

Challenges in Quantification of Acute Renal Replacement Therapy.

Sandeep Mahajan*, Yasir Rizvi**

*Additional Professor, **Senior Resident, Department of Nephrology,
All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

Abstract: The optimal management in patients with acute kidney injury (AKI) including dosing of renal replacement therapy (RRT) remains an important unresolved issue. The concept of dialysis dose tested in patients with end stage kidney disease (ESKD) has now been increasingly being extrapolated in patients with AKI. Urea kinetic modeling the mainstay of dialysis dose and end stage kidney disease has limited utility in AKI because of non-steady state of urea generation, protein catabolism and volume status in these patients. This is further compounded by differing dialysis techniques employed in these patients. Though various models have been proposed like equivalent urea clearance, solute detention index and the ionic dialysance to address these issues they have their own limitations and have limited clinical experience. Few systematic studies have looked at the effect of dialysis dosing on patients outcomes and controversy exists in defining adequate dose of dialysis in these patients. The physician thus should consider various patients characteristics in prescribing these therapies and importantly measure the delivered dose of RRT in each session to accommodate for difference in prescribed and delivered dose.

INTRODUCTION

Acute Kidney Injury (AKI) is a complex clinical entity characterised by an abrupt decline in renal function. Definitions for AKI have only recently been standardised in the form of Risk-Injury-Failure-Loss-End stage renal disease (RIFLE) classification in 2004 followed by modifications by the Acute Kidney Injury Network (AKIN) in 2007^{1,2}. Despite standardised definitions and technological advancements in medical and renal replacement therapy (RRT) the morbidity and mortality in AKI remains unacceptably high¹. The optimal management in these patients' remains uncertain with some debatable issues being timing of initiation of renal replacement therapy (RRT), choice of modality (intermittent vs continuous) and quantification of dialysis dosing in AKI³. The problem is further compounded by significant influence of other co-morbidities on outcomes making it difficult to assess and compare various therapies. The dosing of acute renal replacement therapy in AKI is an area of intense interest and research and in this review we will focus on the concept of dialysis dosing in AKI and studies looking at influence of dialysis dosing on patient outcomes.

CONCEPT OF DIALYSIS DOSING IN AKI

- The uraemic state is characterised by the accumulation of small and large solutes, protein bound substances and sequestered solutes. Dialysis effectively removes small and middle molecular solutes and corrects dyselektrolytemia/acid base and fluid imbalances by adding solutes while achieving a net ultrafiltration. Accordingly, the effect of dialysis can be quantified either by measuring the clearance of solutes or by the fluid removed. The clearance of solute may be measured either by blood based or dialysate based kinetics. In patients with end stage renal failure (ESRF), urea (a small solute) is an ideal clearance marker for dialysis since it is easily removed by the dialyser and can be readily measured in blood. This further evolved into the concept of Urea Kinetic Modelling (UKM). The dose of dialysis in ESRF is invariably measured and quantified as Kt/V_{urea} (Kt/V) and it has been linked with clinical outcomes in these patients. This has resulted in extrapolation of Kt/V as a unit of expression of dialysis dose in AKI as well. However, the existence of a steady state is a fundamental assumption of formal UKM in ESRF patients. Steady state assumes that patient is in a state of no net anabolism

or catabolism and has stabilized dry weight. Thus even if Kt/V is similar in two patients dialysis dose might not be similar if they have variable urea generation or volume status. In comparison AKI is inherently a non-steady-state situation with typically high rates of protein catabolism (>1.5 g/kg/day) and generally large net nitrogen deficits (>5 g/day)⁴. Another common occurrence in critically ill patients is severe volume overload resulting in overestimation total body water⁴. In addition, according to the regional blood flow model formulated by Daugirdas and Schneditz⁵, urea disequilibrium during HD is attributed to a mismatch between blood supply and urea content in different body compartments. This mismatch may get exaggerated in critically ill patients with AKI having shock and requiring vasopressors. This makes extrapolation of urea kinetic modelling (Kt/V) difficult in critically ill patients with AKI as in these patients urea does not have single pool kinetics. Various models have thus been proposed to address these drawbacks, however almost all of these models have been derived in ESRF patients and only validated in small sample of AKI patients. Also some of these models also require repeated samplings making them difficult to implement in day to day practice. Commonly proposed models include equivalent renal urea clearance⁶, solute reduction index^{7,8} and ionic dialysance⁹⁻¹³. However most of these tests are either too cumbersome or require further studies before they can be used on a routine basis in the setting of AKI.

DOSING BEYOND SMALL SOLUTE CLEARANCE

There has been an increased interest in improving clearance of middle molecules which include various pro-inflammatory cytokines with techniques like high volume hemofiltration to potentially decrease the high rates of mortality associated with AKI¹⁴. However no significant trial has assessed the effect of these therapies on patient outcomes and renal recovery to currently justify the inclusion of middle molecule clearance in dialysis dosing in AKI. Ongoing IVOIRE (hIgh Volume in Intensive CAre) trial looking at effect of high volume hemofiltration on 28 day mortality in patients of septic shock with AKI, might further clarify the role of these therapies¹⁵. Removal of fluid is also an important component of any renal

replacement therapy and fluid status is increasingly been recognized as an independent predictor mortality in AKI patients¹⁴. However, fluid removal by RRT and fluid status in AKI patients has not been systematically evaluated in any of the trials and therefore is not included in any of the current definitions of dialysis adequacy in AKI.

It has also been suggested¹⁶, that adequate removal of “very small waste products” (sodium, potassium and hydrogen) should be main determinant of adequacy of renal replacement in AKI since their accumulation could be lethal. These parameters have never been highlighted as markers of adequacy of renal replacement therapy in AKI.

DIALYSIS DOSE AND PATIENT OUTCOMES IN AKI

A number of studies starting from the initial experience Korean and Vietnam wars suggested improved outcomes in AKI patients when the intermittent hemodialysis (iHD) was delivered either in an ‘early’ (initiated when BUN <100-150 mg/dl) or in ‘intensive’ manner (prescribed to maintain serum creatinine < 5 mg/dl)¹⁷. These encouraging early observations are however diluted by the methodological shortcomings and non-representativeness of this cohort in present day scenario. Controversy still exists in defining ‘adequate dose’ of RRT in AKI and benefit if any of intensive RRT.

In **table 1** we have listed important trials looking at the effect of dose of dialysis on patient outcomes in AKI. As can be seen most of the studies have been single centre studies, conducted on predominantly ICU patients using varying RRT techniques and markers for dialysis adequacy.

In intermittent hemodialysis or hybrid techniques duration and

frequency of therapy and the clearance of dialyzer used are factors which determine the dosage. Only 2 studies have been done which have evaluated systematically the role of these modalities in AKI. In 2002, Schiffel et al³ assigned a total of 160 patients with acute renal failure in alternative order to receive daily ‘high’ (average single pool Kt/V of 0.92 delivered 6.2 times/week) or alternate day ‘low’ (average single pool Kt/V of 0.94 delivered 3.2 times/week) intermittent hemodialysis. The study showed a reduction in 28-day mortality from 46% with alternate-day dialysis to 28% with daily dialysis. However this study was subject to large variations in delivered dose and a time averaged BUN of 104 mg/dl in low dose group indicates inadequate dialysis. More recently Hannover trial¹⁸ compared mortality and renal recovery of patients with AKI receiving either standard or intensified dose of extended dialysis therapy (SLED) in an intensive care unit setting. A total of 156 patients with AKI requiring renal replacement therapy were randomly assigned to receive standard dialysis (dosed to maintain plasma urea levels between 120 and 150 mg/dl) or intensified dialysis (dosed to maintain plasma urea levels <90 mg/dl). High-flux polysulphone dialysers (F60S, 1.3 m², Fresenius Medical Care) were used for all treatments. No differences between intensified and standard treatment were seen for survival by Day 14 (70.4% versus 70.7%) or Day 28 (55.6% versus 61.3%), or for renal recovery amongst the survivors by Day 28 (60.0% versus 63.0%).

Most of the other studies have looked at various forms of continuous renal replacement therapy (CRRT). The prescription of dose of CRRT is usually expressed in terms of effluent per kilogram of body weight per unit of time (UFR) as sieving coefficient for small molecule is unity in CRRT. The efficiency of the CRRT depends also upon the type of therapy used, site of replacement fluid infusion (pre or post-filter) and dialyzer clotting. The first systematic study was a single centre trial by

Table 1: Clinical Trials looking at dose of renal replacement therapy in Acute kidney injury.

Author	Study period	Study design	Study population	n	Dialysis modality	Dialysis dosing criteria	Results
Schiff et al ³	1993-1998	Single centre alternate assignment	Severe ATN	160	HD	Daily vs IHD	Reduction in 28-day mortality from 46% with alternate-day dialysis to 28% with daily dialysis
Walter et al ¹⁸	2003-2006	Multicentre RCT with parallel group	Patients with AKI requiring RRT	156	Extended dialysis	Standard Dialysis (dosed to maintain plasma urea 120-150 mg/dl) vs Intensified dialysis (dosed to maintain plasma urea levels <90 mg/dL)	No differences between intensified and standard treatment were seen for survival by Day 14
Ronco et al ¹⁹		Single centre RCT	Critically ill patients with AKI	425	CVVH (Post dilution)	Ultrafiltration rate of 20 ml/kg/hr, 35 ml/kg/hr and 45 ml/kg/hr	Reduction in mortality from 59% to 43% when UF was increased from 20 to ≥35 ml/kg/hr
Bouman et al ²⁰		2-centre RCT	ICU patients with AKI	106	CVVH (Post dilution)	Ultrafiltration rate of ≥3L/h within 12 hrs of recruitment, 1-1.5L/hr within 12 hrs, and 1.5L/hr as clinically indicated	No improvement in survival
Saudan et al ²¹	Oct 2000 – Dec 2003	Single centre RCT	AKI	206	CVVH vs CVVHDF	Ultrafiltration flow rate (1–2.5 l/h) in CVVH vs additional dialysate flow rate between 1 and 1.5 l/h in CVVHDF	Better survival in CVVHDF
Tolwani et al ²²	Aug 2003 – Mar 2006	Single centre RCT	ICU patients with AKI	200	CVVHDF	Ultrafiltration flow rate High dosage (35 ml/kg/hr) vs Standard dosage (20 ml/kg/hr)	No significant difference in survival
Palevsky et al ²³	Nov 2003 – July 2007	Multicentre RCT with 2 parallel groups	ATN requiring RRT with failure of one or more non renal organ	1124	IHD/SLED and CVVHDF	Intensive strategy : IHD/SLED 6 times/wk, CVVHDF 35 ml/kg/h vs Less-intensive strategy : IHD/SLED 3 times/wk, CVVHDF 20 ml/kg/h	No significant difference between the 2 groups in the duration of RRT or the rate of recovery of kidney function
Bellomo et al ¹⁷	Dec 2005 – Nov 2008	Multicentre RCT with parallel group	Critically ill patients with AKI requiring RRT	1508	CVVHDF	Higher intensity (40 ml/kg/hr) vs Lower intensity group (25 ml/kg/hr)	No difference in mortality at 90 days

Ronco et al¹⁹. It was randomized controlled trial (RCT) including 425 critically ill patients treated with post-dilution continuous venovenous hemofiltration (CVVH) in 3 doses of UFR 20, 35 or 45 mL/kg/hr. There was reduction in mortality from 59% to around 43% when UFR was increased from 20 to 35 mL/kg/hr. Bouman et al²⁰ in 2 centres from the Netherlands randomly assigned 106 patients to 3 different regimens of post-dilution CVVH characterized by 'early high volume' (UFR 35 mL/hr started routinely within 12 hr of enrolment), 'early low volume' (UFR 1-1.5 L/hr started routinely within 12 hr of enrolment) and 'late low volume' (UFR 1-1.5 L/hr started when clinically indicated). Survival in this study was not influenced by dose or timing of the RRT. Saudan et al²¹ in another single centre RCT assigned 206 patients to predilution CVVH or continuous venovenous hemodiafiltration (CVVHDF). Patients on CVVHDF therapy had received a mean dose of 42 mL/kg/h with better survival than CVVH patients, who received a mean dose of 25 mL/kg/h. In another single centre RCT Tolwani et al²² assigned 200 critically ill patients with AKI to receive CVVHDF with pre-filter replacement fluid at an UFR of either 35 mL/kg/h (high dosage) or 20 mL/kg/h (standard dosage). There were no differences in ICU survival (p=0.47), hospital survival (p=0.56), or renal recovery at either ICU discharge (p=0.17) or hospital discharge (p=0.75) between the treatment arms. 2 recent multi-centric RCTs deserve a special mention. The VA/NIH Acute Renal Failure Trial Network Study (ATN Study)²³ was designed to assess whether there was a benefit of delivering more intensive RRT in critically ill patients. This was a multicenter, prospective, randomized, parallel-group trial of two strategies for RRT in critically ill patients with AKI. Patients with AKI clinically consistent with acute tubular necrosis and requiring RRT, as well as failure of one or more nonrenal organ systems were included. In both treatment groups, patients underwent intermittent hemodialysis when they were hemodynamically stable (SOFA cardiovascular score of 0 to 2) and underwent continuous venovenous hemodiafiltration or sustained low-efficiency dialysis when they were hemodynamically unstable (SOFA cardiovascular score of 3 to 4). Patients were allowed to be shifted from modality to the other as per SOFA scoring. In the intensive RRT strategy, IHD and SLED was provided six times per week and CVVHDF was dosed to provide a total effluent flow rate of 35 mL/kg/hr. In the conventional RRT strategy, IHD and SLED was provided three times per week and CVVHDF was dosed to provide a total effluent flow rate of 20 mL/kg/hr. The assigned therapy was provided for up to 28 days after randomization or until recovery of kidney function, discharge from acute care, withdrawal of life-sustaining therapy, or death. 1124 patients were randomly assigned to a treatment group: 563 to the intensive treatment strategy and 561 to the less-intensive treatment strategy. There were no significant differences in mortality, rate of recovery of kidney function, duration of renal-replacement therapy, or evolution of non-renal organ failure. In the other multicenter RENAL study, Bellomo et al²⁴ randomized critically ill AKI patients to two different doses of CVVHDF 'lower intensity group' (UFR 25 mL/kg/h, n=743) and 'higher intensity group' (UFR 40 mL/kg/h, n=721). They also included patients who had pre-existing CKD. Between the two groups they did not find a difference in primary outcome (mortality at 90 days) or any of the secondary outcomes (including mortality within 28 days, ICU and in-hospital deaths) across all the pre-specified patient sub-groups.

All of the above trials reviewed differ from each other in study design, patient recruitment and RRT associated issues like modality chosen, prescribed and delivered dose etc. One factor which also needs to be factored is the timing of initiation of RRT, which has not been assessed in any of the studies¹⁴. It might be reasonable to assume that though a critical dose of dialysis is essential for better survival the exact value of same is undecided. However from the various trials available it would be reasonable to presume that RRT dose should be targeted to prescribe at

least a single pool Kt/V of 1.4 and an effluent volume of 25mL/kg/hr.

CONCLUSIONS

Increasing interest in RRT quantification in AKI has led to use of methods of quantification originally meant for ESRF patients. We should appreciate the difference between the patient and therapy characteristics in setting of AKI and select appropriate target measures for these patients. Importantly the delivered dose of RRT should be measured in each session to counter the difference between prescribed and delivered dose. Though the exact dose of such therapies is controversial the physician should focus on altering the technique to best meet the changing needs of the patient like the acid-base, electrolytes, volume and hemodynamic status.

BIBLIOGRAPHY

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. "Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group." *Critical Care* 2004;8:R204–R212.
2. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. "Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury." *Critical Care* 2007;11: R31
3. Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002;346:305-310.
4. Clark WR, Mueller BA, Kraus MA, Macias WL. Renal replacement therapy quantification in acute renal failure. *Nephrol Dial Transplant*. 1998;13 (Suppl 6):86-90.
5. Daugirdas J, Schmeditz D. Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. *J Am Soc Artif Intern Org* 1995; 41: M719–M724.
6. Casino FG, Marshall MR. Simple and accurate quantification of dialysis in acute renal failure patients during either urea non-steady state or treatment with irregular or continuous schedules. *Nephrol Dial Transplant*. 2004;19(6):1454-66.
7. Keshaviah P, Star RA. A new approach to dialysis quantification: An adequacy index based on solute removal. *Semin Dial* 1994;7: 85-90.
8. Ratanarat R, Permpikul C, Ronco C. Renal replacement therapy in acute renal failure: which index is best for dialysis dose quantification? *Int J Artif Organs*. 2007;30:235-43.
9. Polaschegg, HD. Automatic non-invasive intradialytic clearance measurement. *Int J Artif Organs* 1993 16:185–191.
10. Peticlerc T, Goux N, Reynier AL, Béné B. A model for non-invasive estimation of in-vivo dialyzer performances and patient's conductivity during hemodialysis. *Int J Artif Organs* 1993 16:585–591.
11. Ridel C, Osman D, Mercadal L, Anguel N, Peticlerc T, Richard C, Vinsonneau C. Ionic dialysance: a new valid parameter for quantification of dialysis efficiency in acute renal failure? *Intensive Care Med*. 2007;33:460-5.
12. Lindsay RM, Bene B, Goux N, Heidenheim AP, Landgren C, Sternby J. Relationship between effective ionic dialysance and in vivo urea clearance during hemodialysis. *Am J Kidney Dis*. 2001;38:565-74.
13. Kuhlmann U, Goldau R, Samadi N, Graf T, Gross M, Orlandini G, Lange H. Accuracy and safety of online clearance monitoring based on conductivity variation. *Nephrol Dial Transplant*. 2001;16:1053-8.
14. Bouchard J, Macedo E, Mehta RL. Dosing of renal replacement therapy in acute kidney injury: lessons learned from clinical trials. *Am J Kidney Dis* 2010;55:570-579
15. Honoré PM, Joannes-Boyau O, Gressens B. Blood and plasma treatments: the rationale of high-volume hemo-filtration. *Contrib Nephrol*. 2007;156:387-395.
16. Davenport A, Farrington K. Dialysis dose in acute kidney injury and chronic dialysis. *Lancet*. 2010;375:705-6.
17. Marshall MR. Current status of dosing and quantification of acute renal replacement therapy. Part 2: dosing paradigms and clinical implementation. *Nephrology* 2006;11:181-191
18. Faulhaber-Walter R, Hafer C, Jahr N, et al. The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. *Nephrol Dial Transplant* 2009;24: 2179–2186.
19. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet*. 2000;356:26-30.
20. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med*. 2002;30:2205-2211.
21. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006;70:1312-1317.
22. Tolwani AJ, Campbell RC, Stefan BS, Lai KR, Oster RA, Wille KM. Standard versus High-Dose CVVHDF for ICU-Related Acute Renal Failure. *J Am Soc Nephrol* 2008;19: 1233–1238
23. Palevsky PM, Zhang JH, O'Connor TZ, et al for the VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359:7–20.
24. Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med*. 2009;361:1627-38.