Artificial Kidney and Dialysis

A randomized comparative crossover study to assess the affect on circuit life of varying pre-dilution volume associated with CVVH and CVVHDF

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ABSTRACT: Objective: To determine if circuit life is influenced by a higher pre-dilution volume used in CVVH when compared with a lower pre-dilution volume approach in CVVHDF.

Design: A comparative crossover study. Cases were randomized to receive either CVVH or CVVHDF followed by the alternative treatment.

Subjects: All patients > 18 yrs of age who required CRRT while in ICU were eligible to participate, but excluded if coagulopathic, thrombocytopenic or unable to receive heparin. Based on an intention-to-treat, 45 patients were randomized to receive either CVVH or CVVHDF followed by the alternative treatment.

Setting: A 24-bed, tertiary, medical and surgical adult intensive care unit (ICU).

Intervention: Blood flow rate, vascular access device and insertion site, hemofilter, anticoagulation and machine hardware were standardized. An ultrafiltrate dose of 35 ml/kg/h delivered pre-filter was used for CVVH. A fixed pre-dilution volume of 600 ml/h with a dialysate dose of 1 L was used for CVVHDF.

Results: Thirty-one patients received CVVH or CVVHDF out of 45 participants followed by the alternative technique. There was a significant increase in circuit life in favor of CVVHDF (median=16 h 5 min, range=40 h 23 min) compared with CVVH (median=6 h 35 min, range=30 h 45 min). A Mann-Whitney U test was performed to compare circuit life between the two different CRRT modes (Z=3.478, p<0.001).

Measurements of circuit life on the 93 circuits which survived to clotting (50 CVVH and 43 CVVHDF) were log transformed prior to under taking a standard multiple regression analysis. None of the independent variables - activated prothrombin time (aPTT), platelet count, heparin dose, patient hematocrit or urea - had a coefficient partial correlation >0.09 (coefficient of the determination=0.117) or a linear relationship which could be associated with circuit life (p=0.228).

Conclusion: Pre-diluted CVVHDF appeared to have a longer circuit life when compared to high volume pre-diluted CVVH. The choice of CRRT mode may be an important independent determinant of circuit life. (Int J Artif Organs 2008; 31: 221-7)

KEY WORDS: Renal replacement therapy, Continuous veno-venous hemofiltration, Continuous veno-venous hemodialifiltration, Circuit life, Randomized controlled study

INTRODUCTION

Continuous Renal Replacement Therapy (CRRT) is an established treatment option widely used in different regions of the world for critically ill patients with severe Acute Renal Failure (ARF) (1). The techniques of Continuous Veno-Venous Hemofiltration (CVVH) and Continuous Veno-Venous Hemodialifiltration (CVVHDF) both effectively manage the removal of solutes and excessive fluid in the critically ill patient to achieve metabolic and fluid volume control (2). Both modes are widely used in clinical practice (3, 4), however, the effectiveness of the-
se treatments for renal support is dependent on maintaining continuity of therapy. It has been reported that the ability to stabilize urea and creatinine plasma concentrations with CVVH was threatened when actual delivered treatment time within a 24-hour cycle was less than 16 hours (5). A reduction in solute clearance due to inadequate circuit life was a possible factor influencing the clinical course and mortality of critically ill patients (6). A definition as to what is an adequate circuit life has not been determined, but experience coupled with reported findings suggests 18 to 20 hours is sufficient to achieve adequate solute and fluid removal and manage the demand on nursing time and the expense of resetting the circuit (7-10).

The majority of incidents which interrupt the continuous nature of CRRT are caused by circuit clotting which follows blood exposure to non-biological surfaces (5, 11, 12). When delivering CRRT, the reliability of blood flow from the vascular access (13), the use of anticoagulant agents (14), and the replacement of fluid in the predilution mode (15, 16) have been identified as useful strategies which can delay clotting and improve the duration of circuit life. Several authors have also suggested the selection of convection-based (CVVH) versus diffusion-based (CVVHDF) CRRT modes may affect circuit life (17-20). In a retrospective analysis of circuit survival time between Continuous Arterio-Venous Hemofiltration (CAVH) and Continuous Arterio-Venous Hemodiafiltration (CVVHDF) no difference in circuit life was observed (21). To our knowledge the question of whether differences in the mode of CRRT affects circuit life has not been investigated using a prospective randomized, controlled study. The aim of this study was to investigate whether circuit life is influenced by the higher pre-dilution volume technique of CVVH when compared with the lower pre-dilution volume diffusion based approach of CVVHDF.

**Materials and Methods**

This study was granted ethical approval by the Human Research Ethics Committee at Royal Perth Hospital, which operates under guidelines consistent with those issued by the National Health and Medical Research Council (NHMRC) on research involving humans (22). Informed written consent was obtained from patients wherever possible prior to enrolment, otherwise consent was sought from the patient's next-of-kin.

**Patient selection**

Any patient ≥18 years of age admitted to the adult intensive care unit (ICU) requiring CRRT was eligible for inclusion. Patients unable to receive the unit standard heparin regimen for anticoagulation of the extracorporeal circuit, such as recent trauma or surgical intervention, an existing coagulopathy (aPTT >80 s, INR >3) and/or thrombocytopenia (platelet count <50x10^9/L) were excluded. Information relating to age, gender, admission diagnoses and reason for CRRT was obtained on all patients who were enrolled in the study.

**Design**

The impact of higher volume predilution CVVH versus CVVHDF on circuit life was investigated using a randomized crossover study design. Patients participating in the trial were randomly selected to receive either CVVH or CVVHDF and thereafter alternated sequentially between the two techniques until a crossover had occurred and the life of both circuits had been reached. The primary endpoint was circuit life, which was measured from the time of commencement to the point of spontaneous circuit failure. Spontaneous circuit failure was defined as visual evidence of clot formation within the filter and/or venous chamber in association with a progressive rise in blood pressure to 250 mmHg as measured by the in-line circuit manometer. Circuit life could not be determined if the circuit was taken down electively due to:

- problems with vascular access or hemodynamic instability,
- procedures which required the patient to be transported outside of the unit,
- clinical reasons such as return of urinary output,
- or if death of the patient had occurred.

The design of the study used each patient as the control to measure the effects of higher pre-dilution volume CVVH and CVVHDF on circuit life. Only one crossover was undertaken for each patient. Circuit failure on both modes were analyzed in patients who either completed the crossover or when circuit failure occurred in isolation to the other mode.

**Technique**

An ultrafiltrate dose of 35 ml/kg/h delivered pre-hemofilter was used for CVVH. A fixed pre-dilution volume of 600 ml/h replacement fluid with a dialysate dose of 1 l/h was used for CVVHDF. The same dialysate and replacement fluids were used during both crossover periods in the same patients. Most patients received lactate-based solutions (Hemofiltration...
Replacement Fluid, Baxter Health Care, Sydney, Australia). Some patients, who tended to be acidic, received lactate-free bicarbonate-buffered solutions (Hemaccel, Gambro, Sydney, Australia). Blood flow was set between 150-200 mls/min. Routine blood samples were collected daily from a separate arterial line and aPTT, INR, platelet count, hemostatic, urea and creatinine plasma serum levels recorded. The laboratory values collected represented a daily record of the patient’s biochemical progress and were not intended as a reflection on the efficiency of each treatment modality.

Hardware

The Kima™ semi-automated CRRT machine (Kimal Plc, Middlesex, England) was used to perform both CVVH and CVVHDF. Circuit components, including hemofilter (Nephral 300ST AN69 membrane; Hospal, Lyon, France), were the same for both treatment modalities except in the provision of the dialytic component for CVVHDF.

Anticoagulation

Low-dose heparin anticoagulation of the circuit was used for both CVVH and CVVHDF. A continuous heparin infusion of 10,000 IU diluted in 50 mls of 5% dextrose using a separate syringe driver was delivered pre-hemofilter based on 8-10 IU/kg/h and adjusted to maintain an aPTT of 40 to 55 seconds. The amount of heparin delivered during the life of each circuit was recorded.

Vascular access site and catheter device

Vascular access was achieved using non-cuffed, non-tunneled, dual-lumen catheters with a gauge size of 11 or 12 to access blood from the subclavian, internal jugular or femoral central veins. In the event of problems associated with vascular access, manipulation of the catheter and flushing of the lumen to achieve a blood flow > 150 mls/min was allowed. If at any stage the vascular access site and catheter device changed, the process of treatment randomization was repeated until both modalities had been evaluated using the same site and catheter.

Statistical analysis

Past experience with pre-dilution CVVHDF at the study site had recorded a mean circuit life of 18.2 h and a SD of ±13.4 h (23). This provided a reference point on which to base sample size estimation. In order to detect a mean difference of 4 h and assuming a SD of 13.5 h, a sample size of 30 patients was required to give a power of 80%. Measurements of circuit life were log transformed using "ln" (basee logarithm) as data was not normally distributed. A multiple linear regression analysis was undertaken using the coefficient of the determination, Pearson and Spearman’s statistical correlation tests, with circuit life against aPTT, platelet count, heparin dose, patient hematocrit and urea. A Kaplan-Meier survival analysis was used to determine the cumulative effect and probability of circuit durability over time and to detect survival curves for CVVH and CVVHDF circuits. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 45 patients were randomized to receive CVVH and CVVHDF between December 2004 and July 2006. They included patients with a primary admission diagnosis of pneumonia (12), septic shock (9), coronary artery bypass grafting and/or valve replacement (8), cardiogenic shock (5), multiple trauma (3), acute pancreatitis (2), resection of ischemic bowel (2), repair of ruptured abdominal aortic aneurysm (2), hepatic failure (1) and acute on chronic renal failure (1). All patients required mechanical ventilation and the severity of illness was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE II) worst in first 24-hour score (Mean=25.53, SD=±6.20). Oliguria was the main reason for the instigation of CRRT (21), followed by hyperkalemia (9), metabolic acidosis (7), fluid overload (5) and uremia (3). Treatment adequacy was reviewed daily based on clinical and biochemical assessment. No detrimental difference was observed in the control of urea and creatinine plasma concentrations and in the restoration of blood pH and fluid balance when patients were treated with either CVVH or CVVHDF. Data on crossover and non-crossover patient characteristics are presented in Table I.

As a result of circuits taken down for other reasons besides clotting, out of the 45 patients enrolled, crossover to the alternative mode was not possible in 14 cases. This was due to death (3 patients), violations in study protocols (2 patients), stabilization of the patient’s condition allowing transfer out of the unit (1 patient), or because assessment of circuit life in the crossover treatment was not possible due to elective discontinuation (8 patients). Clotting of the circuit in the remaining 31 patients occurred sequentially. The main
insertion sites used for vascular access included the femoral vein (18) followed by subclavian (6) and internal jugular (5) veins. During each modality, vascular access allowed both techniques to operate at a blood flow rate between 150 to 200 ml/min.

The difference in circuit life between both techniques of the 31 paired circuits is illustrated in Figure 1. For patient Number 1 the difference in circuit life was in favor of CVVHDF with an extended circuit life of 536 minutes (8 h and 56 mins) for patient Number 13 the difference in circuit longevity was in favor of CVVH with a recorded circuit life of 320 minutes (5 h and 20 mins). In 25 patients, CVVHDF was observed to extend circuit life, while extended circuit life in favor of CVVH only occurred in 6 patients. The mean circuit life for CVVHDF was 18 hours 42 minutes (SD±13 h 3 mins), with a median circuit life 16 hours 5 minutes and a range of 40 hours 23 minutes. The mean circuit life for CVVH was 8 hours 33 minutes (SD±5 h 35 mins), with a median circuit life of 6 hours 35 minutes and a range of 30 hours 45 minutes. A Mann-Whitney U Test of the 31 paired comparisons showed the difference in circuit life between CVVHDF and CVVH was statistically significant (Z=-3.48, p<0.001). At the start of each crossover no mode was repeatedly chosen over another (CVVHDF n=15, CVVH n=16), nor did the order reverse the difference in circuit life between CVVHDF (mean=19 h 55 mins; SD±14 h 7 mins; median=16 h 5 mins; range=40 h 23 mins) and CVVH (mean=7 h 45 mins; SD±3 h 16 mins; median=6 h 30 mins; range=11 h 31 mins). The aPTT value was observed to be comparable during CVVH (mean=44.2; SD±11.9) and CVVHDF (mean=44.8; SD±11.3).

A Kaplan-Meier survival analysis was undertaken to estimate the probability of circuit survival time between the two treatment modalities and was performed on 93 circuits (50 CVVH and 43 CVVHDF) which had survived to clotting either as part of a crossover (62 circuits) or, when circuit failure had occurred in isolation (31 circuits). The circuit time of 960 minutes (16 h) was used as the truncation point for circuit survival. This time was derived from our past clinical records using CVVHDF and represented a measurement of circuit life which has been reported by others using CVVH as sufficient to ensure adequate treatment is delivered (5). As shown in Figure 2, at 960 minutes there was a 5% survival rate for CVVH circuits compared to a survival rate of 50% for CVVHDF circuits.

A multiple linear regression analysis was performed on the same data set of 93 circuits following "ln" (base-e logarithm) transformation of circuit life measurements to achieve distribution normality. The regression analysis was undertaken to determine whether circuit life was influenced by differences in treatment modality (CVVH or CVVHDF) rather than the effect of independent variables- aPTT, platelets, heparin dose, patient hematocrit or urea. None of the independent variables had a partial correlation coefficient value > 0.09 against the dependent variable of circuit life. The degree of variability in circuit life attributed to the independent variables was small (coefficient of the determination=0.117, p=0.228) and not statistically significant as shown in Table II. No significant correlations were shown between the dependent and independent variables when the alternative non-parametric Spearman's rank correlation coefficient was calculated (p>0.05).

TABLE I - CHARACTERISTICS OF THE 45 PATIENTS WHO PARTICIPATED IN THE STUDY

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<tr>
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<th>Crossover Patients</th>
<th>Non-Crossover Patients</th>
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<tr>
<td>Number of Patients</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Sex (Male / Female)</td>
<td>24 / 7</td>
<td>6 / 9</td>
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<tr>
<td>Mean Age and SD</td>
<td>56.7 ± 17.2</td>
<td>60.8 ± 11.2</td>
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<tr>
<td>Mean Body Weight (Kg) and SD</td>
<td>88.2 ± 17.7</td>
<td>97.6 ± 14.7</td>
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**DISCUSSION**

In considering our results, despite an increase in the dilution of blood associated with a higher volume of replacement fluid, CVVH in the pre-dilution mode showed a statistically significant reduction in circuit life compared to CVVHDF. The difference was substantial and clinically significant in terms of its potential to increase the proportion of time in which patients on CRRT are actually receiving treatment. A similar observation to ours was made by Ricci and associates in a recent prospective comparative crossover study. The authors recorded a significantly longer circuit life during continuous veno-venous hemodialysis (CVVHD) when compared with circuits exposed to CVVH (24).

The survival of circuits using pre-dilution CVVH in our study was lower than reported in other studies using this mode of CRRT (13, 16). The reason for this is uncertain. Many patients were admitted following trauma or surgery which may have led to cautious anticoagulation of the circuit and the choice of smaller gauge size vascular access catheter. However, the circuit life observed with pre-dilution CVVHDF was similar to the unit’s previous experience and a duration which is reported by others as consistent with treatment efficacy (5). This suggests the approach and management of patients requiring CRRT using both approaches had not differed from our usual practice. The survival of some CVVH circuits was comparable with circuit life for CVVHDF as shown in Figure 1. Instead of a gradual improvement in circuit life which might have suggested inexperience as a confounding factor, the occurrence of longer circuit life using CVVH when compared with CVVHDF was evenly distributed throughout the duration of the study. The superior circuit life observed with CVVHDF could in theory be explained by the mechanisms of solute and plasma water removal. The larger plasma fluid passage in CVVH might result in greater protein adsorption and fouling of the membrane, while increased blood-filter membrane interaction may lead to more hemostatic activation and the development of blood clots. In contrast, diffusive mechanisms employed in CVVHDF do not require the same level of plasma water removal and degree of membrane interaction. This occurs without compromising the ability of CVVHDF to achieve a similar solute clearance rate for smaller molecular weight substances compared to convective mechanisms associated with CVVH. The effect of convection during intermittent hemofiltration and hemodialfiltration was shown to be associated with increased procoagulatory activity when compared with diffusion during intermittent hemodialysis (25).

This study has several limitations. The nature of the intervention makes it impossible to blind this type of study. As a single-center study, it is unknown if similar results would be obtained with different anticoagulation regimens or access catheters or machine hardware. Circuit life during CVVH was unusually short but did vary considerably. The use of central tendency statistical analysis that is associated with a wide variation of circuit life and based on small sample sizes may have confounded the results due to the accumulative effect of short circuit life recorded for CVVH. While the

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**TABLE II - MODEL SUMMARY OF THE MULTIPLE LINEAR REGRESSION ANALYSIS**

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<th>Model</th>
<th>R</th>
<th>R Square</th>
<th>Std. Error of Estimate</th>
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<th>Mean Square</th>
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<td>0.342</td>
<td>0.117</td>
<td>0.633</td>
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<td>Residual</td>
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<td>Total</td>
<td>24,511</td>
<td>59</td>
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**Fig. 2** - A Kaplan-Meier plot displaying the cumulative survival comparison of circuit life between CVVH and CVVHDF in the 93 circuits which survived to clotting.
filtration fraction differed between the two techniques, both used the pre-dilutional method of fluid replacement delivery and maintained a recommended filtration fraction <30% (26). The dose between CVVH and CVVHDF was different for the removal of small solutes. The weight-based dose for CVVH in patients whose body mass was larger may have operated at higher ultrafiltration volumes than was necessary for the technique to match the fixed-dose prescribed for CVVHDF. This introduced variability in the effluent volume required, which may have disadvantaged CVVH circuits by imposing an "unnecessary" increase in membrane interaction. Nevertheless, the use of a crossover study design allowed the patient to be the control measure and careful attention taken to standardize the approach of each technique constituted a rigorous attempt to evaluate differences in circuit life between both treatment modalities. The crossover between each technique occurred sequentially; the machine hardware and hemofilter were common to both treatment modalities; circuit life was compared using the same vascular access device and insertion site; the method accepted for circuit anticoagulation did not differ between the modalities; and both operated at a similar rate of blood flow.

This study demonstrates that circuit life may be superior with CVVHDF compared with CVVH. Diffusion-based techniques might have a protective effect on membrane integrity which could delay the onset of clotting. As short circuit life is a problem for many patients on CRRT, reduced down-time with CVVHDF may lead to more effective treatment.

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