Update of Renal Replacement Therapy in the ICU

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Introduction

In 2004, the term Acute Kidney Injury (AKI) was proposed to represent the entire spectrum of acute renal failure (ARF) with clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure. The reported prevalence of AKI in critically ill patients could be as high as 25% in some developed countries, and only about 4% of this group received renal replacement therapy (RRT), with an ensuing hospital mortality up to 60%. Controversies exist in many aspects of RRT for AKI despite decades of development. However, definitive findings on the dose of RRT were available last year. It is hoped that, with the continued international collaboration, a clearer picture would emerge in other areas of RRT.

Classification of Acute Kidney Injury

The RIFLE Classification

In evaluating the clinical efficacy in AKI studies, meaningful conclusions can only be drawn when there is a common standard of reference. An expert panel from the Acute Dialysis Quality Initiative (ADQI) established a consensus definition called RIFLE in 2002 (www.ADQI.net). In summary, the acronym RIFLE refers to three severity grades (in ascending order of Risk, Injury and Failure) and two clinical outcomes (Loss and End-stage renal failure). The severity grading is based on the change from baseline of either serum creatinine or urine output, whichever is greater. In the subsequent years, RIFLE criteria have been validated by different groups worldwide. With these new criteria, the prevalence of acute kidney injury is 2-to-10 fold greater than previously reported, ranging from 15.4 to 78.3%. RIFLE was also valuable in outcome prediction and correlated well with mortality.

The AKIN Classification [Table 1]

However, according to the data that have emerged using RIFLE staging criteria, smaller changes in serum creatinine than those considered in the RIFLE criteria might also be associated with adverse outcomes. The ADQI group, and representatives from three nephrology societies (American Society of Nephrology, International Society of Nephrology and National Kidney Foundation) and the European Society of Intensive Care Medicine met and decided to modify the RIFLE criteria. A new classification system, the Acute Kidney Injury Network (AKIN) Classification, was developed. It retained the emphasis on changes in both urine output and serum creatinine [Table 1]

Indications & Timing for RRT

The usual indications for initiating RRT are:

1. Fluid overload unresponsive to diuretic treatment
2. Hyperkalaemia (>6.5 mmol/L or rapidly rising level)
3. Azotaemia (urea >36 mmol/L)
4. Severe acidemia (pH <7.1)
5. Oliguria (urine output <200ml in 12 hours) or anuria (urine output < 50ml in 12 hours)
6. Uraemia complications like bleeding, pericarditis or encephalopathy

However, in the past decade, the indications for RRT have been extended widely to include many other non-renal indications including:

1. Drug overdose with dialysable or filtratable toxins
2. Patients requiring a large amount of fluid, parenteral nutrient, or blood product but at risk of developing pulmonary oedema or acute respiratory distress syndrome
3. Cardiac failure
4. Hyperthermia or hypothermia (core temperature > 39.5oC or <30oC)
5. Severe dysnatraemia ([Na] >160 mmol/L or < 115 mmol/L)
The concept of ‘prophylactic haemodialysis’ was first introduced in 1960. Patients with ARF receiving early dialysis tended to have better wound healing, fewer haemorrhages, improved nutritional support and better survival. Since then, blood urea has been regarded as one of the markers for the timing of intervention; the threshold having decreased from 54 mmol/L in the 1960s to 33 mmol/L in 1970s. In the Conger’s study of post-traumatic ARF, five out of eight patients survived after receiving early dialysis at a mean blood urea of 18 mmol/L; while only two out of 10 survived when dialysis was initiated at a mean urea of 43 mmol/L.

Survival benefit was also demonstrated in patients suffering from ARF after cardiac surgery. One recent study addressed early versus late intensive initiation of continuous veno-venous haemodiafiltration (CVVHDF) in patients with less than 100 mL urine in the 8 consecutive hours after operation. Early versus late initiation (average lapse 0.88 vs 2.56 days) was associated with reduced ICU stay (8 vs 12 days), reduced ICU mortality (18 vs 48%), and reduced hospital mortality (24 vs 56%).

Nevertheless, this observed benefit could not be repeated in the Bouman’s study. One-hundred and six critically ill patients were prospectively evaluated to assess the combined effect of early against late-initiation as well as low-volume (LVHF) against high-volume haemofiltration (HVHF). Patients were randomised into one of the three groups: early HVHF (72-96 L/day), early LVHF (24-36 L/day), and late LVHF (24-36 L/day). On average, the early group started haemofiltration 7 hours after inclusion with the mean starting urea of 17.1 mmol/L; while the late group starting 42 hours after inclusion with a mean urea of 37.4 mmol/L. There was no difference in 28-day mortality nor renal recovery among the three groups.

Thus, the best evidence on the optimal timing for initiating RRT is still lacking and more studies are needed to address these issues. Based on the currently available data and the author’s experience, early initiation of RRT is preferable.

### Dose of Renal Replacement Therapy

#### Dose Required

While in end-stage renal failure, the delivered spKt/V of 1.2 per dialysis (or urea reduction ratio of 65%) are the accepted minimal standards in reducing morbidity/mortality. The minimum dose for patients with ARF has once been a great controversy in the field of Intensive Care. Thanks to the recent release of two large randomised control trials on the dose of RRT for patients with ARF, it has been concluded that there is no evidence to support the use of continuous renal replacement therapy (CRRT) at a dose greater than 25 mL/kg/hour. A summary of studies on dosing and outcome in CRRT is listed in Table 2.

The ATN trial (Acute renal failure Trial Network) published in 2008 in the United States did not show any survival benefit with intensive dialysis therapy. This study recruited 1164 critically ill patients with ARF to compare any mortality difference between the conventional dose group with the more intense dose group. The rate of death was similar; 53.6% in the intensive therapy and 51.5% in the less-intense therapy groups. There was no difference in the duration of RRT or recovery of renal function.

Similarly, the RENAL trial (Randomised Evaluation of Normal against Augmented Level of renal replacement therapy in the ICU) conducted by the Australian and New Zealand group showed no 90-day mortality difference between the conventional dose group and the intensive therapy group (44.68% vs 44.66%, p=0.993). This study recruited 1,465 patients with severe ARF in ICUs, who were randomised to receive post-dilutional CVVHDF at 25 mL/kg/h in the conventional group against 40 mL/kg/h in the intensive therapy group. The primary outcome of 90-day mortality showed no difference between the two dosages, and besides, all secondary outcome indicators including ICU mortality, hospital mortality, mechanical ventilation day, ICU length of stay, hospital length of stay, RRT day, RRT dependence at day 28 and day 90 also showed no difference.

### High-volume Haemofiltration (HVHF) in Sepsis Patients

For patients with severe sepsis or septic shock, there is an overwhelming systemic overflow of pro-inflammatory and anti-inflammatory mediators, leading to generalised endothelial damage, multiple organ dysfunction and altered cellular immunological responsiveness. The removal of sepsis pro-inflammatory and anti-inflammatory mediators may help in the treatment of severe sepsis. Cytokines levels in sepsis were found to be lowered only with HVHF (~45 mL/kg/h) but not conventional continuous veno-venous haemofiltration (CVVH) (17 mL/kg/h). Early animal studies and small scale human trials provided good data on improving the haemodynamic status and survival with HVHF. In the Ronco study published in the Lancet in 2000, although there was no overall survival difference between the two groups with 35 and 45 mL/kg/h doses, a significant survival difference was detected between these groups in a subgroup analysis for patients with sepsis.

A large randomised trial is going on to confirm this unsettled dosing issue in RRT for patients with sepsis. The IVOIRE study (High VOLUME in Intensive care) in Europe will study the use of standard volume (35 mL/kg/h) against HVHF (70 mL/kg/h) in ARF patients with septic shock. It aims to enroll 460 patients to detect a 15% absolute risk reduction in 30-day mortality.

### Circuit Patency in CRRT

In an international survey of 345 centres, the major concerns of health care workers about CRRT was the use of anticoagulant, frequent clotting of extracorporeal circuit and the subsequent increased nursing workload. CRRT downtime ranged from 8 to 28% of the total treatment time. Clotting of circuit was the major reason (74%) for the treatment loss. Therefore, it is essential to maintain circuit patency in order to minimise the discrepancy between prescribed and delivered doses.
Commonly used anticoagulants in CRRT are:
1. unfractionated heparin
2. low-molecular-weight heparin (LMWH)
3. citrate
4. prostacyclin / prostaglandin E1
5. nafamostat mesilate
6. direct thrombin inhibitor, e.g. r-hirudin

However, if the use of systemic anticoagulation is contraindicated, one of the alternatives is to flush the system with saline and administer the replacement solution pre-dilutionally. Even with these measures, significant clotting is still encountered in up to 15 to 40% of patients. According to the recently published BEST Kidney multi-national observational study,18 around one third of the patients received CRRT without any anticoagulation. Among the various anticoagulants, use of un-fractionated heparin ranked the highest (42.9%), followed by regional citrate anticoagulation (9.9%) and then nafamostat mesilate (6.1%).

Unfractionated heparin remains the standard systemic anticoagulant with the benefit of wide clinical experience, low cost, ease of use, ability to monitor the level of anticoagulation and availability of antidotes like protamine if needed. Heparin acts by binding to and activating anti-thrombin III, which in turn inhibits factors IXa, Xa, and thrombin. The anticoagulant effect can be achieved by giving an initial bolus of 10 to 20 U/kg heparin; followed by continuous infusion of 3 to 20 U/kg/h to achieve 1.5 to 2 times of the normal activated clotting time or activated partial thromboplastin time. For patients at risk of bleeding, a lower dose or a 'tight' heparin regimen with a bolus of 5 to 10 U/kg; followed by infusions of 5 to 10 U/kg/h can be used.19

Low-molecular-weight heparin consists of only short polysaccharide chains with average molecular weight in the range of 3000 to 7000 daltons and its biological activity is quantified by the extent of factor Xa inhibition. Hence, dosing differs between different brands of LMWH and the haemofilter used. With respect to unfractionated heparin, LMWH has the advantage of longer half-life, greater bioavailability, dose-independent clearance, less heparin induced thrombocytopenia and less bleeding because of less impact on platelet function. In addition, the half-life of LMWH is prolonged in renal failure and a single injection at start of CRRT usually suffices for up to 5 hours.19 For example, enoxaparin 40 mg (4000-5000 anti-factor Xa units or 60-70 anti-factor Xa units/kg) can be given as a loading dose, followed by 10 to 40 mg every 6 hours if needed.19

### TABLE 2. Summary of Studies on Continuous Renal Replacement Treatment (CRRT) Dosing and Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Randomisations</th>
<th>CRRT mode</th>
<th>Prescribed dose (mL/kg/h)</th>
<th>Delivered dose</th>
<th>Primary outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronco et al, 2000</td>
<td>425</td>
<td>3 Arms comparing 3 different doses (n=146 vs 139 vs 140)</td>
<td>Post-dilution CVVH: Qs 120-240 mL/min</td>
<td>20 vs 35 vs 45 &gt;85% prescribed dose</td>
<td>Survival at 15 days</td>
<td>41% vs 57% vs 58%</td>
<td></td>
</tr>
<tr>
<td>Bouman et al, 2002</td>
<td>106</td>
<td>3 Arms comparing EHV vs ELV vs LLV (n=35 vs 35 vs 30)</td>
<td>Post-dilution CVVH: EHV-Qs 200 mL/min, Qs 72 L/day ELV-Qs 100-150 mL/min, Qs 24-36 L/day LLV-Qs 150 mL/min, Qs 24-36L/day</td>
<td>48.2 vs 20.1 vs 19.7</td>
<td>Not mentioned</td>
<td>Survival at 28 days; renal recovery</td>
<td>74.3 % vs 68.8% vs 75% (all except 1 in ELV)</td>
</tr>
<tr>
<td>Saudan et al, 2006</td>
<td>206</td>
<td>2 Arms comparing 2 different doses (n=102 vs 104)</td>
<td>Pre-dilution: CVVH (low dose)-Qs 100-125 mL/min, Qs 1-2.5 L/h CVVHDF (high dose)-Qs 100-125 mL/min, Qs 1-2.5 L/h, Qs 1-1.5 L/h</td>
<td>25 vs 44</td>
<td>Achieved 87% vs 83% of the delivered dose</td>
<td>28 days survival; 90 days survival</td>
<td>39% vs 59% vs 59%</td>
</tr>
<tr>
<td>ATN trial, 2008</td>
<td>1124</td>
<td>2 Arms comparing intense vs less-intense therapy (n=563 vs 561)</td>
<td>CVVHDF: Intensive-Qs 150 mL/min, Qs 1410 mL/h, Qs 1390 L/h Less intensive-Qs 140 mL/min, Qs 820 mL/h, Qs 83 mL/h</td>
<td>36.2 vs 21.5</td>
<td>35.8 vs 22.0</td>
<td>60 days mortality</td>
<td>51.2% vs 48.0%</td>
</tr>
<tr>
<td>Tolivani et al, 2008</td>
<td>200</td>
<td>2 Arms comparing 2 different doses (n=100 vs 100)</td>
<td>Pre-dilution CVVHDF: Standard dose-Qs 100-150 mL/min, Qs 1055 mL/h, Qs 793 mL/h High dose-Qs 100-150 mL/min, Qs 1831 mL/h, Qs 1406 mL/h</td>
<td>20 vs 35</td>
<td>17 vs 29</td>
<td>Survival to ICU discharge or 30 days</td>
<td>56% vs 49%</td>
</tr>
<tr>
<td>RENAL study, By ANZ group 2009</td>
<td>1465</td>
<td>2 Arms comparing 2 different doses (n=743vs 722)</td>
<td>Post-dilution CVVHDF Qb &gt;150 mL/min</td>
<td>25 vs 40</td>
<td>22.0 vs 33.4</td>
<td>90 day mortality</td>
<td>44.68 vs 44.66%</td>
</tr>
</tbody>
</table>

* CVVH denotes continuous veno-venous haemofiltration; CVVHDF continuous veno-venous haemodiafiltration; EHV early high volume; ELV early low volume; ICU intensive care unit; IHD intermittent haemodialysis; LLV late low volume; Qs blood flow; Qd dialysate flow; Qr replacement rate; SLED sustained low-efficiency dialysis

† Statistically significant
Regional Citrate Anticoagulation (RCA)

Citrate chelates the calcium in the extracorporeal circuit to mediate its anticoagulant effect. This citrate-calcium complex is biologically inert and is partly removed through the haemofilter. The remaining calcium citrate enters the body and mixes with the central venous blood. As the central venous blood flow is much greater than the circuit blood flow rate, the low ionised calcium concentration in the circuit is raised to such a level that any systemic anticoagulant effect is minimal. Therefore, citrate anticoagulation only exists regionally within the circuit. The citrate-calcium complex re-entered the body is dissociated back to free ionised calcium and citrate. All the residual effects of citrate are terminated by the liver, where it is metabolised through the tricarboxylic acid cycle into bicarbonate in a 1:3 ratio. To prevent filter clotting, a pre-filter citrate concentration of 3.5 to 4 mmol/L is needed to keep the ionised calcium concentration in the circuit to below 0.25 mmol/L. Because of the net loss of calcium in the form of citrate-calcium complex in the ultrafiltrate, a small amount of calcium supplement is needed. It is usually given intravenously via a separate central venous line and its rate is titrated to give a normal ionised calcium concentration.

Citrate is commonly formulated in 4% tri-sodium citrate or anticoagulant-citrate-dextrose A (ACDA) or as proprietary products like Gambro Prismocitrate 10/2 and Fresenius multiFiltrate Ci-Ca system (4% trisodium citrate).

The advantages of using RCA are:
1. longer circuit / filter life
2. safe for use even in patients with bleeding tendency or who had recent surgery
3. less microthrombi formation within filter tubules
4. less platelet activation
5. less blood transfusion required

Although RCA is superior in keeping circuit patency, the metabolic problems associated with it make it unpopular. These include: hypernatremia, metabolic alkalosis and the potential for hypocalcaemia (secondary to accumulation of citrate). The contraindications for RCA are severe liver dysfunction and massive blood transfusion. Its underlying rationale is the increased risk of citrate accumulation causing toxicity. Citrate toxicity should be suspected whenever ionised calcium is persistently low or the total to ionised calcium ratio is higher than 2.5. Symptoms of hypocalcaemia include paraesthesia, nausea, cramps, tetany, hypotension, decrease in cardiac output, or a prolonged QT interval.

In order to reduce the metabolic side effects related to RCA, the concentrations of sodium and bicarbonate in the replacement solution, during RCA setup, should be carefully adjusted. Close monitoring of electrolytes including sodium, potassium, arterial blood gases, ionised and total calcium, during CRRT, is essential.

RCA has been adopted as the default mode for CRRT in our department since 1995. Our experience with RCA is promising. It is safe and well accepted by our doctors and nurses. Overt metabolic complications have never occurred.

Conclusion

AKI is common among the critically-ill and RRT is frequently used to support these patients. Emerging international consensus classification is available to better stratify AKI patients so that future studies are meaningful for comparison. Although the adequacy of RRT dosing has been determined in recent good quality trials, there still exist areas of uncertainties about RRT. Further studies are needed to address the indications, optimal timing of initiation and the types of anticoagulants.

References