Intensity of Continuous Renal Replacement Therapy in Acute Kidney Injury

Paul M. Palevsky
Renal Section, VA Pittsburgh Healthcare System and Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

ABSTRACT

The intensity of continuous renal replacement therapy (CRRT) is generally assessed on the basis of small solute clearance with dosing usually expressed in terms of total effluent volume per unit time (e.g., ml/kg/hour). Although several clinical trials have suggested an improvement in survival with higher doses of CRRT, results have not been consistent across all studies. The results of recent trials of intensity of CRRT are reviewed. The largest and most recent trials suggest that there is no additional benefit to using effluent flow rates in excess of 20 ml/kg/hour, although earlier studies suggested improved survival with doses of 35 to 45 ml/kg/hour.

Dosing and intensity of continuous renal replacement therapy (CRRT) are generally defined in terms of solute clearance. Although issues related to volume management are of paramount importance in critically ill patients, one of the key features of CRRT is the ability to dissociate solute clearance from volume management. Since, by definition, continuous therapy is intended to be performed 24 hours per day, intensity of therapy is generally characterized in terms of the delivered dose per unit time, often indexed to body mass (1–4). However, the reality is that continuous therapy is often interrupted; the actual intensity of therapy is therefore dependent not only on the delivered dose per unit time but also on the relative percentage of time that the patient actually receives therapy (4,5).

Solute Clearance in CRRT

Solute clearance can be analyzed based on either the removal of solute from the blood, or its appearance in effluent fluids (6). As the change in solute concentration in the blood over the length of the hemodialyzer/hemofilter tends to be small, the latter approach is most commonly employed. Using this method, clearance can be expressed as:

$$K = (Q_E C_E - Q_D C_D)/C_B \quad (1)$$

where K is clearance, Q_D and Q_E are the dialysate inflow and effluent outflow rates, respectively, and C_B, C_D, and C_E are the concentrations of solute in the blood, dialysate, and effluent, respectively. As the ultrafiltration rate (Q_{UF}) is equal to the difference between the effluent outflow and dialysate inflow rates:

$$Q_{UF} = Q_E - Q_D \quad (2)$$

Equation 1 may therefore be rewritten as:

$$K = Q_D(C_E - C_D)/C_B + Q_{UF}C_E/C_B \quad (3)$$

The first term of this equation, $Q_D(C_E–C_D)/C_B$, quantifies the clearance that occurs in the absence of ultrafiltration and approximates the diffusive component of clearance. For solutes that are not present in the dialysate ($C_D = 0$), this term can be simplified to $Q_D C_E/C_B$, or the product of the dialysate flow rate and the degree of solute equilibration between dialysate and blood (C_E/C_B). The second term, $Q_{UF}C_E/C_B$, is the clearance that occurs in the absence of dialysate flow ($Q_D = 0$), and approximates the convective clearance. Although this mathematical analysis is useful conceptually, it must be recognized that it does not describe the actual diffusive and convective processes, particularly the component of convective solute flux which may occur during continuous hemodialysis as the result of filtration and backfiltration (7), and the interactions between diffusive and convective solute flux.

Unlike conventional intermittent hemodialysis (IHD), the dialysate flow rate (Q_D) during continuous hemodialysis is substantially lower than the blood flow rate (Q_B). As a result, near complete equilibration

Address correspondence to: Paul M. Palevsky, MD, Room 7E123 (111F-U), VA Pittsburgh Healthcare System, University Drive Division, Pittsburgh, PA 15240, or e-mail: palevsky@pitt.edu.

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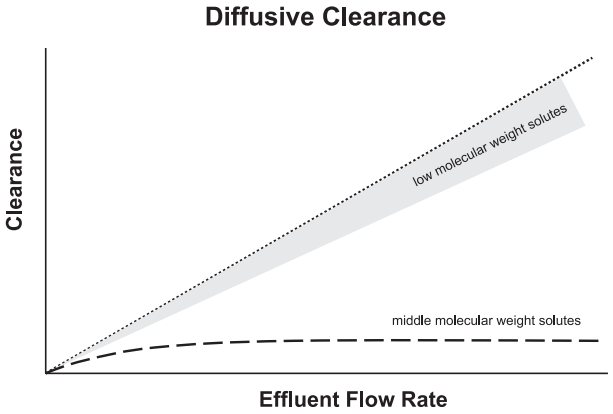

FIG. 1. Relationship between effluent flow rate and solute clearance during diffusive therapy (continuous hemodialysis). The shaded zone represents the range of clearances for low molecular weight solutes illustrating the approximately linear relationship between effluent flow rate and clearance. The broken line represents the effluent flow-independent clearance of middle molecular weight solutes. The dotted line is the line of identity (clearance equal to effluent flow rate).

between blood and dialysate can occur for low molecular weight solutes ($C_E/C_B \sim 1$), particularly at low dialysate flow rates, although equilibration is less complete as dialysate flow rates are increased (8). As a result, there is an approximately linear relationship between dialysate flow and small solute clearance (Fig. 1). By contrast, the clearances of higher molecular weight solutes, such as β-2 microglobulin, are limited by their slower rates of diffusion and exhibit minimal dependence on dialysate flow (8).

As predicted from the mathematical model, for low molecular weight solutes with sieving coefficients (C_E/C_B) close to unity, solute clearance during continuous hemofiltration is approximately equal to the ultrafiltration (effluent) flow rate (Fig. 2) (8,9). For higher molecular weight solutes, such as β-2 microglobulin, a more complex and variable relationship has been observed, with some studies reporting an increase in sieving coefficients as the hemofiltration rate increases (8) and other studies suggesting constant or even decreasing sieving coefficients with increasing hemofiltration rates (9). The site of infusion of replacement fluids also has an important impact on clearance during hemofiltration. When replacement fluids are administered into the inflow limb of the extracorporeal circuit (predilution), the concentration of solutes within the hemofilter is diluted, thereby reducing the effective solute clearance as compared with administration into the blood return line (postdilution). The magnitude of this reduction is dependent on the relationship between the blood flow and replacement fluid infusion rates. When blood flow and total effluent flow are kept constant, increasing the infusion rate of predilution replacement fluid will result in a progressive decrease in clearance. By contrast, increasing the blood flow rate will decrease the impact of predilution fluid administration. It has been suggested, however, that the reduction in clearance associated with predilution continuous venovenous hemofiltration (CVVH) is offset by improved hemofilter patency and decreased time off of therapy (10).

In summary, as the equilibration of small solutes, such as urea, is virtually complete during continuous hemodialysis, at equivalent total effluent flow rates small solute clearance will be similar during continuous venovenous hemodialysis (CVVHD) and postdilution CVVH. Although clearances will be lower during predilution CVVH, this reduction in clearance appears to be offset by improved filter patency. Thus the modality of CRRT appears to have little impact on effective daily clearance of small solutes. By contrast, however, convective therapies will provide greater removal of higher molecular weight species than comparable doses of diffusive therapy.

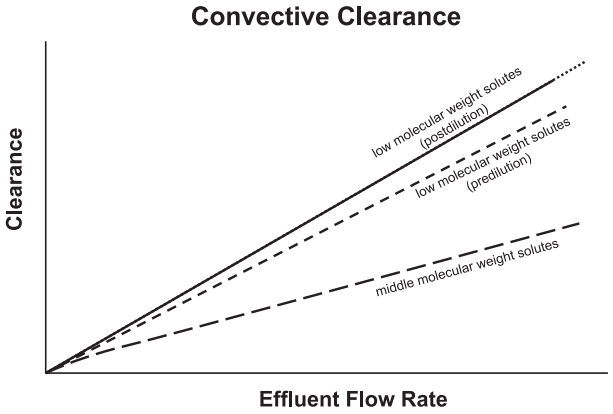

FIG. 2. Relationship between effluent flow rate and solute clearance during convective therapy (continuous hemofiltration). The solid line represents the clearance of low molecular weight solutes with a sieving coefficient approximately 1 during postdilution hemofiltration. The small broken line represents the reduced clearance achieved for these solutes during predilution hemofiltration. The large broken line represents the lower, but still flow-dependent clearance of middle molecular weight solutes. The dotted line is the line of identity (clearance equal to effluent flow rate).

Relationship between Intensity of CRRT and Clinical Outcomes

Four randomized controlled trials have assessed the relationship between intensity of CRRT, assessed in terms of total effluent flow rate, and outcomes of acute kidney injury (AKI) (Table 1) (1–3,11). In the earliest of these trials, Ronco et al. randomized 425 critically ill patients with AKI treated with postdilutional CVVH at a single center to ultrafiltration rates of 20, 35, or 45 ml/kg/hour (1). Survival 15 days after discontinuation of CRRT was 41% in the lowest dose arm as compared with 57% and 58% in the intermediate and highest dose arms, respectively ($p < 0.001$). In a second single center randomized trial, Saudan et al. compared CVVH with a mean ultrafiltration rate of 25 ± 5 ml/kg/hour in 102 patients to continuous venovenous diafiltration (CVVHDF) with a mean total effluent flow rate of 42 ml/kg/hour (mean ultrafiltration rate of 24 ± 6 ml/kg/hour; mean dialysate flow rate of 15 ± 5 ml/kg/hour) in 104 patients (2). Survival after 28 days was 39% in the CVVH group and 59% in the

TABLE 1. Summary of studies evaluating the dose of CRRT

			Lower dose			Higher dose		
Study	Year	*n*	Modality	Dose	Survival	Modality	Dose	Survival
Ronco et al. (1)	2000	435	CVVH	20 ml/kg/hour	41%	CVVH	35 ml/kg/hour 45 ml/kg/hour	57% 58%
Bouman et al. (11)	2002	106	CVVH	19 ml/kg/hour	72%	CVVH	48 ml/kg/hour	74%
Saudan et al. (2)	2006	206	CVVH	25 ml/kg/hour	39%	CVVHDF	42 ml/kg/hour	59%
Tolwani et al. (3)	2008	200	CVVHDF	20 ml/kg/hour	56%	CVVHDF	35 ml/kg/hour	49%
Palevsky et al. (4)	2008	1124	IHD & SLED CVVHDF	3x/week 20 ml/kg/hour	48%	IHD & SLED CVVHDF	6x/week 35 ml/kg/hour	46%

CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous diafiltration; IHD, intermittent hemodialysis; SLED, sustained low-efficiency dialysis.

CVVHDF ($p = 0.03$) and 34% and 59%, respectively, after 90 days ($p = 0.0005$).

In contrast to these two studies, Bouman et al. observed no improvement in survival with high volume postdilutional CVVH (3 l/hour; median: 48 ml/kg/hour) as compared with low volume postdilutional CVVH (1–1.5 l/hour; median: 19 ml/kg/hour) in 106 patients (11). Twenty-eight day survival was 74.3% in the early high-volume hemofiltration arm, 68.6% in the early low-volume hemofiltration arm and 75.0% in the late low-volume hemofiltration arm ($p = 0.80$). Similarly, Tolwani et al. observed no difference in survival in 200 patients randomized to two doses of predilutional CVVHDF (3). Survival to the earlier of either ICU discharge or day 30 was 49% in 100 patients randomized to receive CVVHDF at 35 ml/kg/hour as compared with 56% in 100 patients who received CVVHDF at a dose of 20 ml/kg/hour ($p = 0.32$).

In distinction to these four studies that utilized only CRRT, the recently completed VA/NIH Acute Renal Failure Trial Network (ATN) Study compared two strategies for the management of renal replacement therapy (RRT) in AKI that allowed patients to switch between CRRT and IHD as hemodynamic status changed over time, and observed no improvement in outcome with their more intensive treatment strategy (4). In both treatment strategies, patients received IHD, with a mean delivered Kt/V of 1.2 per treatment, when they were hemodynamically stable, and either predilutional CVVHDF or sustained low-efficiency dialysis (SLED) when hemodynamically unstable. Paralleling current practice, CVVHDF was the predominant modality used in hemodynamically unstable patients, and only a small percentage of patients were treated with SLED. In the less intensive treatment arm, IHD and SLED were to be provided every other day, excluding Sunday (actual treatment frequency: 3.0 sessions per week) and the target dose for CVVHDF was a total effluent flow of 20 ml/kg/hour (actual delivered dose: 22 ± 6 ml/kg/hour); in the more intensive treatment arm, IHD and SLED were to be provided daily, except Sunday (actual treatment frequency 5.4 sessions per week) and the target dose for CVVHDF was a total effluent flow of 35 ml/kg/hour (actual delivered dose: 36 ± 6 ml/kg/hour).

Mortality in the ATN Study at day 60 was 53.6% in the 563 patients randomized to the more-intensive treatment strategy as compared with 51.5% in the 561 patients randomized to the less-intensive strategy (odds ratio: 1.09; 95% confidence interval: 0.86–1.40; $p = 0.47$). There were no differences in mortality in any of the prespecified subgroups including gender, and oliguric versus nonoliguric status, presence or absence of sepsis, and cardiovascular SOFA score 0–2 versus 3–4 at baseline. In addition, no differences in outcomes were observed between the two strategies when evaluated based on percentage of time treated with CVVHDF. Although the ATN Study evaluated a more complex strategy of renal support than the prior studies, the results strongly suggest that there is no additional benefit to doses of CRRT above 20 ml/kg/hour.

Another large multicenter randomized controlled trial comparing similar doses of CVVHDF is nearing completion. The Randomized Evaluation of Normal versus Augmented Level of RRT (RENAL) study will randomize approximately 1500 patients in Australia and New Zealand to CVVHDF at effluent flow rates of either 25 ml/kg/hour or 40 ml/kg/hour (12). Enrollment is anticipated to be completed in September 2008 with follow-up for the primary endpoint of 90-day all cause mortality to be completed in December 2008.

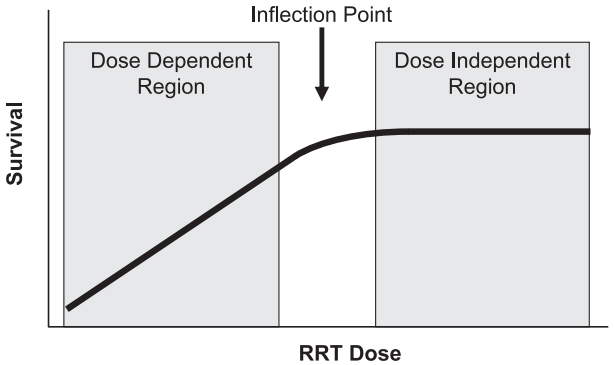

FIG. 3. Conceptual illustration of the relationship between intensity of renal replacement therapy (RRT) and survival. At low doses of RRT, survival increases with increasing dose of RRT (dose dependent region) while at higher doses of therapy further increments in dose are not associated with improved survival (dose independent region). These two portions of the dose-survival relationship are separated by an inflection point, representing the dose of therapy beyond which further increments in intensity are not associated with improvements in outcome.

The conflicting results in the studies discussed previously and summarized in Table 1 do not challenge the fundamental hypothesis that there is a relationship between intensity of RRT and outcomes in AKI (Fig. 3) (13,14). Rather, the results differ in where they place the inflection point separating the dose-responsive portion and dose-independent portions of the relationship. The studies by Ronco et al. (1) and Saudan et al. (2) suggest that this inflection point falls at a dose between 25 and 35 ml/kg/hour whereas the studies by Bouman, et al., (11) Tolwani et al. (3) and the ATN Study (4) suggest that the inflection point is at a dose less than 20 ml/kg/hour. A multitude of factors may have contributed to the differences between the studies; including differences in the study populations and potentially differences in the actually delivered, as opposed to the prescribed, dose of therapy.

Several additional studies have suggested potential additional benefit with even higher doses of convective therapy (e.g., high-volume hemofiltration) in patients with sepsis, postulating modulation of the inflammatory response through removal of humoral mediators (1,15,16). However, the data from these studies are not sufficiently robust to allow any definitive conclusions to be drawn. Thus, the use of high-volume hemofiltration in sepsis should continue to be considered an investigational therapy.

Conclusions

The intensity of CRRT is generally assessed on the basis of small solute clearance, with dosing usually expressed in terms of total effluent volume per unit time (e.g., ml/kg/hour). Although several clinical trials have suggested an improvement in survival with higher doses of CRRT, results have not been consistent across all studies. While the largest and most recent trials suggest that there is no additional benefit to using doses above 20 ml/kg/hour, earlier studies suggested improved survival with higher doses of therapy. The results of the soon to be completed RENAL study should provide additional high-quality evidence regarding the optimal intensity of CRRT.

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