initiation of RRT (39 percent vs 55 percent of patients died in each group, respectively). More patients in the early group recovered renal function by day 90 (54 percent vs 39 percent). Duration of RRT (9 days vs 25 days), mechanical ventilation (125.5 hours vs 151 hours) and length of hospital stay (51 days vs 82 days) were significantly shorter in the early group than in the delayed group. There was no significant effect on requirement of RRT after day 90, organ dysfunction, and length of ICU stay.

Prof. Zarbock (pictured) explained in an email to *ICU Management & Practice* that patients assigned to the delayed group were randomised 2h (median) after meeting the KDIGO stage 3 criteria. The time between meeting KDIGO stage 2 criteria and RRT initiation was 25.5h (Q1-Q3:18.8h-40.3h). The main reason for this might be the illness severity, which is related to a rapid deterioration of renal function underlined by high biomarker concentrations. This means that patients in the delayed group were caught "early" in the course of KDIGO stage 3 before the development of other complications. He added: "Compared to common strategies of RRT initiation, both study related strategies might be "early" in the common sense. But earlier initiation of RRT allows for better control of fluid and electrolyte imbalances, removal of uremic toxins and prevention of metabolic complications and our results demonstrate a significant benefit for initiation of RRT at KDIGO stage 2 in severe critically ill patients with high NGAL levels."

The researchers noted that the data demonstrate that the combination of the KDIGO classification system in combination with plasma NGAL can reliably detect patients with progressively deteriorating AKI. Prof. Zarbock confirmed that they selected NGAL as the biomarker as it is a good predictor for need for RRT and due to its ease of measurement at the bedside within 20 minutes, which was well suited to the trial's time-sensitive intervention.

See Also: Protocol for Identifying Patients at Risk of AKI

"Our study provides important feasibility data for an AKI stage-based, biomarker-guided interventional trial in AKI. However, an adequately powered multicentre trial is needed to confirm our results and establish the best time point for the initiation of RRT in critically ill patients with AKI," the researchers conclude.

In an accompanying editorial, Glenn Chertow, MD, MPH, Stanford University School of Medicine, Palo Alto and Wolfgang C. Winkelmayer, MD, MPH, ScD, of the Baylor College of Medicine, Houston, and Associate Editor, *JAMA* write: "In view of the provocative findings reported by Zarbock et al., it is the responsibility of the nephrology and critical care communities to confirm or refute these findings across multiple sites in a much larger, diverse population."

AKIKI Trial Showed No Difference Between Early and Late Initiation

Publication of the ELAIN trial results comes shortly after publication of the findings of the multicentre Artificial Kidney Initiation in Kidney Injury (AKIKI) trial (31 ICUs, 620 patients) (Gaudry et al. 2016). This trial included patients with AKI stage 3 according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, who needed mechanical ventilation, vasopressor therapy or both. The groups were randomised between early, i.e. immediate RRT, or delayed RRT, when therapy was initiated if patients had development of severe hyperkalaemia, uremia, metabolic

acidosis, pulmonary oedema, or severe oliguria that persisted for more than 72 hours after randomisation. Mortality at 60 days was similar in both groups (48.5% in the early group and 49.7% in the delayed group). More than half the patients were treated with intermittent haemodialysis. Forty-nine percent of the patients in the delayed-strategy group never received dialysis. The researchers note that delaying the initiation of therapy allowed many patients to recover from acute kidney injury without embarking on RRT. They add: “Our study should not be interpreted as suggesting that a “wait and see” approach is safe for all patients… careful surveillance is mandatory when deciding to delay renal-replacement therapy in patients with severe acute kidney injury so that any complication will be detected and renal-replacement therapy initiated without delay.”

In an accompanying editorial, Ravindra L. Mehta, MD, of the University of California, San Diego, cautions against delaying RRT based on these results. He notes that the difference in RRT initiation of more than 50 hours between the early group and the delayed group meant that the clinicians had time to administer diuretics, treat hyperkalemia and acidosis, and identify patients who did not need renal-replacement therapy. He says: “The findings highlight a need for dynamic risk-stratification tools to identify patients who will not need renal replacement therapy for management of their acute kidney injury.”

Sources: JAMA; Prof. Dr. Alexander Zarbock; NEJM

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