Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey

The RENAL Study Investigators

ABSTRACT

Background: There are few published data on the practice of renal replacement therapy (RRT) in Australian and New Zealand intensive care units. These data are essential for designing trials to compare new treatment approaches with "standard care".

Design: A prospective survey of RRT practice in ICUs interested in participating in the Australian and New Zealand Randomised Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy in ICU Trial.

Setting and participants: 34 ICUs in Australia and New Zealand.

Outcome measures: Information on choice of therapeutic modality, technique, dose prescription, dose adjustment, technology, and replacement fluid composition before the initiation of the trial.

Results: All ICUs used continuous veno–venous RRT (CRRT) as the therapy of first choice. The most common technique, continuous veno–venous (CVV) haemodiafiltration, was used in 62% (21/34) of ICUs, followed by CVV haemofiltration in 35%, (12/34) and CVV haemodialysis in 3% (1/34). Replacement fluid was given pre-filter (pre-dilution) in most cases (94%). Lactate-based replacement fluid or dialysate accounted for 55% of all commercial fluid supplied by pharmacies to participating ICUs, bicarbonate-based fluid for 43% and citrate-based fluid for 2%. In all ICUs, CRRT was prescribed by critical care physicians alone, according to unit policy. The effluent dose varied from 1.5 L/h to 4 L/h, and was not adjusted to body weight in any of the ICUs surveyed. The median (and mode) effluent dose was a fixed regimen of 2 L/h. The most commonly used machine was the Gambro Prisma (38%), followed by the Gambro AK 10 blood module combined with volumetric fluid infusion pumps (29%), and the Kimal Hygieia (18%). The median (and mode) blood flow was 200 mL/min. Given the information supplied on pre-dilution rates, the median blood flow, and estimates of haematocrit and body weight based on previous surveys, the "typical" prescribed CRRT urea clearance dose ("standard") before the RENAL trial was estimated to be approximately 25 mL/kg/h.

Conclusions: These findings provide insight into RRT practice in ICUs in Australia and New Zealand, as well as useful data to assess whether the control group in the RENAL trial receives "standard" therapy as delivered in Australian and New Zealand trial centres at the time.

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There are limited data on the current practice of renal replacement therapy (RRT) in Australian and New Zealand (ANZ) intensive care units. Studies conducted in the state of Victoria and in Australia in the mid-1990s[1,2] showed that continuous RRT (CRRT) was the dominant modality of treatment for ICU patients with acute kidney injury, and that most CRRT prescription was by critical care physicians. These studies reported limited information on RRT technique, and no information on the dose of CRRT prescribed or comparisons with national or international practices.

Data from the United States and Canada covering the same period indicated that practice in those countries clearly differed from ANZ practice, with intermittent haemodialysis (IHD) being the most common modality, and nephrologists the most common prescribing specialists.[3,4] These survey data were more recently confirmed in a multicentre US study.[5] The use of slow extended daily dialysis (SLEDD) was uncommon. Again, as in the ANZ studies, no information was provided on the dose of RRT prescribed.

An international survey conducted in 2004[6] obtained some information on dose, but these data were confined to patients with sepsis and acute kidney injury. More recently, a US survey involving all centres participating in the Veterans Affairs/National Institutes of Heath (NIH) Acute Renal Failure Trial Network (ATN) study, obtained information on modality, technique and dose of RRT from clinicians, to establish normative data for a study control group.[7] The investigators confirmed that IHD was the dominant RRT modality, and that dose was rarely adjusted to body weight. They estimated that the "average" prescribed dose corresponded to a weight-based dose of 20–25 mL/kg/h. This dose was similar to that recently reported in an international study of more than 50 ICUs in 24 countries,[8] and demonstrated that the results of a randomised controlled trial of CRRT dose published in 2000[9] have not been widely adopted into clinical practice.

A large-scale study to determine the optimal dose for CRRT was designed in 2004 by ANZ critical care researchers of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS

Table 1. Survey questions asked of ICU directors

- Who prescribes RRT in ICU patients with AKI?
- Which RRT modality does your unit use as treatment of first choice in critically ill patients with AKI?
- Is RRT prescription practitioner-dependent or based on unit protocol?
- If CRRT is the therapy of choice, what is the technique of choice?
- If replacement fluid was given, where in relation to the filter was it given (before the filter or after the filter)?
- What RRT machines do you use for CRRT?
- What is the typical pump blood flow during CRRT in your unit?
- What is the typical dialysate flow rate during CRRT?
- What is the typical replacement fluid flow rate during CRRT?
- Is the dose of RRT the same for all patients or is it adjusted to body weight?
- What is the replacement fluid/dialysate buffer typically used in your unit?

RRT = renal replacement therapy. AKI = acute kidney injury. CRRT = continuous renal replacement therapy.

CTG) and George Institute for International Health. The study — the Randomised Evaluation of Normal vs. Augmented Level (RENAL) Replacement Therapy Trial — is a multicentre, randomised, controlled trial in critically ill patients with acute kidney injury that compares CRRT at an effluent dose of 25 mL/kg/h versus 40 mL/kg/h. In the absence of robust data about "average current clinical practice" in ANZ, the appropriate dose for the control arm of the trial was unclear. To obtain information on current clinical practice in the ICUs planning to participate in the RENAL trial, we conducted a survey of renal replacement therapy practice in those ICUs.

Methods

Directors or principal investigators of ICUs interested in participating in the study were emailed a questionnaire in October 2004, requesting information on their practice (Table 1). After determining which ICUs used CRRT as the technique of choice, we obtained specific information from each ICU or their pharmacy detailing the amount of commercial fluid acquired in the preceding 6 months to establish current unit use of lactate, citrate or bicarbonate fluids in exact detail.

Estimation of urea clearance dose

To determine measure of the dose of RRT expressed as mL/kg/h, we estimated urea clearance using the above data on CRRT technique, published data on average body weight for a cohort of Australian patients treated with CRRT,[8] and published data on haemoglobin values in Australian ICU patients.[10]

The estimated urea clearance dose (U Cl) was calculated using Equation 1:

$$U\ Cl = [U_{effl}] \times Q_{effl} / [U_{fil}]$$

where $[U_{effl}]$ is the concentration of urea in the effluent (mmol/L), Q_{effl} is the rate of effluent generation (mL/min), and $[U_{fil}]$ is the concentration of urea in the blood within the filter (mmol/L).

This final variable can be calculated from Equation 2:

$$[U_{fil}] = [U_{pl}] \times [1 - Q_{rf}/Q_p]$$

where $[U_{pl}]$ is the urea concentration in plasma (mmol/L), Q_{rf} is the flow rate of the pre-filter replacement fluid (mL/min), and Q_p is the plasma flow into the filter (mL/min).

Q_p in turn can be calculated according to Equation 3:

$$Q_p = Q_b \times [1 - Htc]$$

where Q_b is blood flow into the filter set by the blood pump (mL/min), and Htc is the patient's haematocrit as a fraction of 1 (eg, haematocrit of 30% = Htc of 3).

Data analysis and presentation

Aggregate data are summarised using descriptive statistics. The choice of technique is presented as percentage of surveyed units using a given CRRT approach, as all data were unit-based rather than practitioner-based. Using this method, we describe the percentage of units using a specific technique of CRRT, the average volume of effluent generated, and the percentage use of pre-dilution. For CRRT machines, we present values as the percentage of all machines in use that belonged to a particular model. Finally, for the use of different fluids, we describe the percentage of each given fluid supplied by pharmacies to participating units over a 6-month period.

Results

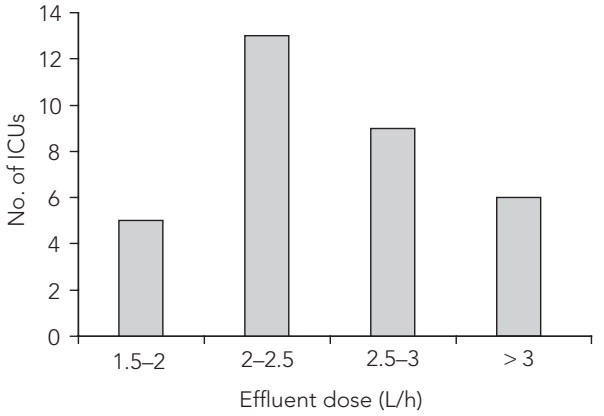
We obtained information from 34 ICUs. An additional ICU, which joined the RENAL trial in 2006, was not surveyed.

All investigators reported applying protocols where all practitioners in that ICU prescribed RRT according to the agreed approach.

Type of renal replacement therapy

In all ICUs, the therapy of first choice was veno–venous CRRT, which was applied initially to all patients with acute kidney injury. This therapy was applied until recovery to independence of RRT, discharge or death to all patients in 23 of 34 units. In the remaining 11 units, IHD or SLEDD was occasionally prescribed in clinically selected patients (estimated as < 10%) who were haemodynamically stable and approaching ICU discharge. If IHD was applied, its prescription was left to the nephrology unit that would be responsible for the patient's renal condition after ICU discharge. If SLEDD was applied, it was typically under the prescription

Figure 1. Number of ICUs practising CRRT in each hourly effluent dose bracket in Australia and New Zealand



CRRT = continuous renal replacement therapy.

of the critical care physician, with unit protocols less strictly defined than for CRRT. No further details were obtained on IHD and SLEDD dose prescription.

Method of continuous renal replacement therapy

All ICUs used only veno–venous CRRT techniques. The most common technique was continuous veno–venous haemodiafiltration (CCVHDF), which was used in 21 ICUs (62%), followed by CVV haemofiltration (CCVH), which was used in 12 ICUs (35%), and CVV haemodialysis (CCVHD), which was used in one ICU (3%). When replacement fluid was used, it was delivered before the filter (pre-dilution) in 94% (32/34) of ICUs. The median reported blood flow during CRRT was 200 mL/min. When using CVVHDF, 91% (19) of ICUs reported delivering dialysate and replacement fluid at a ratio of 1 : 1.

Pharmacy reports revealed that lactate-based fluid accounted for 55% of all acquired commercial replacement fluid and dialysate, bicarbonate-based fluid for 43%, and citrate-based fluid for 2%.

The most commonly used CRRT machine was the Prisma (Gambro, Lund, Sweden) (38%, 13), followed by the Gambro AK-10 blood module combined with volumetric fluid infusion pumps (29%, 10), and the Hygieia (Kimal, Uxbridge, UK) (18%, 6). Where a Prisma machine was used, blood flow was prescribed at between 150 and 180 mL/min in all cases. Where a Prisma was not used (62%), blood flow of 200 mL/min was applied in all cases.

No ICU reported dosing CRRT according to patient weight. All used a fixed-dose regimen; the fixed dose was 2 L/h of effluent generation in 62% of ICUs, with this value ranging from 1.5 L/h to 4 L/h (Figure 1). The average effluent dose in ANZ trial centres was 2280 mL/h, typically delivered in CVVHDF mode with a dialysate to replacement fluid ratio of 1 : 1, and pre-filter delivery of replacement fluid, in the setting of a typical blood flow of 200 mL/min.

Urea clearance dose

We used the above information and estimates of body weight (80 kg) and haematocrit (0.25) to calculate the approximate typical weight-adjusted urea clearance dose delivered in ANZ before the RENAL trial. This was calculated to be 24.3 mL/kg/h.

Discussion

This survey of RRT practice in 34 ANZ hospitals participating in the RENAL trial had several important findings. First, in all centres, the therapy of choice at the time of trial inception was CRRT, with very limited use of IHD or SLEDD, which were typically delivered in the subacute phase before ICU discharge. Second, it was not practice to adjust dose according to body weight. Third, CVVHDF was the technique of CRRT most commonly used, typically using pre-filter fluid replacement in a ratio of dialysate to replacement fluid flow rate of 1 : 1. Fourth, prescribed blood flow rate varied from 150 to 200 mL/min, with 200 mL/min being the most commonly prescribed rate. Fifth, pharmacy-supplied fluids contained lactate as buffer in 55% of cases, bicarbonate in 43%, and citrate in 2%. Finally, we were able to estimate a likely "average" weight-adjusted urea-clearance equivalent dose before trial initiation and found it to be close to 25 mL/kg/h.

Our finding that CRRT is the treatment of choice applied to all patients at the start of RRT in all ICUs contrasts starkly with the recently published pre-trial findings of the US Veterans Affairs/NIH ATN study.[11] The latter reported that IHD was the most common RRT modality applied to the treatment of critically ill patients with acute kidney injury in 27 academic university-affiliated and veterans affairs medical centres in the US. Moreover, we found that the prescription of RRT was exclusively done by critical care physicians in ANZ, contrasting with nephrologists in the US, and that such prescription was based on unit-developed protocols in ANZ, contrasting with practitioner preference in the US. Finally, in contrast to US centres, ANZ centres did not use arterio–venous therapy. These differences in the prescription and practice of RRT in ANZ compared with the US are consistent with previous reports[1-4] and echo a long-standing and unresolved debate[12] on how best to treat critically ill patients with acute kidney injury. They also highlight the impossibility in ANZ of designing a dose study that is not fully based on the narrow concept of CRRT dose, rather than the broader concept of RRT dose. In this regard, it is likely that the Veterans Affairs/NIH ATN trial and the

RENAL trial may prove complementary in their findings, as they assess the issue of dose in two distinct health care contexts, with two different styles of practice. Together, these studies will greatly strengthen our knowledge of the effect of RRT dose on patient outcomes.

As in the US, ANZ clinicians do not adjust RRT dose to body weight. The reason remains unknown, but it highlights the need to know the average dose being used (in L/h) and the average weight of patients with acute renal failure (80kg) in order to design a trial that prescribes an "average weight-adjusted dose" to its control group. It is important to note several differences from the Veterans Affairs/NIH ATN trial survey in terms of the practice of CRRT. Although most of the CRRT in the US trial centres was conducted using CVVHD, only one ANZ centre used this technique. CVVHDF was the most common CRRT technique used in ANZ. The US centres also used CVVHDF commonly, and both US and ANZ centres used CVVH in about a third of patients.

Such use of CVVHDF and CVVH implies the administration of replacement fluid. Knowledge of the site of replacement fluid administration is important, as the average urea clearance dose ceases to be equivalent to the effluent dose when pre-filter fluid replacement is applied. Taking into account these factors, our survey revealed a self-reported effluent dose which was 25% higher than the mean self-reported "effluent dose" from the Veterans Affairs/NIH ATN trial investigators. These observations suggest that ANZ practitioners, while not prescribing CRRT on the basis of body weight or at the doses used in the study by Ronco et al,[9] appear to be delivering an average dose that is 25% higher than that delivered to the control group in the Ronco et al study.

When the average effluent dose was corrected for the effect of pre-dilution, blood flow, likely average haematocrit[10] and body weight,[8] the typical weight-adjusted urea clearance dose delivered in our trial centres was about 25 mL/kg/h. As recently argued in other trials of critically ill patients,[13] this finding suggests that, in the RENAL trial, control patients should receive this same dose using the CVVHDF technique and a dialysate to replacement fluid ratio of 1 : 1. This is representative of the control group treatment dose in the RENAL trial. However, in the RENAL trial, the practice of delivering replacement fluid in the pre-filter position was changed to avoid the solute dilution effect of such an approach. This effect would lead to greater solute dilution (and decreased urea and creatinine clearance) in the high-dose group compared with the low-dose group, and would significantly diminish the dose separation between the two treatments. Accordingly, it was agreed that post-filter replacement fluid administration was necessary.

The choice of fluids for replacement fluid and dialysate reported in our survey also differed from that reported in the US, with much less use of citrate-based fluids. We found that lactate-based fluids were used most commonly, but that use of bicarbonate was also quite common, representing 43% of all fluids used. Citrate-based fluids represented only 2% of total consumption. All ICUs used commercial fluids, with the same type of fluid used for both replacement fluid and dialysate. The nature and concentration of the buffer can have profound effects on acid–base balance; in particular, lactate-based fluids given at high dose can induce hyperlactataemia.[14] This effect would have led to a differential impact on blood lactate between the two study groups and generated a major confounder. Accordingly, it was agreed that in the RENAL study, all patients should receive CVVHDF using bicarbonate-based fluids with an identical concentration of bicarbonate.

Our study has both limitations and strengths. The accuracy of the responses to the survey could not be independently verified, and the description of CRRT practice was self-reported rather than an observation of actual practice. However, there was no reason for ICUs not to report their practice as accurately as possible, and an approach based on self-report was also used by the Veterans Affairs/NIH ATN study. The estimate of the typical prescribed dose relies on assumptions concerning likely mean haematocrit and body weight. However, as we used previously acquired and published data from ANZ ICUs,[8,12] these estimates are likely to approximate the actual value in the population under study. In addition, if the mean haematocrit was 0.3 rather than 0.25, the estimated dose would decrease by only 1.65 mL/min. Information obtained as part of the RENAL trial will confirm or refute the accuracy of our assumptions. We did not obtain specific information on the prescription of IHD and SLEDD as we estimate, from the responses obtained, that patients in ANZ ICUs spend < 5% of their RRT time receiving a therapy other than CRRT. In contrast to other studies of RRT practice, our study obtained verifiable data (from hospital pharmacies) on the type of commercial fluids used, which gave us a precise estimate of fluid choice and amount.

In conclusion, we surveyed self-reported practice in RENAL trial centres before the start of the trial to ensure that the dose to be delivered in the control group of the trial was consistent with existing standard therapy. These valuable data tell us much about current dialysis treatment for acute kidney injury in ANZ ICUs, as well as confirming that the treatment given to the lower-dose group in the RENAL trial is consistent with standard ANZ practice.

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