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Continuous Renal Replacement Therapy

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ABSTRACT

Continuous renal replacement therapy (CRRT) is commonly used for acute kidney injury (AKI) in intensive care units (ICU) for renal support, especially in hemodynamically unstable patients in much of the developed world. However, despite its widespread use, there is no formal evidence regarding the improvement in patient related outcomes when CRRT is used instead of intermittent hemodialysis (IHD). Various techniques can be used that differ in the mode of solute removal, including continuous venous hemofiltration with primarily convective solute removal, continuous venous hemodialysis with primarily diffusional solute removal, and continuous venous hemodiafiltration, which is a combination of both dialysis and hemofiltration methods. In this review, we compare CRRT with other renal support modalities and examine the indications for initiation of renal replacement therapy, as well as dosage and technical considerations for administering CRRT. We also describe some of the controversies and questions that remain to be answered regarding the use of CRRT.

Keywords: Renal failure; Hemodialysis; Renal replacement therapy; Acute kidney injury

INTRODUCTION

Acute kidney injury (AKI) is a common complication of critically ill patients and is associated with significant morbidity and mortality.[1,2] About 5-10% of patients with AKI require renal replacement therapy during their ICU stay, with a mortality rate of 30-70%. Over the past two decades, the incidence of AKI requiring renal replacement therapy has increased by approximately 10% per year.[3] Risk factors for AKI requiring active treatment include

older age, male sex, African-American race, disease severity, sepsis, decompensated heart failure, cardiac surgery, liver failure, and use of mechanical ventilation.

Continuous renal replacement therapy includes spectrum of dialysis techniques developed in the 1980s that were developed specifically for the treatment of critically ill patients with acute kidney injury who could not undergo traditional intermittent hemodialysis due to hemodynamic instability or whose volume or metabolic abnormalities could not be controlled with intermittent hemodialysis.[4] Slower solute clearance and fluid removal per unit time with continuous renal replacement therapy compared with intermittent hemodialysis is thought to allow for better hemodynamic tolerance. Although once considered an extraordinary procedure, the provision of RRT care has become routine, even in the setting of significant hemodynamic instability.[5,6] However, considerable uncertainty remains regarding many key aspects of active care management, including the optimal timing of initiation and termination and the choice of treatment modalities. This article provides an overview of key issues in critical care management of critically ill patients, with a primary focus on the use of continuous renal replacement therapy (CRRT).

RRT modalities

Several modalities of renal replacement therapy can be used in the treatment of critically ill patients with renal failure.[7] These include CRRT, conventional intermittent hemodialysis (IHD), and prolonged intermittent renal replacement therapy (PIRRT), which is a combination of CRRT and IHD. All of them use relatively similar extracorporeal circulation and differ mainly in the duration of treatment and thus in net ultrafiltration rate and solute removal. IHD ensures rapid removal and ultrafiltration of the solute during a relatively short (4 hour) treatment; continuous therapy provides more gradual fluid removal and solute clearance over a longer treatment period (optimally 24 hours per day, but often interrupted by systemic coagulation or diagnostic or therapeutic procedures). Different forms of PIRRT are characterized by treatments that typically last 8-16 hours, solute absorption and ultrafiltration are slower than IHD but faster than CRRT. PIRRT is most often delivered by IHD-like devices, but with lower blood and dialysate flow rates.[8] PIRRT can also be performed with equipment designed for CRRT, but with higher rates of dialysate and/or ultrafiltration to achieve a similar treatment response in shorted period of time. Peritoneal dialysis offers an effective alternative to extracorporeal renal replacement therapies.[9,10]

Choice of RRT modality

Although CRRT and PIRRT are most commonly used in hemodynamically unstable patients, there is considerable variation in practice. Some centers use CRRT (or PIRRT) in most patients with renal failure, regardless of hemodynamic status, while others may use intermittent hemodialysis even in some patients who are vasopressor-dependent. Although the benefit of slow, continuous renal support in hemodynamically unstable patients may seem self-evident, randomized trials have failed to show any significant differences in terms of important outcomes such as mortality or recovery of renal function comparing CRRT with IHD or PIRRT.[11,12] However, it should be appreciated that to provide IHD in hemodynamically unstable patients, the dialysis prescription may require

modifications, such as increasing the treatment time to allow more gradual ultrafiltration, using higher sodium dialysate concentrations and lowering dialysis temperatures. Although the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for AKI recommend the use of CRRT in hemodynamically unstable patients, the strength of this recommendation is low. However, observational data indicate that CRRT is more effective than IHD in achieving negative fluid balance. Furthermore, in brain-damaged patients with acute liver failure or increased intracranial pressure, CRRT is associated with better preservation of cerebral perfusion than IHD.[13,14]

Although CRRT was originally developed as arteriovenous therapy, it is now performed using pump-driven veno-venous circuits. Pump-driven venous circulation provides greater and more consistent blood flow and eliminates the hazards associated with long-term arterial cannulation with a large-bore catheter. Several techniques have been developed to deliver CRRT. If the treatment is used only for volume control, it is called slow continuous ultrafiltration (SCUF). When CRRT is delivered as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), or continuous venovenous hemodiafiltration (CVVHDF), it provides both solute clearance and volume removal, and the differences between these methods relate to solute clearance.

In CVVH, the hydrostatic gradient across the semipermeable hemofilter membrane creates a high ultrafiltration rate, and solute transport occurs by convection. Dissolved substances are carried by the water flow through the membrane, often referred to as "solvent drag".[15] High ultrafiltration rates are required to achieve sufficient solute uptake, and a volume of ultrafiltrate greater than that required to remove the desired fluid is replaced with balanced IV crystalloid solutions. These replacement solutions can be infused into the extracorporeal circulation either before or after the hemofilter. Because the high ultrafiltration rate hemoconcentrates the blood as it passes through the hemofilter fibers, the risk of contamination and clogging of the fibers increases. An infusion of prefilter replacement fluid dilutes the blood entering the hemofilter, thereby reducing the hemoconcentration.[16,17] However, administration of a replacement fluid prefilter dilutes the blood solute, reducing the effective solute clearance at a fixed ultrafiltration rate. A post-filter infusion has no such effects.

In CVVHD, the dialysate is perfused through the outer surface of the dialysis membrane and solutes are removed from the blood by diffusion of the dialysate along its concentration gradient. Ultrafiltration rates are relatively low compared to CVVH levels, allowing negative fluid balance without the need for IV replacement fluids.[18] CVVHDF is a hybrid that combines CVVHD dialysis flow with high ultrafiltration rates and the use of CVVH replacement fluids. The different solute removal mechanisms provided by CVVH and CVVHD result in different solute removal profiles for each method. Diffusion ensures effective removal of low molecular weight solutes (< 500-1500 daltons); however, diffusion clearance decreases rapidly as the molecular weight of the solute increases.[19,20] In contrast, the solute movement in convection is largely limited by the pore size of the hemofilter membrane. Removal of lower and higher molecular weight solutes is similar until the molecular radius of the solute approaches the membrane pore size. Thus, at equivalent outlet flow rates, CVVH provides greater clearance than CVVHD for solutes ranging from 1000 to 20,000 daltons, or even greater when larger pore membranes are used. Independent of diffusion and

convection, solute adsorption in the CRRT chain can also contribute to complete solute uptake, depending on the saturation of membrane binding sites. Thus, the choice of CRRT modality (CVVH, CVVHD, or CVVHDF) depends primarily on provider preference rather than patient characteristics or objective outcome data.

Initiation of renal replacement therapy:

Indications for starting renal replacement therapy Indications for initiation of CRRT generally correspond to the general indications for the dialysis, including volume overload, severe metabolic acidosis and electrolyte imbalance, and overt uremic symptoms.[21-24]

Volume overload

Volume overload in AKI occurs when the kidney's ability to maintain fluid balance is compromised when IV fluids, blood products, and/or other medications are administered to resuscitate and support a critically ill patient. Renal replacement therapy is usually indicated when volume overload impairs organ function and is resistant to diuretics. [25] Although observational data from both pediatric and adult populations show a strong association between the severity of volume overload at the start of intensive care and the risk of mortality, causality has not been established.

Acid-base abnormalities

Progressive metabolic acidosis is an inevitable consequence of renal failure that develops due to impaired renal acid secretion.[26-28] Either intermittent or continuous RRT is effective in patients with severe acidosis unresponsive to therapy, such as a fluid overloaded patient who cannot tolerate alkali therapy. The generally recommended threshold values for starting RRT are pH < 7.1 to 7.2 or serum bicarbonate < 12 to 15 mmol/L. Earlier initiation of RRT may be necessary in patients with acute lung injury receiving lung protective ventilation, as the combination of metabolic and respiratory acidosis may lead to severe acidemia. Although RRT increases lactate clearance, there is little evidence that initiation of active therapy to increase lactate clearance changes clinical outcomes in patients with lactic acidosis unrelated to drug toxicity (eg, metformin).[29-31]

Severe electrolyte imbalance

Severe hyperkalemia is the most life-threatening and requires prompt treatment to prevent cardiotoxicity and arrhythmias.[32-34] Initiation of RRT is appropriate when hyperkalemia is refractory to medical therapy or recurs after initial therapy. Although no rigid thresholds based on serum potassium can be given, active treatment of hyperkalemia alone is rarely appropriate when potassium levels are < 6 mmol/l. Conversely, RRT is generally indicated if potassium level is > 6.5mmol/L despite treatment.[35,36]

Other electrolyte disturbances, such as severe hyponatremia or hypernatremia and severe hyperphosphatemia, may be associated with AKI and can lead to the initiation of RRT.[37,38] In patients with severe hyponatremia associated with AKI, CRRT may allow a slower and more controlled correction of sodium concentration, which is necessary to prevent the neurological consequences of osmotic demyelination, compared to IHD.

Uremia and progressive azotemia

The use of RRT in overt uremic symptoms such as encephalopathy and pericarditis is well established. Although these are relatively late complications of AKI, other manifestations of uremia such as platelet dysfunction, nutritional disorders, increased susceptibility to infection and sepsis, heart failure, and pulmonary edema may be difficult to distinguish in the critically ill patients with multiple organ dysfunction.[39-41] In the absence of specific indications for active therapy, it is much more common to initiate it prophylactically in response to persistent or progressive azotemia before the onset of uremic manifestations. The appropriate timing of such an initiation is still a matter of debate.

Elimination of drugs and toxins

Many toxins and drugs, such as toxic alcohols, lithium, salicylate, valproic acid and metformin, are dialyzable, and the timely use of RRT for poisoning and drug poisoning can prevent serious complications.[42,43] The ability of an RRT to remove a particular drug or toxin from the bloodstream depends on its size, volume of distribution, and protein binding.[44,45] Thus, RRT is effective in removing smaller non-protein bound molecules with a volume of distribution < 1 L/kg body weight. The role of RRT in the treatment of hyperammonemia is uncertain. As in the treatment of drug intoxication, IHD also reduces the concentration of ammonia in the blood more quickly. However, in small case series, high-dose CRRT has been shown to be effective in the acute treatment of severe hyperammonemia (> 400 µmol/L) in infants with congenital metabolic disorders.[46,47] The role of CRRT in adults with hyperammonemia as a consequence of liver failure is still less certain.

Timing of RRT initiation

In the absence of specific indications, the optimal time of initiation of RRT for AKI is uncertain.[48,49] Early initiation of RRT allows optimization of volume status, early correction of acid-base and electrolyte disturbances, and control of azotemia before the development of serious metabolic disturbances, which are objective indications. However, these potential benefits of early initiation must be balanced against the risks and burdens associated with active treatment, including vascular access (eg: hemorrhage, thrombosis, vascular injury, infection), intra-dialysis hypotension, and resource use, as well as potential worries that active treatment may prevent the subsequent recovery of renal function.[50,51]

Several observational studies have shown improved survival associated with earlier initiation of RRT. However, these studies only included patients who ultimately received RRT and did not consider patients with AKI who did not receive early RRT and who either recovered renal function or died without RRT. Excluding these patients from the analysis introduces a potential bias, as the real clinical question is not early versus late initiation of RRT, but rather early versus non-early RRT in patients without an urgent indication.

CRRT dose

Solute Control

The CRRT dose is calculated from the sum of the total flow rates of effluent, dialysate and ultrafiltrate. Although several studies published 15 to 20 years ago suggested that higher flow rates of effluent were associated with improved survival, the results were inconsistent and this association was not confirmed in two large multicenter randomized controlled trials.[52] Based on the available data, the KDIGO clinical practice guidelines recommend a CRRT target dose of 20 to 25 mL/kg per hour, noting that a higher prescribed dose may be necessary to achieve this target dose.

Volume management

Another important aspect of RRT prescription is volume control. Net ultrafiltration can be regulated independently of solute clearance.[53] As previously noted, the severity of volume overload is strongly associated with mortality risk in both children and adults with AKI who require RRT. However, optimal volume management strategies are uncertain. Treatment must be individualized for each patient, and ultrafiltration goals must be frequently reevaluated. It should be noted that short-term blood pressure variability is not usually related to volume status, and that transient hypotension during CRRT should be carefully evaluated for non-volume-mediated factors and often requires therapy regardless of changes in ultrafiltration goals.

The role of CRRT in sepsis

Although cytokine modulation with CVVH has been proposed as an adjunctive therapy for sepsis, clinical trials have not shown any significant benefit.[54,55] In a study of 80 patients randomized to isovolumic hemofiltration or standard therapy, hemofiltration did not improve clinical parameters or mortality. Current data do not support the use of CRRT as adjunctive therapy for sepsis in addition to renal support.

Drug dosing during CRRT

Drug dosing during CRRT can be challenging because drug dosing must consider many factors in addition to extracorporeal drug elimination, including non-renal elimination, residual renal function, and changes in volume of distribution and protein binding.[56,57] Medication dosing errors can lead to both toxicity due to insufficient dose reduction and treatment failure due to underdosing. The latter is particularly important for antibiotic dosing in patients with sepsis associated with AKI.

Medications with a noticeable clinical effect, such as analgesics, sedatives and vasopressors, should be titrated according to the desired clinical response.[58,59] Drugs with high molecular weight, strong protein binding, or very large volume of distribution are poorly eliminated by CRRT, and no dose adjustment is necessary for active therapy. Extracorporeal elimination of nonprotein-bound small molecule drugs approximates effluent flow. Estimated clearance of protein-bound drugs must be adjusted for the percentage of unbound fraction. For all drugs whose blood levels are easily measured, dosage adjustments should be made based on pharmacokinetic monitoring. Finally,

it should be recognized that although published guidelines provide dosing estimates for many agents, they only provide general parameters that may not correspond to the specific form and dose of CRRT used.

Nutritional management

AKI patients undergoing CRRT usually have a markedly negative nitrogen balance due to high protein catabolism. [60,61] In addition, CRRT causes a loss of amino acids and water-soluble vitamins and other micronutrients. Caloric intake should be around 35 kcal/kg per day, aim for a protein intake of 1.5 g/kg and supplement with water soluble vitamins. Although enteral feeding is preferred, parenteral support may be necessary.

Complications of CRRT

As with all medical procedures, CRRT is not without risks. Initiation of CRRT requires placement of a large-bore central venous catheter, which may require long-term maintenance. Known complications of catheter placement include vascular or visceral injury causing hemorrhage, pneumothorax, hemothorax, and arteriovenous fistula formation.[62,63] Prolonged use of the catheter is associated with venous blockage or stenosis. Exposure to blood in the extracorporeal circulation can induce immediate allergic or delayed immunological responses due to cytokine activation. Bradykinin-mediated membrane reactions have been associated with certain synthetic membranes when angiotensin-converting enzyme inhibitors are used. Air embolism can occur during catheter insertion or removal and at any time during therapy if air enters the circuit outside the return line air detector.

Circuit clotting and anticoagulation

The most common complication during CRRT is clotting of dialysis circuit, and the most common cause is inadequate catheter function, leading to flow restrictions and pressure towers that interrupt blood flow.[64] If the blood flow cannot be maintained at 200-300 ml/min, a quick catheter change may be necessary. An excessive filter fraction can cause hemoconcentration in the hemofilter, which also contributes to filter coagulation.[65, 66] If there is no catheter failure, blood flow is maximized and the filtration fraction is < 20%, initiation or intensification of anticoagulant therapy should be considered. Complications of heparin anticoagulant therapy may include bleeding and heparin-induced thrombocytopenia. Citrate anticoagulation can cause citrate toxicity due to citrate accumulation, overt hypocalcemia due to insufficient calcium replacement, and both metabolic acidosis and metabolic alkalosis as a result.

Electrolyte abnormalities

One of the most common electrolyte imbalances observed during CRRT is hypophosphatemia.[67] Hypophosphatemia may result from continued removal in the circulation and may potentially lead to delay in weaning from mechanical ventilation. Hypophosphatemia can be prevented by prophylactic enteral or parenteral phosphate supplementation or the use of phosphate-containing dialysate or replacement fluids.

Hemodynamic instability

Dialysate and replacement fluids are not often warmed up, in contrast to traditional hemodialysis. Thermal losses during CRRT can mask the onset of fever, but they may trigger vasoconstriction and supposedly increase hemodynamic stability. Significant hypothermia may develop from more severe thermal loss, necessitating extensive external rewarming. In certain studies, more than one third of patients have hypotension during CRRT; nevertheless, this condition is typically unrelated to the actual CRRT process.[68,69] Ultrafiltration, which exacerbates hemodynamic instability, is the most common cause of hypotension.[70] Hypotension can also be observed at the beginning of treatment, especially if the circulation is not reinfused; this result was of particular concern in children and can be alleviated by the use of albumin in priming the circuit.[71,72] If hypotension is associated with fluid depletion, treat with fluid re-infusion and adjust ultrafiltration targets; in other cases, alternative causes should be considered and hypotension treated with vasopressors.

Termination of CRRT

There are no specific criteria for discontinuation of CRRT due to recovery of renal function or switching to other forms of RRT.[73] The first manifestation of recovery of renal function is usually increased urine output, although specific criteria are rare. In a study titled, observational Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney), urine output > 400 mL/d without concomitant diuretic therapy predicted successful discontinuation of CRRT.[74] In this observational cohort, patients who successfully discontinued CRRT without restarting it were more likely to survive to hospital discharge compared with patients who required restarting CRRT. Another study proposed urine output > 500 mL/d as a criterion for discontinuation of renal replacement therapy in patients with AKI. Although these strategies may aid in clinical decision-making, there are no precise criteria for stopping RRT. Patients with improved hemodynamic status but persistent AKI also have a very different transition to other forms of RRT.[75] Based on the clinical context, PIRRT can be utilized as a transitional therapy, or patients can be referred directly to IHD. Converting from CRRT to PIRRT or IHD may make it simpler to begin physical therapy and bed mobilization. In general, patients with persistent ICU-dependent AKI should be transferred to IHD before ICU discharge.

CONCLUSIONS

CRRT remains the mainstay of therapy for AKI in critically ill patients. In practice, the provision of CRRT in the ICU remains highly variable. In patients without objective indications for initiation of renal therapy, the optimal time of RRT remains controversial. Although the use of continuous regimens may facilitate the management of hemodynamically unstable patients, the available data do not show that the use of CRRT improves survival or recovery of renal function compared with alternatives such as conventional IHD and PIRRT. Large, well-designed clinical trials have shown that in most patients, increasing solute clearance at effluent flow rates >20–25 mL/kg/h is not associated with improved outcomes. however, optimal volume management strategies remain to be defined. Other aspects of CRRT management also vary considerably in practice, including anticoagulant strategies. Finally,

the role of CRRT in setting overall treatment goals and the use of other life-sustaining treatment strategies must be considered.

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