Continuous Renal Replacement Therapy: Modality of Choice in the Intensive Care Unit?

By Ashita Tolwani

Acute kidney injury (AKI) is a frequent complication in critically ill patients and is associated with a high mortality rate. Continuous renal replacement therapy (CRRT) represents a spectrum of dialysis modalities developed in the 1980s specifically for the management of critically ill patients with AKI who could not tolerate traditional intermittent renal replacement therapy (IRRT). Over the years, CRRT has found widespread use and acceptance due to its ability to provide effective volume and metabolic control in hemodynamically unstable patients.

Despite its physiologic benefits, randomized controlled trials (RCTs) have not shown a mortality benefit of CRRT over IRRT. Vinsonneau et al. performed the largest RCT comparing the effect of IRRT and CRRT on patient survival in 360 patients at several French institutions (1). Although the investigators found no significant difference in patient survival, several aspects of the study limit the applicability of the results to general clinical practice. First, patients with pre-existing chronic kidney disease (CKD) were excluded. Second, for unclear reasons, survival progressively increased in the IRRT group while it remained constant in the CRRT group, suggesting systematic changes occurred in the delivery of IRRT. Third, maintaining hemodynamic stability in the IRRT group required longer sessions with a mean IRRT treatment duration of 5.2 h per session.

As such, the applicability of the IRRT results to the "real world," where IRRT treatment times are significantly less than this on a routine basis, is questionable.

Another concern is that the study only required achieving a mean urea concentration of 84 mg/dL or less, which is a low target according to current standards. This resulted in metabolic control not being achieved any better with CRRT than with IRRT. Finally, patients crossed over from CRRT to IRRT due to inadequate metabolic control from technical issues such as inability to keep the circuit patent and complications of anticoagulation. Multiple published meta-analyses of RCTs comparing CRRT with IRRT in ICU patients with AKI also have not demonstrated a survival benefit with CRRT. However, the validity of the data from the studies is dubious because of issues related to study design, such as exclusion of patients with hemodynamic instability, improper randomization, differences in baseline characteristics between arms, and high crossover rates between modalities. Finally, no trial standardized the dose delivered or the timing of initiation. Notably, even though the meta-analysis by Bagshaw et al. (2) found no statistical difference in survival between the two modalities, there was a higher occurrence of hemodynamic instability and greater cumulative fluid balance in the IRRT groups.

If current studies cannot demonstrate a survival benefit of CRRT compared to IRRT, are there other outcome benefits for CRRT?

Hemodynamic stability

Hypotension is one of the most common complications associated with IRRT, occurring in approximately 20 percent to 30 percent of all treatments. This complication can lead to further organ ischemia and injury. Several observational studies and randomized studies have demonstrated better hemodynamic stability associated with CRRT. In a small RCT, Augustine et al. (3) reported a significant reduction in mean arterial pressure (MAP) during IRRT, which was not observed during CRRT. On the other hand, others have not reported any difference in hemodynamics between the two modalities. Uehlinger et al. (4) reported a similar frequency of hypotension between IRRT and CRRT.

The VA/NIH Acute Kidney Failure Trial Network (ATN) study by Palevsky et al. (5) aimed to determine the optimal intensity of renal replacement therapy (RRT) in critically ill patients with AKI and at least one other failing organ or sepsis. The study compared two strategies for the management of RRT in critically ill patients with AKI. Both treatment strategies employed both conventional IRRT in patients whose hemodynamics were stable and either sustained low-efficiency dialysis (SLED) or CRRT in patients who were hemodynamically unstable.

In one strategy, IRRT and SLED were provided three times per week, and CRRT was dosed to provide a clearance of approximately 20 mL/kg/h. In the other treatment arm, IRRT and SLED were provided six times per week and CRRT was dosed to provide a clearance of approximately 35 mL/kg/h. Overall, there was no significant improvement in patient outcomes with the more intensive treatments. Notably, only 4.6 percent of treatments performed in hemodynamically unstable patients were SLED. This low utilization of SLED in hemodynamically unstable patients occurred despite physicians’ ability to prescribe either SLED or CRRT in the study. Moreover, hypotension was a more serious complication among patients treated with IRRT. Approximately 1.7 percent of all IRRT treatments required discontinuation of therapy due to hypotension compared to only 0.7 percent of CRRT/SLED treatments. These differences were observed despite the fact that the IRRT patients were considered hemodynamically stable.

The rate of renal recovery at hospital discharge was substantially lower in the ATN study than what has been reported previously, even with the exclusion of patients with moderate to severe CKD. A possible explanation is that the high rate of severe hypotension in the IRRT patients may have contributed to the relatively low rate of renal recovery. Finally, fluid removal was much less aggressive in the IRRT patients (approximately 6–9 L/week) compared to that in the CRRT patients (greater than 20 L/week). These findings support CRRT as the standard of care for hemodynamically unstable patients with AKI.

Renal recovery

Renal recovery is another important outcome for patients with AKI and may be affected differently by RRT modality. Failure to recover renal function after AKI has both short- and long-term implications with respect to morbidity and health care costs. Multiple observational studies and one randomized study support greater rates of renal recovery in patients with AKI requiring CRRT compared to IRRT. Macht et al. randomized 166 patients to four centers to receive CRRT or IRRT and demonstrated no difference for hospital mortality using multivariate logistic regression analysis (6). However, CRRT was associated with a significantly higher rate of complete renal recovery in surviving patients who received an adequate trial of therapy with no crossover (92.3 percent versus 59.4 percent; p < 0.001).

Two recent large epidemiologic studies have also reported increased rates of renal recovery in patients on CRRT. In the Beginning and Ending Supportive Therapy (BEST) kidney trial (7), a multinational, prospective, epidemiologic study of AKI in the ICU including over 30,000 patients in 23 countries, 1218 patients received RRT. Although no mortality difference was detected between patients treated with CRRT compared to IRRT, dialysis independence at hospital discharge was higher after CRRT (85.5 percent versus 66.2 percent; p < 0.0001). Bell et al. (8) retrospectively studied 2202 patients treated with RRT for AKI from 32 ICUs in Sweden. CRRT was used for 1111 patients and IRRT for 291. Nineteen percent mortality was not significantly different between the two groups. Among survivors, 83 percent treated with CRRT became dialysis dependent compared to 16.5 percent treated with IRRT. Multivariate analysis showed that the adjusted odds ratio of dialysis independence at hospital discharge in CRRT was 2.60 compared with CRRT. Moreover, in patients who did develop chronic dialysis dependence, the subsequent survival rate was significantly lower in patients treated with HD compared to CRRT-treated patients.

In the ATN trial by Palevsky et al. (5), over 70 percent of patients in both treatment strategy arms (intensive and less intensive) had no recovery of kidney function by 28 days and were dialysis dependent. This is quite high compared to other trials, given that patients with CKD were excluded. It is important to realize that the two arms consisted of a mix of patients on CRRT, SLED, and IRRT. In the Renal Replacement Therapy Study of dose intensity (9), patients were randomized to CV-HDF at 25 mL/kg/h versus CVVHDF at 40 mL/kg/h.

In contrast to the ATN trial, the RENAL investigators reported 14 percent of patients were dialysis dependent in both treatment arms by 28 days. Unlike the ATN trial, the two intensity arms only included patients on CRRT, and not on other modalities. Moreover, unlike the ATN trial, the RENAL study included patients with CKD. This finding supports the notion that CRRT leads to higher rates of renal recovery.

Fluid management

In critically ill patients, nutritional requirements and the use of intravenous medications necessitate the administration of large amounts of fluid, resulting in excessive volume overload. Excessive fluid administration can cause pulmonary edema, hypoxia, and the need for mechanical ventilation. In addition, excessive fluid accumulation can impair cardiac function and renal perfusion. Several observational studies have shown a direct relationship between fluid accumulation and mortality in critically ill patients. The Acute Respiratory Distress Syndrome (ARDS) clinical trial network (10) demonstrated that a more liberal fluid...
administration regimen (to CVP of about 12 cm H2O) resulted in greater lung function impairment than a more conservative approach (target CVP of about 8 cm H2O). Although survival at 60 days was not significantly different between the two groups, ventilator-free days and ICU-free days were both significantly lower in the conservative group. Moreover, the percentage of patients requiring dialysis in the conservative group (10 percent) was lower than in the liberal group (14 percent).

In the Program to Improve Care in Acute Renal Disease (PICARD) database (11) of critically ill patients with AKI in whom nephrology consultation was sought, volume overload in patients with AKI was independently associated with increased mortality. Fluid overload was defined as a percentage of fluid accumulation >10 percent over baseline weight at hospital admission. In 542 patients in whom fluid data were available, those with a >10 percent accumulation had a significantly higher risk of death at 30 and 60 days of enrollment.

Within the group requiring RRT, those with greater fluid accumulation at dialysis initiation had worse outcomes with an OR for death (adjusted for severity of illness and dialysis modality) of 2.07 (95 percent CI 1.27–3.37). Patients who remained fluid overloaded had a higher mortality rate that was proportional to the degree of fluid accumulation. Volume control was significantly better in those treated with CRRT versus IRRT. Importantly, the correction of volume accumulation had a positive effect on survival, making this an important therapeutic target in critically ill patients with AKI. Prospective randomized studies with different regimens of fluid administration are necessary to know their effects on mortality and the outcome of AKI in critically ill patients.

Augustine et al. (3) compared net fluid balance provided by IRRT and CRRT in an RCT. Even over a relatively short three-day period, significant differences were observed. In the CRRT group, a net loss of 4005 mL (approximately 4 kg) occurred, while the IRRT group sustained a net gain of 1539 mL (approximately 1.5 kg) on an average basis. Although RCTs have not been consistent in this area, these data are corroborated by other studies and general clinical practice and represent one of the therapeutic targets in critically ill patients with AKI. Prospective randomized studies with different regimens of fluid administration are necessary to know their effects on mortality and the outcome of AKI in critically ill patients.

In summary, although there is a call for more outcomes-based RCTs, mounting evidence published in the last decade has propelled CRRT to become the preferred modality of choice in the ICU patient with AKI. This is due to the recognition by its users of the advantages of CRRT in volume management and hemodynamic stability in the critically ill patient.

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Internationally, the multinational epidemiologic BEST Kidney Study (7) reported that CRRT was the initial modality used in 80 percent of AKI treatments in the ICU, followed by IRRT (17 percent). Finally, a recent survey of an international multidisciplinary cohort of renal practitioners showed that CRRT had become the standard for AKI support outside of the United States (15).

In summary, although there is a call for more outcomes-based RCTs, mounting evidence published in the last decade has propelled CRRT to become the preferred modality of choice in the ICU patient with AKI. This is due to the recognition by its users of the advantages of CRRT in volume management and hemodynamic stability in the critically ill patient.
Biomarkers of Acute Kidney Injury: Dawning of a New Era

By Joseph Bonventre

The kidney community has devoted a great deal of effort to building consensus regarding the definition of acute kidney injury (AKI). This has resulted in RIFLE classification and AKIN network (AKIN) criteria focused on changes in serum creatinine (SCr) and rate of urine production. These changes in SGs are important and have been shown to be predictive of outcome in a number of studies. SCr changes, however, can be affected by a large number of things unrelated to kidney injury, including drug interference with secretion of creatinine into the tubule, muscle mass, gender, age, and renal reserve, a measure of how much the kidney can compensate for injury.

Kidney injury, which leads to a reduction in GFR, is not immediately followed by an increase in SCr. This lag time greatly impedes the early diagnosis of AKI, delays therapeutic opportunities to test new therapies early in the course of the disease when AKI is much more likely to be amenable to interventions that might alter its natural history. SCr concentration can also increase due to functional decreases in GFR that are not associated with tubular injury. This is the case in prerenal azotemia. It has thus been recognized for a number of years that new biomarkers of injury would be very desirable. A “kidney troponin,” for example, would allow for the identification of true injury to the kidney as troponin does for the myocardium.

A biomarker is defined as a characteristic that can be objectively measured and evaluated as an indicator of normal biologic or pathogenic processes of pharmacological responses to a therapeutic intervention (1). Examples of biomarkers are proteins; lipids, glycans, metabolic, or proteomic patterns; imaging determinations; electrical signals; and cells present in a urine sample.

Having a biomarker that directly reflects injury is also measured from fluid that is easily obtained, such as blood or urine, would introduce a new paradigm in which we would be directly monitoring injury rather than a secondary consequence of injury—a reduction in GFR, as manifest by an increase in SCr.

In commenting on a major initiative of the FDA that focuses on biomarkers, Janet Woodcock, MD, deputy commissioner for operations and head of FDA’s Critical Path Initiative, said: “Most researchers agree that a new generation of predictive biomarkers would dramatically improve the efficiency of product development, help identify safety problems before a product is on the market (and even before it is tested in humans), and facilitate the development of new types of clinical trials that will produce better data faster” (2). The FDA has provided guidance that a biomarker can be considered “valid” if (i) it is measured in an analytical test system with well established performance characteristics and (ii) there is an established scientific framework or body of evidence that elucidates the physiological, pharmacologic, toxicologic, or clinical significance of the test result (3).

We need better biomarkers to diagnose AKI earlier, to predict outcome in a patient with AKI with standard therapy, and to identify who will respond to an intervention and whether the intervention is working. In addition, better biomarkers will permit better stratification of patients for clinical trials and potentially lead to definition of new therapeutic targets for AKI. A good predictive biomarker will have a significant effect on evaluation of potential therapies because it will enable the identification of subgroups of patients who will have a high incidence of kidney injury and hence reduce the number of patients needed to study in order to test potential therapeutic strategies.

A clinically useful new kidney biomarker will improve the sensitivity and specificity for the detection of renal injury and discriminate renal injury, which may have long-term consequences, from adaptive responses that may be reflected by transient BUN/creatinine increases that return to pre-elevated levels over time, even with continued exposure to the agent in question. It is also likely that some of these biomarkers will be useful not only for AKI, but also to monitor severity and progression of glomerular or tubular-interstitial disease in patients with chronic kidney disease.

Over the years, a large number of biomarkers of kidney injury have been suggested, yet for various reasons, none have been routinely accepted in animal or clinical studies. In some cases, the biomarker was felt to be too sensitive, not sensitive enough, or too nonspecific. In other cases, the biomarker was unstable with storage. More recently, however, there have been a number of advances in the application of biomarkers to AKI.

Promising biomarkers

A limited number of biomarkers are currently being evaluated by a number of groups, and clinically useful reagents have been developed. Some of the most promising urinary biomarkers for AKI include: microalbuminuria, kidney injury molecule-1 (KIM-1), N-acetyl b-D glucosaminidase (NAG), neutrophil gelatinase associated lipocin (NGAL), cystatin C, L-fatty acid binding protein (L-FABP), and interleukin-18 (IL-18) (4).

These biomarkers that can be measured in blood or urine in both experimental and humans and are of particular interest. It may be possible to draw on the experimental information obtained for such biomarkers in animals to help guide the use and interpretation of biomarker studies in humans. Biomarkers that have been well studied and characterized as very sensitive biomarkers of injury in animals, if they function similarly in man, may make it possible to monitor safety and efficacy in clinical trials when the ability to obtain kidney tissue is severely constrained and when the severity of the injury early on is insufficient to result in an increase in SCr.

Kidney biomarkers in drug approval

The importance of the identification of kidney injury biomarkers for patient safety was manifest quite clearly in July 2008 when the FDA and the European Medicines Agency (EMEA) agreed to accept data for seven kidney injury biomarkers as part of the drug approval process. This was the first time that a single application was submitted to both regulatory agencies.