Dialysis in Intensive Care Unit Patients with Acute Kidney Injury: Continuous Therapy is Superior

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When comparing continuous renal replacement therapy (CRRT) with intermittent therapy, it is wise to remember that the very reason for the development and introduction of CRRT into clinical practice in the late 1970s and early 1980s was to compensate for the clear inadequacies of conventional intermittent hemodialysis (IHD) in the treatment of critically ill patients with multi-organ failure (1). If there had not been serious problems with conventional IHD, CRRT would not be the subject for discussion.

In the ensuing 10 to 15 yr, substantial clinical experience accumulated in the use of CRRT, and its technology evolved a great deal from adaptive arteriovenous techniques to dedicated CRRT machines for venovenous therapy. During this period, multiple studies confirmed the many physiological advantages of CRRT over conventional IHD (3 to 4 h/d every second day as typically delivered to end-stage renal failure patients) (2–7). This was especially true in centers that had developed appropriate and necessary physician and nursing expertise in its application. Importantly and predictably, not a single comparative study showed IHD to be physiologically better than CRRT—ever.

In response to such evidence, over the last two decades physicians and nurses worldwide have literally "voted with their feet" in many countries by increasingly shifting from conventional IHD to CRRT (8). In fact, conventional IHD has essentially disappeared from the Australian intensive care unit (ICU) (9). However, the controversy as to which therapy is "best" from the point of view of mortality or other major clinical outcomes (duration of ICU stay, hospital stay, and rate and time to renal recovery) remains. This is because no sufficiently powered, multicenter, randomized controlled trials have yet been conducted to assess these outcomes and because there have been major and continuing changes in what experts consider optimal continuous therapy or optimal intermittent therapy.

So far, as mentioned above, continuous and intermittent therapies have only been compared in several small studies. Unfortunately, none of these studies were sufficiently powered to detect a realistic difference in relevant clinical outcomes between these two therapies. As if that was not enough, all studies minimized any chance of detecting a differential effect on outcome by allowing frequent crossover from continuous to intermittent therapy in ICU. To draw a comparison, this approach would be equivalent to comparing the effect of metoprolol on survival after myocardial infarction to that of nifedepine, but designing a study where patients randomized to metoprolol crossed over to nifedepine on day one or two (*e.g.*, once their heart rate slows down) according to physician judgment. Inevitably, finding no difference in the incidence of secondary myocardial ischemia or death, the investigators would then come to the conclusion that metoprolol confers no benefit to patients with myocardial infarction. Such a trial would never be allowed to proceed by the Food and Drug Administration, as it could not possibly answer the question at hand. Yet, this is how continuous therapy has, so far, been compared with intermittent therapy.

Despite these crucial shortcomings in trial design, it is still useful to review additional aspects of such trials. In the first, Mehta *et al.* (10) randomized 166 critically ill patients with severe acute kidney injury to either CRRT or IHD therapy. There was a significantly higher ICU mortality rate in subjects randomized to CRRT (60% *versus* 42%; $P = 0.02$). After *post hoc* adjustment for severity of illness, the increased risk attributed to CRRT was no longer statistically significant (odds ratio 1.6). This is because there was clear baseline imbalance with patients randomized to CRRT having greater illness severity (higher APACHE III and greater incidence of liver failure). The reasons for such imbalances remain unclear. However, several other aspects of this study are still of interest. First, patients were allowed to cross over (see above), making a true comparison impossible. Second, patients with hemodynamic instability (mean arterial pressure <70 mmHg) were excluded. These are the very patients where the advantages of CRRT are most evident. This selection bias was the expression of an acknowledged lack of equipoise: In such patients intermittent therapy is physiologically inferior. Third, despite these limitations, one very relevant observation emerged: If patients received a sufficient trial of CRRT and survived, renal recovery was dramatically increased (92.3% *versus* 59.4%; $P < 0.01$). In other words, intermittent therapy delayed or impeded renal recovery. Fourth, CRRT delivered superior control of uremia.

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In another single-center randomized trial, 125 patients were randomized to CRRT or IHD. In-hospital mortality rates did not differ by treatment assignment (47% for CRRT *versus* 51% for IHD; $P = 0.72$) (11). However, this trial suffered from extraordinary logistic constraints in that these patients could not be randomized on a 1:1 basis because of a lack of CRRT machines or staff who were untrained in CRRT. This is hardly the environment that would create a scientific "level playing field" for the two therapies. More importantly, if the near 4% absolute decrease in mortality still seen with CRRT were true, it would have taken 5000 patients to detect it at a β of 0.2 and an α of 0.05. The investigators randomized only 125 patients! Such a 4% decrease might seem small but would be clinically relevant because it would imply that the number needed to treat to save one life is only 25. The number needed to treat to save one life with percutaneous coronary intervention in patients with myocardial infarction with ST segment elevation is 50 (12).

In a third single-center prospective randomized trial, 80 patients were randomized to treatment with CRRT or IHD (13). Survival was 67.5% for CRRT and 70% for dialysis. Again the study was dramatically underpowered to detect differences in survival between the two therapies and crossover from CRRT to IHD occurred in 22.5% of CRRT patients. Of interest, this trial confirmed the hemodynamic problems associated with IHD as 40% of patients required an increase in vasopressor therapy during initial treatment with IHD compared with only 12.5% for CRRT ($P = 0.005$). In this study, CRRT was associated with a 6-d reduction (close to 15%) in hospital stay. Nine patients were converted from CRRT to IHD because of frequent filter clotting, a concept that seems strange to practitioners who only use CRRT in the well-established era of citrate and regional heparin/protamine anticoagulation.

Most recently, the Continuous Venovenous Haemodiafiltration *Versus* Intermittent Haemodialysis for Acute Renal Failure in Patients with Multiple-Organ Dysfunction Syndrome: A Multicenter Randomized Trial (HEMODIAFE) Study Group reported the results of a randomized multicenter study comparing the results of CRRT to IHD in 360 critically ill patients with acute kidney injury (14). Overall, there was no difference in the primary end point of 60-d survival (33% with CRRT *versus* 32% with IHD). However, the authors noted an unexpected and significant increase in survival rates within the IHD group over time (relative risk 0.67/yr), an effect not seen in the CRRT group. This creates a major bias. How was IHD changed? Who changed it? Was advice offered to trial sites? This is of significant concern because if this had not happened and the initial trend in outcome seen with IHD had continued, the conclusions would have been diametrically opposite. In this regard, it is of interest to see how the average duration of dialysis became 5.2 h (significantly longer than conventional IHD), while CRRT continued to deliver a calculated creatinine clearance of 25 ml/kg per h (not 29 ml/kg per h as reported by the authors who did not correct for the effects of predilution). Such clearance is much lower that what is considered an optimal CRRT dose (15). Again, this trial reported a 10% crossover from CRRT to IHD. Furthermore, this study excluded people with chronic acute renal failure who normally make up about 30% of patients receiving acute renal replacement therapy (8) in the ICU. These are the patients most at risk of developing end-stage renal failure after acute renal replacement therapy and the ones most likely to benefit from CRRT in terms of renal recovery. Accordingly, dialysis dependence at hospital discharge was an extraordinary 1 out of 360 patients. The relevance of such a selected population to the real world situation is limited.

Finally, two additional key aspects of any interpretation of all studies in this field are the variation in how CRRT techniques are offered and delivered and the training and knowledge of the caregivers as well as the fact that none of the trials standardized the timing of dialysis or concurrent care offered to patients. These factors are very relevant to determining outcomes and need to be addressed in future studies.

Recently, the Program to Improve Care in Acute Renal Disease (PICARD) Group compared the outcomes of different renal replacement therapy modalities (16). This analysis incorporated five sites in the United States and used multivariable regression analysis and a propensity score approach to address the effect of confounding variables. Within the PICARD cohort, using this methodology, the provision of CRRT in comparison to IHD was associated with a significantly higher relative risk for mortality. However, patients with CRRT were obviously sicker: they had more organ failure (central nervous system, liver, hematologic and respiratory disorders), higher mechanical ventilation rate, more sepsis, lower blood presssure, higher total bilirubin, lower platelet count, and so on. These observations cast serious doubt on the accuracy of this analysis and the ability of a propensity analysis to make sufficient adjustments.

Thus, there is clear lack of suitably designed, multicenter, randomized controlled trials where all ICU patients with acute renal failure are randomized to either CRRT or IHD (doses to be defined) from start to finish. Until such a trial is done, the question of *clinical* superiority cannot be answered.

Reforming IHD and CRRT

Whatever future trials might wish or might be able to compare, the evidence is clear that renal replacement therapy is not like a "tablet." Its effects are modified by the expertise of those who prescribe it and guide it (physicians) and those who execute it (nurses). For example, it is clear from the HEMODIAF study that the quality of IHD can be improved and better outcomes follow. Another study has recently confirmed that priming the dialysis circuit with isotonic saline, setting dialysate sodium concentration >145 mmol/L, discontinuing vasodilator therapy, and setting dialysate temperature <37°C (17) improves IHD-related outcomes. Finally, the introduction of slow extended daily dialysis (SLEDD) introduces the final step in the rehabilitation of dialysis in the ICU (18). Indeed, as IHD becomes more and more like CRRT through SLEDD, the protagonists of CRRT will be filled with delight: Their battle was not with dialysis *per se*, but rather with the mindless application of it in conventional mode to critically ill patients. When IHD in the ICU is reformed, adjusted to account for the needs of the critically ill, and extended to 6 h (or 8 or maybe even 12 h) so

that fluid removal is performed safely and uremic control is optimized, little of the controversy will remain.

As a continuous extracorporeal therapy, CRRT frequently requires continuous anticoagulation, which may increase bleeding risk. Thus, it also needs reform. Citrate and regional heparin/protamine anticoagulation are safe and effective but underused. This needs to change. Machine operation and safety need more attention and specific training for personnel is essential for full compliance to required operations (19). Finally, and more importantly, the dose of CRRT might well require readjustment because two recent randomized controlled trials show that increasing the dose of CRRT improves survival (20). All studies that compare IHD to CRRT have used much lower CRRT doses than those shown to improve survival. The optimal weekly Kt/V for CRRT in an 80-kg man would appear to be close to 10. If multicenter trials currently under way confirm this observation, CRRT will also have to reform. More importantly, by implication, its twin (IHD) will have to reform further as well to be able to deliver such an optimal dose intermittently. Both techniques also have to look further than dose. The issue of timing of intervention is likely very important and yet not studied well so far (21). Timing of cessation may be equally important but has not yet been studied. Much work needs to be done in the field of acute renal replacement therapy.

Conclusion

In conclusion, the evidence that CRRT is physiologically superior to conventional IHD is clear. The evidence that this physiologic superiority can be translated into clinically important gains is not. Appropriately powered, designed, conducted, and analyzed studies have simply not yet been done. In addition, the evolution of both therapies presents a fluid environment where the terms of comparison constantly change. The correct focus for clinicians might actually be not so much to compare the two, but to make sure that, whatever therapy is applied, it is done right. Clinicians need to ensure that patients receive the best therapy for their condition at a given time in the course of their illness in the ICU, receive it safely, in a timely fashion, with the correct dose, and for long enough. The evidence is clear that this does not normally happen. Spending time comparing two kinds of cars seems futile if users have not yet learned to drive safely.

Disclosures

None.

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See the related editorial, "Comparing Dialysis Modalities for Critically Ill Patients: Are We Barking up the Wrong Tree?" on pages 413–415.