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Renal Replacement Therapy in 2013: New Insights on Dosing, Timing, Modalities and Membranes

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Renal replacement therapy (RRT), particularly continuous veno-venous haemofiltration (CVVH), is increasingly used in the ICU. CVVH and derived modalities have become first-choice bedside techniques in the ICU for treatment of septic shock complicated by acute kidney injury (AKI). Despite controversial and inconclusive results emanating from randomised controlled trials, interest in continuous renal replacement therapy (CRRT) is growing steadily and even beyond its sole use in AKI. This article highlights some new insights and evolutions in the field of CRRT and RRT that may have direct or future impact on daily ICU practice, in particular, important issues such as dosing, time of initiation, and the introduction of novel highly-adsorptive dialysis membranes.

Renal Replacement Therapy in ICU Patients

What Dose?

Several large randomised controlled trials (RCTs) have focused on dose and intensity of renal RRT. In a landmark study Ronco et al. determined a haemofiltration dose of 35 ml/kg/h as most optimal for ICU patients (Ronco et al. 2010). An improved outcome was reported in patients undergoing daily rather than thrice weekly haemodialysis (Schiffl et al. 2002), suggesting that thrice weekly intermittent haemodialysis (IHD) was less convenient for treating AKI in an ICU setting. Another study showed better outcome when the convection dose was increased and dialysis combined with haemofiltration at doses matching those used by Ronco (Saudan et al 2006). In contrast, the VA/NIH Acute Renal Failure Trial Network showed that less intensive therapy (ie IHD thrice weekly, continuous veno-venous haemodiafiltration (CVVHDF) at 20 ml/kg/h or sustained low efficiency dialysis (SLED) for unstable patients) did as well as intensive therapy (ie daily IHD or CVVHDF at 35 ml/kg/h for unstable patients) (VA/NIH Acute Renal Failure Trial Network 2008). However, and despite the high quality of this large randomised study, more than 65% of the patients had already received IHD or SLED before randomisation. Interventions were started much later than commonly accepted, which may have worsened outcome in the intensive therapy group (Ronco et al. 2008; Cruz et al. 2008). In addition, the rather limited use of continuous therapy may have affected renal recovery rate (Prowle et al. 2010).

More convincing data regarding dose finding for treatment of AKI in the ICU emerged from the RENAL trial, which demonstrated no beneficial effect of CVVHDF at 40 ml/kg/h as compared with 25 ml/kg/h (RENAL Replacement Therapy Study Investigators 2009). Hence, consensus exists that CRRT dose in septic AKI should be 25 ml/kg/h with no additional benefit from a dose increase. Most experts recommend avoiding undertreatment and delivering at least 25 ml/kg/h of fluid exchange. In practice, this implies prescribing 30- 35 ml/kg/h to compensate for predictable (changing bags, nursing etc.) or unpredictable (surgery, filter clotting etc.) treatment interruptions (Vesconi et al. 2009).

Two recently published trials activated the debate on ideal haemofiltration dose in septic AKI. The IVOIRE study compared haemofiltration doses of 35 and 70 ml/kg/h in patients with septic shock, AKI and multiple organ failure. No difference in mortality at 28 and 90 days was observed, yet global mortality was comparable (39% at 28 days and 52% at 90 days) to the RENAL study cardiovascular sequential organ failure assessment (SOFA) score 3 and 4 subgroups despite inclusion of more severely ill patients (Joannes-Boyau, Honoré et al 2013). Zhang et al. compared doses of 50 and 85 ml/kg/h in septic patients with AKI, and also found no difference in mortality (Zhang et al. 2012). Mortality was higher than in the IVOIRE study, which could be perhaps explained by a more rapid inclusion (24 hours versus ± 7 days) and start of haemofiltration (at RIFLE Injury level) in the IVOIRE trial (Honoré et al. 2011). Taken together, 25 ml/kg/h must remain the standard delivered dose, in particular in septic shock. An earlier start-up time in septic AKI seems desirable, but its benefit remains to be proven.

When to Start?

Until recently AKI was ill-defined, which precluded stratification according to degree of renal impairment. Nowadays, the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications of AKI have become universally accepted (Levey et al. 2013). These criteria not only alert clinicians to the presence of AKI, but also promote early intervention. However, convincing evidence for the ideal moment to start haemofiltration in critically ill patients with AKI is still awaited. Bouman et al. found no effect of time to start haemofiltration on outcome of cardiac surgery patients, but their study was insufficiently powered and the patient population too selective (Bouman et al. 2002). Late initiation of CRRT was found to worsen outcome of AKI after major abdominal surgery (Shiao et al. 2009). A recent meta-analysis confirmed a beneficial effect of initiating CRRT at an early stage (Seabra et al. 2008). Early CRRT may also benefit patients with ARDS undergoing extracorporeal membrane oxygenation (Ricci et al. 2010; Santiago et al. 2009). In contrast, a French trial demonstrated that starting CRRT before fulfillment of AKI criteria might harm the patient (Payen et al. 2009). The IVOIRE trial suggested starting CRRT at RIFLE Injury level (or AKIN stage 2) for treatment of AKI accompanying septic shock (Honoré et al. 2011). Finally, fluid overload refractory to diuretics may trigger early initiation of CRRT in ICU patients without AKI (Ricci et al 2010). Ideally, a

decision to start CRRT should be based on a composite index, including variables such as disease severity (e.g. SOFA score), AKI level (based on RIFLE, AKIN or KDIGO criteria), degree of fluid overload, time from ICU admission, and eventually specific biomarkers (Kashani et al. 2013).

Which Modalities and Membranes?

CRRT and related techniques are attractive not only for treatment of AKI, but also for use in various ICU conditions not primarily associated with AKI (e.g. haemodynamic instability, hepatorenal syndrome, raised intracranial pressure, acute or severe fluid overload, and persistently positive fluid balance). Yet, the Hemodiafe study, comparing IHD with CVVHDF in ICU patients, showed that both techniques performed equally well in terms of patient outcome (Vinsonneau et al. 2006). However, a recent meta-analysis confirmed better control of haemodynamics and fluid balance by CRRT (Bagshaw et al. 2008). In addition, the PICARD group showed that CRRT was more efficacious for fluid removal in AKI patients with severe fluid overload than any intermittent or semi-continuous method (Bouchard et al. 2009). Based on aggregated results of the ATN (VA/NIH Acute Renal Failure Trial Network 2008) and RENAL (RENAL Replacement Therapy Study Investigators 2009) trials, most opinion leaders recommend CRRT as the most appropriate approach in vasopressor-dependent ICU patients with AKI (Prowle et al. 2010; Schneider et al. 2013).

One important reason to embrace CRRT in this context was the observation that a majority of shock patients receiving IHD evolved towards chronic dialysis (Prowle et al. 2010). This ominous finding was recently underpinned by a meta-analysis (Schneider et al. 2013), which showed that initial IHD was associated with higher rates of dialysis dependence than CRRT in 3,500 AKI survivors, regardless of whether haemodynamic instability was present or not. More robust RCTs are awaited to solve this controversial issue.

Current research is focusing on novel dialysis membranes that can eliminate a wide spectrum and/or large amounts of unbound mediators during CRRT, such as the AN69 ST (surface treated), SEPTEX, PMMA (polymethylmetacrylate), and AN69 OXIRIS membranes (Honoré et al. 2013). The AN69 Oxiris and PMMA membranes enable capturing of endotoxin and many cytokines (Hirasawa et al. 2010). The AN69 ST membrane is also a potent cytokine scavenger. In particular, it adsorbs the high mobility group box 1 protein, a highly inflammatory upstream cytokine that is not removed by convection (Yumoto et al. 2011). Finally, the high-porosity SEPTEX membrane was shown to beneficially influence haemodynamics in unstable septic patients treated withCVVH (Morgera et al. 2006).

Polymyxin (PMX) B column haemoperfusion is a specific form of high-surface selective membrane therapy (Cruz et al. 2009). A recent clinical study using this treatment modality showed improvement of haemodynamics and mortality (Cruz et al 2009). Given their very large surface (at least 500 and up to 10,000 m^2), adsorptive columns and sorbents are commercialised as cartridges that can run with a haemoperfusion device (Honoré et al 2013).Apheresis or selective plasma exchange are other treatment options, but data regarding their use in sepsis are scarce. The cytokine filter CytoSorb effectively eliminates most inflammatory mediators with the exception of endotoxin and IL-10 (Quintel 2012).

Conclusions and Perspectives

With time, CRRT has evolved from a pure AKI treatment to a more sophisticated therapy in terms of indication, dosing and timing. Optimising CRRT filtration dose has a proven positive effect. An ultrafiltration rate of at least 25 ml/kg/h, adjusted for pre-dilution and downtime, is required for treatment of septic and non-septic patients with AKI. Practically, 30-35 ml/kg/h needs to be prescribed to deliver a dose of 25 ml/kg/h. High-volume haemofiltration in septic AKI is no longer recommended outside a clinical trial. An early start of CRRT (at RIFLE Injury level?) in septic AKI could be anticipated but further evaluation is needed. CRRT is the preferred first-line therapy in haemodynamically unstable patients with AKI. Whether haemodynamically stable AKI patients might also benefit remains to be established. Newly designed membranes with higher porosity or increased adsorption capacity may tackle the sepsis cascade by eliminating inflammatory mediators. Large trials confirming the benefit of PMX B therapy are eagerly awaited. Cartridges containing a filtration surface as high as 10,000 m^2 (e.g. CytoSorb) placed within a CRRT circuit may represent an exciting next step in treating septic AKI patients. Extended daily IHD has still some room in ICU but mostly as second line therapy.

For full references, please send a request to **editorial@icu-management.org**

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