Best Evidence in Critical Care Medicine

Continuous or intermittent renal replacement for treatment of severe acute kidney injury in critically ill patients

Article appraised

Vinsonneau C, Camus C, Combes A, et al; Hemodiafe Study Group. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. *Lancet* 2006; 368: 379–85.

Structured abstract

Background: In critically ill patients with acute kidney injury (AKI), it remains controversial whether the type of renal replacement therapy (RRT) is associated with improved clinical outcomes.

Objective: To compare the effect of continuous veno-venous hemodiafiltration (CVVHDF) *vs* intermittent hemodialysis (IHD) on survival rates in patients with AKI as part of multiple-organ dysfunction syndrome.

Design: Prospective randomized controlled trial performed from 21 French university and community medical or mixed medical/surgical intensive care units.

Methods: Patients with AKI (urea ≥ 36 mmol·L⁻¹ or creatinine ≥ 310 μ mol·L⁻¹), need for RRT, and multi-organ dysfunction syndrome (logistic organ dysfunction score ≥ 6) were considered eligible. The trial protocol was amended to incorporate oliguria (urine output < 320 mL for 16 hr) to the inclusion criteria. Patients' baseline creatinine > 180 μ mol·L⁻¹, AKI due to vascular/obstructive etiology, continued angiotensin converting enzyme inhibitor therapy, coagulopathy, uncontrolled bleeding, simplified acute physiology II score ≤ 37 , moribund state or expected death within eight days were excluded.

Intervention: Three hundred and sixty patients were randomized to start CVVHDF or IHD. Allocation was concealed and centralized. Recommendations were provided to aid in achieving optimum hemodynamic tolerance and metabolic control in both groups. For CVVHDF, recommended initial settings included blood flow ≥ 120 mL·min⁻¹, dialysate flow $\geq$

500 mL·hr⁻¹ and ultrafiltration rate ≥ 1000 mL·hr⁻¹ and filter change every 48 hr. For IHD, recommended settings included blood flow ≥ 250 mL·min⁻¹ and dialysate flow ≥ 500 mL·min⁻¹ to be performed for four hours every 48 hr. Goals for CVVHDF were to maintain serum urea < 30 mmol·L⁻¹ and for IHD to achieve a urea-reduction-ratio $\geq 65\%$ per session.

Primary endpoint: Survival at 60-days by intention-to-treat. Additional endpoints included 28- and 90-day survival, intensive care unit (ICU) and hospital length of stay, duration of RRT, renal recovery, and occurrence of adverse events. In the final intention-to-treat analysis, 99.7% (359/360) of randomized patients were included.

Results: Survival was no different at 60-days (33% for CVVHDF *vs* 32% IHD, $P = 0.98$). There was also no difference in survival at 28- or 90-days, length of ICU or hospital stay, or in the duration of RRT support or rate of recovery of kidney function. Hypothermia was more common with CVVHDF (17% for CVVHDF *vs* 5% for IHD, $P = 0.0005$).

Conclusion: These data suggest no meaningful differences in survival or several secondary outcomes when stratified by modality of RRT for critically ill patients with AKI as a part of multiple-organ dysfunction syndrome.

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Commentary

Acute kidney injury (AKI) commonly afflicts critically ill patients and generally portends an increased morbidity and mortality.¹ What is more, a majority of patients with severe AKI require, at least provisionally, a period of extracorporeal renal replacement therapy (RRT).¹

Despite extensive use of RRT in this population, there remains controversy and debate about whether the initial type of RRT, either conventional

intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT), can impact survival or recovery of kidney function.^{2,3} This is important given the health care costs and infrastructure (i.e., RRT machines, circuits, replacement/dialysate solutions, training) implications needed for delivery of both types of RRT in critically ill patients.

Increased application of CRRT for patients with hemodynamic instability has largely been predicated on evidence demonstrating its physiologic superiority to conventional IHD (i.e., greater convective clearance, better management of volume status, greater ability to optimize nutritional support, and potential for increased clearance of higher-molecular weight inflammatory mediators). Nevertheless, data establishing a link to improved clinical outcomes have been notably absent.

Accordingly, the publication of the *Hemodiafe Trial*, the largest prospective multicentre trial completed to date on this topic, was eagerly anticipated and expected to largely reconcile this dispute.⁴ This trial found no difference in survival at 60 days or in any other clinically relevant secondary outcomes assessed (i.e., lengths of stay, renal recovery) by allocated type of RRT. These findings largely support the data described in smaller studies.^{5,6} It has therefore been suggested that, given the observed absence of any survival benefit with CRRT, that use of IHD for management of AKI in critically ill patients should logically be expanded.² This argument is further supported by data showing CRRT is more costly, hence, increased use of IHD may translate into cost savings.⁷

Regrettably, such conclusions may be premature. There are a number of important caveats about this trial that deserve attention and potentially greatly undermine its value. First, this trial simply did not have sufficient statistical power to detect a meaningful difference in survival. This could potentially lead to a false assertion of no difference in survival when perhaps one existed, yet could not be detected (i.e., type II error). In fact, this trial was powered to detect a minimum 15% absolute reduction in mortality between allocated RRT groups. While logistically this may have been practical, it was unrealistic. Recent large trials in critical care medicine have concluded that a difference in survival as little as 3–4% is relevant.^{8,9} As such, this trial would have needed to enroll approximately 6,000 patients to show a mortality difference of 4%. Moreover, the authors assumed there would be a baseline mortality of 45% in those receiving IHD. Yet, the reported 68% mortality was much higher than predicted.

Second, the potential for identifying any difference in survival was further contaminated by allowing >

10% of patients to cross-over between CRRT and IHD. This undermines the validity of any direct comparison of these therapies. Such bias was unfortunately also prevalent in prior trials.⁵

Third, this trial did not standardize either the dose of delivered dialysis or timing of initiation of therapy. For CRRT, a delivered dose of at least 35 mL·kg⁻¹·hr⁻¹, when compared with 20 mL·kg⁻¹·hr⁻¹, has been shown to reduce mortality.¹⁰ Yet, the mean calculated dose delivered, after accounting for dilutional effects of pre-filter replacement fluid, was only 25 mL·kg⁻¹·hr⁻¹ (29% lower than accepted practice). For IHD, while a per session urea-reduction-ratio ≥ 65% was recommended, no data were available on the actual dose delivered. This is problematic given prior data showing that the actual dose delivered per IHD session in AKI is often significantly less than prescribed.¹¹ In addition, the authors described an unexpected and curious decrease in mortality with IHD over the trial period (relative risk 0.67 per year). This implies a modification to how IHD was actually delivered during the trial; and is further supported by the authors reporting longer mean durations of applied IHD (~ 5.2 hr). This regrettably introduces a significant bias, as the two therapies were not standardized and thus are not being validly compared.

The authors suggest that under most circumstances, critically ill patients with AKI can receive therapy with IHD.⁴ This trial also reinforces that modifications to conventional guidelines aimed at increasing the quality of IHD delivery in critically ill patients (i.e., measures such as lower blood flow rates, prolonged dialysis duration, sodium profiling, cooling of the dialysate, discontinuing vasodilator therapy) may lead to better hemodynamic tolerance and improved clinical outcomes.² These modifications for IHD, however, more accurately describe a compromise between CRRT and IHD, also known as extended daily dialysis. Extended daily dialysis is a newer hybrid technique, where IHD therapy is performed over a prolonged duration (6–12 hr). Extended daily dialysis has shown comparable hemodynamic tolerance and metabolic control to CRRT, as well as greater capacity for safely and gradually removing fluid and increasing patient mobilization.¹² Regardless, however, the data imply that this trial failed to strictly compare “conventional” IHD with CRRT.

Fourth, while no significant difference in renal recovery to independence from RRT was described in this trial, there was some suggestion of improved recovery with CRRT. However, this finding is likely not generalizable due to exclusion of patients with chronic kidney disease (CKD). Notably, CKD is

common and present in an estimated 20–30% of critically ill patients with AKI.^{1,13} Moreover, non-recovery of kidney function is an important determinant of morbidity and those with CKD are at higher risk for progression to end-stage renal disease and need for long-term RRT. Recently, two large observational studies have described greater rates of recovery to RRT independence with CRRT when compared with IHD.^{14,15}

In summary, the *Hemodiafe Trial* is the largest comparison of IHD and CRRT currently available. Regrettably, due to the concern for bias and statistical limitations, this trial contributed little to resolving the controversy around the ideal type of RRT for critically ill patients with AKI. Thus, a larger, better-designed and suitably-powered randomized trial that standardizes timing of initiation and dose delivery is still needed. In the interim, however, clinicians caring for critically ill patients with AKI should focus on the delivery of timely, adequately-dosed and safely-administered RRT, regardless of the type.

Sean M. Bagshaw MD MSC FRCPC*

Peter G. Brindley MD FRCPC RT*

Noel Gibney MD FRCPC*

Rinaldo Bellomo MD FJFICM†

University of Alberta,* Edmonton, Canada; Austin Hospital,† Melbourne, Australia

E-mail: bagshaw@ualberta.ca

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