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Narrative Review

Dosing of Renal Replacement Therapy in Acute Kidney Injury

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The impact of the intensity of renal replacement therapy on outcomes in patients with acute kidney injury has been studied intensively during the past decade. In this review, we consider the concept of dose of renal replacement therapy in acute kidney injury and summarize the recent clinical trials addressing this topic. Although several single-center trials suggest that more intensive therapy is associated with improved outcomes, 2 large multicenter randomized trials do not find a benefit with higher doses of therapy. Based on these studies, we provide recommendations for the delivered intensity of renal replacement therapy in acute kidney injury.

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Acute kidney injury (AKI) is a prevalent and devastating complication in critically ill patients. It has an incidence of 5%-45%, depending on the specific definition used, with ~4% of intensive care unit (ICU) patients developing AKI severe enough to require renal replacement therapy (RRT).[1-3] The mortality associated with severe AKI remains high, ranging from 40%-60% since the 1960s despite improvements in dialytic techniques, including the use of biocompatible membranes, bicarbonate-buffered dialysate, and integrated ultrafiltration control for intermittent hemodialysis (IHD) and the increased use of continuous RRTs (CRRTs) since the late 1980s.[4-6] Multiple factors have been posited as contributing to the persistently high mortality in patients with AKI. These have included reliance on changes in serum creatinine level, which is a lagging marker of kidney function, for the diagnosis of AKI; delayed initiation of RRT; inadequate dosing of RRT; and inability to fully replace kidney function, particularly endocrine, paracrine, metabolic, and immunologic functions, with current RRT modalities.[7-12] During the past decade, multiple studies have evaluated the relationship between the intensity of RRT and clinical outcomes of AKI.[13-20] In this review, we provide an overview of these studies and summarize current evidence informing clinical practice and future research.

ASSESSMENT OF RRT DOSE

Quantification of the delivery of RRT is based most commonly on clearance of urea as a surrogate for low-molecular weight uremic toxins.[21,22] IHD dose is quantified most commonly based on urea reduction ratio (URR) or fractional urea clearance per treatment, expressed as Kt/V_{urea}.[21,23,24] Although urea kinetic models have been validated extensively for maintenance hemodialysis in end-stage renal disease, there are multiple limitations to their use in quantifying the dose of acute IHD because many of the fundamental assumptions underlying these models are violated in the acute setting.[21,25] Among these is the assumption that predialysis volume status and nitrogen balance remain relatively stable over a repetitive cycle of dialysis treatments. Unlike patients with end-stage renal disease, critically ill patients with AKI often are hypercatabolic and in negative nitrogen balance.[23] In addition, alterations in regional blood flow in hemodynamically unstable patients can result in disequilibrium in urea distribution between body fluid compartments, invalidating standard single-pool models.[26] Finally, the volume of distribution of urea is altered in AKI, often exceeding total-body water, further complicating the application of urea kinetics to the acute setting.[27,28] Despite these limitations, and in the absence of superior metrics, URR and Kt/V_{urea} have been applied satisfactorily for dose quantification in critically ill patients undergoing acute dialysis.[24,26] Furthermore, a retrospective analysis of patients with AKI showed that patients with intermediate severity of illness have a survival benefit with URR >58% (Kt/V_{urea} >1) per treatment.[29]

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A second consideration for the application of urea kinetics in the acute setting relates to assessing the equivalence of treatments provided on different frequencies. Because urea removal during dialysis is proportional to blood urea concentration, the absolute rate of urea removal is greatest at the start of treatment and decreases over its duration. If the same weekly duration of treatment is divided among more frequent treatments (eg, 2 hours 6 times weekly compared with 4 hours 3 times weekly), the effective weekly small-solute clearance is increased.[30] Thus, the effective weekly dose of therapy cannot be expressed as the arithmetic sum of individual treatments. Although multiple mathematical models have been proposed for equating dialytic therapies provided on variable schedules,[31-33] none has been clinically validated, particularly in the acute setting.

The dose of CRRT also commonly is quantified on the basis of urea kinetics. CRRT solute clearance can be calculated as the ratio of the solute concentration in the effluent and plasma multiplied by the rate of effluent flow, in which effluent is equal to ultrafiltrate in continuous hemofiltration, spent dialysate in continuous hemodialysis, and the sum of both in continuous hemodiafiltration. Although the mechanism of solute transfer varies with convective (hemofiltration) as opposed to diffusive (hemodialysis) modalities, under usual conditions, the concentration ratio between effluent and blood for urea and other low-molecular-weight solutes is close to unity.[34,35] Thus, small-solute clearance is approximately equal to effluent flow, allowing CRRT dose to be expressed as effluent volume per unit of time normalized to body weight. An important caveat is that prefilter administration of replacement fluid during hemofiltration or hemodiafiltration will dilute the concentration of solutes entering the hemofilter and decrease clearance by about 15%-20%.[34] In addition, equilibration between the effluent and blood may decrease with time due to clotting and protein deposition fouling the hemofilter membrane.[36] Thus, more precise quantification of small-solute clearance may be achieved by simultaneous measurement of urea in blood and effluent to monitor the decrease in equilibration over time. However, it should be recognized that this degree of monitoring was not included in the clinical trials described next.[13,15,16,18,19] Although the concept of URR does not have meaning in CRRT when a steady-state blood urea concentration is attained, the dose of therapy alternatively could be expressed as Kt/V_{urea} if there was reliable assessment of the volume of distribution for urea. If this volume is assumed to approximate 60% of body weight, CRRT at a dose of 20 mL/kg/h would correspond to Kt/V_{urea} of ~0.8 per day.

Although the paradigm of urea kinetic–based dosing of RRT has provided the basis for most clinical trials of the intensity of acute RRT, assessment of RRT adequacy solely on the basis of urea kinetics provides an incomplete assessment of the delivered therapy. For example, the urea kinetic paradigm ignores the potential impact of the clearance of higher molecular weight solutes, sodium and volume management, and duration of treatment on outcomes. It should be recognized that the potential impact of these aspects on RRT prescription has not been assessed in the studies described next and remains an important area for future investigation.

OVERVIEW OF DOSING TRIALS IN AKI

Eight prospective clinical trials have evaluated RRT dosing in AKI (Tables 1 and 2). Seven of these limited their assessments to individual modalities of RRT; 5 evaluated modalities of CRRT,[13,15-17,19] one evaluated IHD,[14] and one evaluated slow extended dialysis.[20] The remaining study used a treatment strategy that allowed patients to convert between RRT modalities as their hemodynamic status changed while maintaining dose separation.[18]

Continuous RRT

The initial study evaluating the intensity of CRRT dosing was conducted by Ronco et al[13] at a single center in Vicenza, Italy. In this study, 425 patients undergoing continuous venovenous hemofiltration (CVVH) with postfilter administration of lactate-buffered replacement fluid were randomly assigned to 3 doses of treatment based on prescribed effluent volumes of 20, 35, or 45 mL/kg/h, calculated using the patient's weight before admission to intensive care. All patients received at least 85% of the prescribed dose, but dosing was increased to compensate for time off treatment. The patients randomly assigned to receive 20 mL/kg/h had significantly lower survival (41%) at 15 days after discontinuation of CRRT compared with the groups that received 35 (57%) or 45 mL/kg/h (58%).

In another single-center study, Saudan et al[16] evaluated the impact of augmenting the clearance of small molecules by adding dialysis to the convective clearance of CVVH. Two hundred six patients were randomly assigned to CVVH with an effluent volume of 1-2.5 L/h or continuous venovenous hemodiafiltration (CVVHDF) with an additional dialysate flow rate of 1-1.5 L/h. In both groups, the ultrafiltration rate was ~25 ml/kg/h (rounded off to the upper 500 mL/h within the range of 1.0-2.5 L/h) with lactate- or bicarbonate-buffered replacement fluid administered prefilter. Patients randomly assigned to CVVHDF received an additional 1.0-1.5 L/h of dialysate flow,