Renal support in acute kidney injury

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Continuous renal replacement therapy is an alternative to intermittent haemodialysis in critically ill patients with acute kidney injury, especially in patients who are haemodynamically unstable. However, the definition of haemodynamic tolerance of therapy is relative, and even the most haemodynamically unstable patient might be able to be treated with intermittent haemodialysis if the technique is modified to provide more frequent sessions,[1] slower volume removal,[2] or both; or when strict protocols for haemodynamic support are followed.[3] Conversely many clinicians, intensivists, and nephrologists have realised that modern continuous therapy can offer other advantages over intermittent haemodialysis, including increased time-averaged dose, more stable volume management, enhanced drug clearance and, possibly, removal of higher-molecular-weight solutes, including inflammatory cytokines.[4]

Although evidence supporting the superiority of continuous renal replacement therapy over intermittent haemodialysis is scarce, continuous therapies have increased in use over the past one to two decades.[5] Early studies comparing continuous therapy with intermittent haemodialysis tended to select less severely ill patients for continuous renal replacement therapy, whereas later studies were done after continuous therapy had become well established and were biased toward enrolling sicker patients in their continuous arms.[6] Few randomised trials have been done. In 166 individuals, mortality was increased for patients treated with continuous therapy; however, imbalanced randomisation led to disproportionate assignment of more severely ill patients to the continuous group.[7] Additionally, interpretation of the results is confounded by high rates of crossover between groups. There was greater volume removal and better haemodynamic stability associated with continuous therapy in 80 patients randomised to continuous or intermittent treatment, but no difference in survival between groups.[8] Thus investigators[6] and even authors of guidelines[9] have concluded that insufficient evidence exists to establish either technique as better.

However, the question of which treatment is better is influenced by the nature of the task. Continuous renal replacement therapy might be better in terms of total water and solute removal over 24 h and haemodynamic tolerance, but intermittent haemodialysis can remove much more water and solute per hour, is not associated with the need for continuous anticoagulation, and is not as confining for patients who do not require immobilisation. Furthermore, although the advantages of continuous therapy are largely predicated on its performance without prolonged interruptions, that is often not the case.[10,11] The question of superiority of a modality for renal support might be artificial. Except for certain centres that are devoted to providing only one technique, most centres use both continuous therapy and intermittent haemodialysis, changing the method of treatment when clinical status changes. Randomising patients to receive one therapy or the other regardless of the conditions might yield results that are difficult to generalise to clinical practice, even if scientifically valid.

Although the study by Christophe Vinsonneau and colleagues[12] in today's *Lancet* might well fall into this category, its results are important nonetheless. First, the study shows that it is possible to compare intermittent haemodialysis with continuous renal replacement therapy in a randomised clinical trial. Unlike some previous studies, randomisation seems to have been successful and protocol adherence was good. Remarkably, only 3·3% of patients crossed over from intermittent haemodialysis to continuous therapy, despite marked haemodynamic instability. Surprisingly, about three times as many patients (9·7%) crossed over in the opposite direction in violation of the protocol. Reported reasons for these crossovers

included contraindication to the use of anticoagulants, insufficient metabolic control, and technical problems, including recurrent filter-clotting. This crossover rate is unusual because centres with significant experience of continuous therapy find that such therapy can be done without any anticoagulation in patients at risk for bleeding, and insufficient metabolic control is seldom a reason to switch to intermittent haemodialysis. Thus there might have been a bias towards intermittent haemodialysis in this study, a concern heightened by the interesting finding that mortality in the intermittent haemodialysis arm decreased significantly over time, whereas mortality in the continuous therapy arm remained stable. Did management protocols aimed at improving tolerance of therapy disproportionably benefit intermittent haemodialysis?

A second difficulty with Vinsonneau and colleagues' study is that the dose of therapy was not specified in the protocol in either treatment arm and the delivered dose in both arms might have been lower than optimum. A delivered dose of continuous renal replacement therapy at least 35 mL/kg per h is associated with reduced mortality compared with 20 mL/kg per h.[13] The mean delivered dose in Vinsonneau's study of 29 mL/kg per h falls in an intermediate range. In the intermittent haemodialysis arm, treatment was provided every 48 h if the patient was anuric or oliguric, or to maintain a urea less than 40 mmol/L. Although a urea reduction ratio of greater than 65% was targeted, there was no assessment of the delivered dose of intermittent haemodialysis after treatment was started. In a previous study, mortality was reduced from 46% with alternate-day intermittent haemodialysis to 28% with daily intermittent haemodialysis.[1] An important observation in Schiffl's study,[1] confirming earlier reports,[14] was that the actual delivered dose of therapy of each intermittent haemodialysis session was significantly less than prescribed. Thus, despite the fact that the mean time-averaged urea concentration of 15·7±7·5 mmol/L was lower in Vinsonneau's study than the similar value reported in the daily treatment arm of the Schiffl study, this indicates a lower rate of urea generation rather than higher solute clearances. Nevertheless, Vinsonneau's study suggests that improved survival depends on how renal support is provided—as shown by the improvement over time in the intermittent haemodialysis arm. The study also shows that virtually all critically ill patients with acute renal failure can be treated with intermittent haemodialysis. Whether this approach is as good as or even better than treating all patients with continuous renal replacement therapy cannot be answered by Vinsonneau's study, given its limited statistical power.

Practical questions, such as whether a patient will do better with continuous therapy or intermittent haemodialysis and when is it most appropriate to switch from one method to the other, remain unanswered. Unfortunately, protocols that force use of one therapy or the other will not answer these questions.

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