

Continuous venovenous hemofiltration versus continuous venovenous hemodiafiltration in critically ill patients: A retrospective cohort study from a Canadian tertiary centre

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BACKGROUND: Studies comparing continuous renal replacement therapy modalities are lacking. Theoretically, continuous venovenous hemofiltration (CVVH) could be more effective than continuous venovenous hemodiafiltration (CVVHDF), and may be associated with fewer complications; however, there are no published data to support this hypothesis.

OBJECTIVE: To examine the effect of CVVH on mortality and other clinically important outcomes compared with CVVHDF in the intensive care unit (ICU) setting.

METHODS: Using a log of all continuous renal replacement therapy performed at a Canadian tertiary centre between 2007 and 2010, the records of patients meeting the inclusion criteria of being admitted to the ICU, and receiving either CVVH or CVVHDF for management of acute renal failure, were reviewed. The information retrieved included demographic data, death events, and hospital and ICU length of stay.

RESULTS: Data from 153 patients were included in the present study. Hospital and 30-day mortality were similar in the CVVH and CVVHDF groups (OR 0.85 [95% CI 0.38 to 1.89]; P=0.69 and OR 1.35 [95% CI 0.62 to 2.95]; P=0.45, respectively). There was no difference in hospital length of stay (mean difference -34.14 [95% CI -72.92 to 4.65]; P=0.08).

CONCLUSION: The present retrospective review suggests that the use of CVVH does not reduce mortality or hospital length of stay when compared with CVVHDF. Future randomized trials should control for different patient populations and continue to evaluate the removal of small molecules such as hormones.

Key Words: Acute renal failure; Cohort study; Continuous renal replacement therapy; Critically ill patients

Acute kidney injury (AKI) is a common occurrence among critically ill patients. In a recent multinational prospective cohort study that enrolled >29,000 critically ill patients from 32 countries, the incidence of AKI was 6% (1). Patients who developed AKI were at high risk for death (60% died) (1). Randomized clinical trials comparing intermittent hemodialysis with continuous renal replacement therapy (CRRT) failed to show survival benefit with the latter (2-5). A recent meta-analysis that included 1403 patients from nine trials reached a similar conclusion (6). However, observational studies suggest that CRRT is associated with enhanced hemodynamic stability in patients with shock (3,7) and increased ability to clear inflammatory mediators (8-14). Despite the lack of high-quality supporting evidence, the use of CRRT is becoming more frequent. In a recent large observational study, CRRT was used in 60% of critically ill patients with AKI (1).

There are two methods of clearance: diffusion and convection. Continuous venovenous hemodiafiltration (CVVHDF) combines

L'hémodiafiltration veino-veineuse continue ou l'hémodiafiltration veino-veineuse continue chez des patients gravement malades : une étude rétrospective de cohorte dans un centre canadien de soins tertiaires

HISTORIQUE : Il n'existe pas d'études comparant les modalités de thérapie continue en remplacement rénal. En théorie, l'hémodiafiltration veino-veineuse continue (HVVC) pourrait être plus efficace que l'hémodiafiltration veino-veineuse continue (HDFVVC) et provoquerait moins de complications. Cependant, il n'y a pas de données publiées pour soutenir cette hypothèse.

OBJECTIF : Examiner l'effet de l'HVVC sur la mortalité et d'autres résultats importants sur le plan clinique par rapport à l'HDFVVC à l'unité de soins intensifs (USI).

MÉTHODOLOGIE : Au moyen d'un journal de toutes les thérapies continues en remplacement rénal effectuées dans un centre canadien de soins tertiaires entre 2007 et 2010, les chercheurs ont examiné le dossier des patients respectant les critères d'inclusion, soit l'hospitalisation à l'USI l'administration d'une HVVC ou d'une HDFVVC pour traiter l'insuffisance rénale aiguë. Ils ont extrait les données démographiques, les décès et la durée du séjour à l'hôpital et à l'USI.

RÉSULTATS : Les données de 153 patients ont fait partie de la présente étude. L'hospitalisation et le taux de décès au bout de 30 jours étaient similaires dans les groupes d'HVVC et d'HDFVVC (RC 0,85 [95 % IC 0,38 à 1,89]; P=0,69 et RC 1,35 [95 % IC 0,62 à 2,95]; P=0,45, respectivement). Il n'y avait pas de différence dans la durée d'hospitalisation (différence moyenne -34,14 [95 % IC -72,92 à 4,65]; P=0,08).

CONCLUSION : D'après la présente analyse rétrospective, l'HVVC ne réduit pas le taux de mortalité ou la durée d'hospitalisation davantage que l'HDFVVC. Dans de prochains essais, il faudrait contrôler diverses populations de patients et continuer d'évaluer la suppression de petites molécules comme les hormones.

diffusion and convection using a highly efficient hemodiafilter to remove both solute and fluid. In continuous venovenous hemofiltration (CVVH), a large ultrafiltrate volume is generated across a high-permeability membrane (convection). Convective modalities (hemofiltration) may provide enhanced clearance of middle molecular weight solutes compared with diffusive modalities (hemodialysis) (15,16).

There is variation in practice worldwide. In Europe, clinicians primarily use CVVH; in a recent survey from the United Kingdom, 61% of intensive care units (ICUs) who completed the survey used CVVH as a first-line therapy (17). In North America, both CVVH and CVVHDF are used (18), while in Australia and New Zealand, CVVHDF is used more frequently (19). A recent prospective observational study involving 54 ICUs from 23 countries (20) suggested that CVVH is more commonly used than CVVHDF (53% versus 34%, respectively).

It is unknown whether the effects of using CVVH differ from CVVHDF with regard to important patient outcomes. The primary

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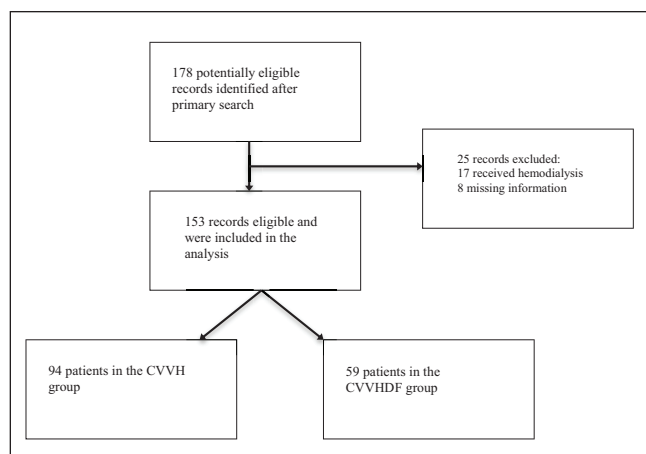


Figure 1 Flow diagram. CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration

purpose of the present study was to examine the effect of CVVH compared with CVVHDF on hospital mortality, 30-day mortality, ICU length of stay and hospital length of stay among critically ill patients with AKI. The secondary aims were to assess the effect of CVVH compared with CVVHDF on lactate and creatinine clearance, thyroid replacement and glucocorticoid levels in critically ill patients with AKI. For subgroup analysis in the postoperative cardiac population, we hypothesized that postcardiac surgery patients would have more benefit with convective therapy using CVVH because these patients carry a high risk of death in the context of AKI requiring dialysis postoperatively (21).

METHODS

Study design

A retrospective cohort study involving patients admitted to three ICUs (43 beds) in one Canadian tertiary care centre (Hamilton General Hospital [Hamilton, Ontario]) from 2007 to 2010 was performed. The study received research ethics approval from the Hamilton Health Sciences Research Ethics Board.

Study population

The inclusion criteria were as follows: age ≥ 18 years; admission to the ICU; primary mode of dialysis received was either CVVH or CVVHDF for AKI requiring renal replacement therapy. CVVH was the primary mode used for CRRT at the authors' institution until 2008, when CVVHDF was introduced and became the primary CRRT mode. Patients who received intermittent hemodialysis as the initial dialysis mode and records with missing information were excluded (Figure 1). In the authors' centre, ST150 membrane filters are used on a Prismaflex (Gambro, USA) with a 13.5 Fr dialysis catheter; the replacement fluid is administered post filter. Using a predesigned hospital protocol, heparin is administered to prevent clotting of the filter. The majority of the dose is administered as CVVHDF.

Data collection

Records for patients admitted to the ICU between 2007 and 2010 were reviewed through a log maintained by the ICU educators. Four reviewers collected the data from electronic and paper records. All identified charts were reviewed and assessed for eligibility. The case report forms were pilot-tested for the first 10 charts in duplicate to measure agreement and reproducibility among data collectors. Data dictionary and the case report forms were revised as necessary before completing the remainder of the cohort. Reviewers abstracted data for dialysis mode and dose, indication for dialysis, patient demographics, date of admission, ICU length of stay, comorbidities, baseline investigation including creatinine, lactate, hemoglobin, vasopressors use, thyroid and steroid replacement, mortality and CRRT-associated complications.

Agreement among the data collectors was assessed using the kappa statistic (crude kappa 0.80).

Outcomes

Primary outcomes included in-hospital and 30-day mortality. Secondary outcomes included ICU and hospital length of stay, reduction in serum lactate and creatinine levels, and the use of thyroid and glucocorticoid supplementation.

Subgroup analysis

Subgroup analysis was planned a priori examining the effects of CVVH compared with CVVHDF in postcardiac surgery patients admitted to the ICU, hypothesizing that the treatment effect will be larger in the CVVH group. The rationale for this was based on the authors' observation in clinical practice. The postcardiac surgery patients were more severely ill and required higher inotropic support. It was also unclear whether this subgroup would respond differently to higher flow during CRRT.

Sample size

Data collection was completed for 153 patients. The sample size was determined based on feasibility considerations. Using the rule of thumb of 10 to 15 events per predictor variable (22), a sample size of 153 with 86 events (mortality at 30 days) enabled the fitting of a logistic regression model with eight predictor variables.

Statistical analysis

Demographic data and medical conditions of the patients were analyzed to compare the difference between the patients in CVVH and CVVHDF group using descriptive statistics reported according to group as mean \pm SD for continuous variables and count (percentage) for categorical variables. P values from χ^2 tests for categorical data and two-group *t* tests for continuous data are reported. The two binary outcomes – hospital and 30-day mortality – were analyzed using logistic regression. The two continuous outcomes – ICU stay (in days) and hospital stay (in days) – were analyzed using linear regression. In the logistic and the linear regression, variables identified by comparing the group balance were adjusted for potential confounding factors. These variables included sex, ischemic heart disease, liver disease, hypertension, Acute Physiology and Chronic Health Evaluation (APACHE) score, central venous pressure and 24 h urine output before initiating CRRT. The results from linear regression are reported as adjusted difference between groups, corresponding two-sided 95% CIs and associated P values. The same analyses were conducted for the subgroup of postcardiac surgery patients admitted to the ICU. Results from logistic regression are reported as OR (95% CI) and associated P values. All statistical tests were performed using two-sided tests at the 0.05 level of significance; P values are reported to two decimal places. All analyses were performed using SAS version 9.2 (SAS Inc, USA).

RESULTS

A total of 178 charts were reviewed and 25 were excluded: 17 because of use of intermittent hemodialysis and eight because of missing information. Data were collected for 153 patients; of these, 59 received CVVHDF and 94 received CVVH for AKI in the ICU (Figure 1). The nursing educators maintained a log of any patients receiving CRRT, which enabled the identification of all potentially eligible patients. The dialysis flow rate was 35 mL/kg/h for all included patients. This flow rate was used before the publication of the Randomized Evaluation of Normal versus Augmented Level Replacement Therapy (RENAL) trial (23).

Given the lack of randomization and the heterogeneous sample, there were minor differences in baseline characteristics between the groups (Table 1). Although the APACHE II score was higher in the CVVH group relative to the CVVHDF group (29.18 versus 26.72; $P=0.04$), the proportion of patients with comorbidities was higher in the CVVHDF group. The majority of patients underwent surgical intervention associated with ICU admission (76% in the CVVH

TABLE 1
Baseline characteristics

Variable	CVVH (n=94)	CVVHDF (n=59)
Male sex	51 (54)	47 (80)
Age, years	67.28±15.30	68.42±12.94
Weight, kg	88.14±24.12	89.93±23.78
Diabetes mellitus	36 (38)	22 (38)
Ischemic heart disease	50 (53)	41 (71)
Congestive heart failure	18 (19)	12 (21)
Chronic lung disease	23 (25)	10 (17)
Chronic renal insufficiency	25 (27)	15 (26)
Liver disease	2 (2)	8 (14)
Brain injury	4 (4)	5 (9)
Hypertension	53 (56)	16 (28)
Coronary artery bypass grafting	13 (14)	10 (17)
Hypothyroidism	8 (18)	12 (20)
Nonoperative	22 (24)	16 (29)
RIFLE		
Risk	13 (14)	11 (19)
Injury	19 (20)	18 (31)
Failure	60 (65)	29 (50)
Loss	1 (1)	0 (0)
End stage	0 (0)	0 (0)
APACHE II score	29.18±7.54	26.72±6.45
Central venous pressure, mmHg	16.84±5.40	18.80±4.98
24 h urine output, mL	617.03±786.38	930.44±1174.6
Days	3.79±2.75	3.76±3.86

Data presented as mean ± SD or n (%). APACHE Acute Physiology and Chronic Health Evaluation; CABG Coronary artery bypass graft; CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration

group, 71% in CVVHDF group), and approximately 25% in both groups had a history of chronic kidney disease that was not dialysis dependent. The indications for starting renal replacement therapy are summarized in Table 2. If more than one indication for dialysis was present, the one that was reported was considered to be the primary indication as described in the medical record.

Using univariate analysis, there was no difference in hospital or 30-day mortality between the groups. A trend toward shorter ICU length of stay was observed in the CVVH group (mean difference -27.51 [95% CI -59.46 to 4.43]; P=0.09) and a statistically significant reduction in hospital stay for CVVH (mean difference -34.32 [95% CI -68.03 to -0.60]; P=0.05 (Table 3). After adjusting for multiple variables using multivariate regression analysis (Table 3), there was no difference in hospital mortality, 30-day mortality or ICU length of stay. However, there was a trend toward reduction in hospital length of stay in favour of the CVVH group (mean difference -34.14 [95% CI -72.92 to 4.65]; P=0.08).

Although serum lactate and creatinine levels for the first 48 h of CRRT were higher in the CVVH group, the difference was not statistically significant (Table 4). Interestingly, more patients required thyroid replacement when receiving CVVHDF (39%) compared with those receiving CVVH (17%) (P<0.01); the difference was statistically significant. Similarly, significantly more patients required glucocorticoids therapy in the CVVHDF (58%) group compared with CVVH (36%) (P<0.01), the main indication for glucocorticoids therapy was vasopressor refractory shock. The results are summarized in Table 4.

Subgroup analysis

The postcardiac surgery population included 67 patients (40 in the CVVH group and 27 in the CVVHDF group). Subgroup analysis showed that hospital mortality was similar in both groups: 23 patients (57.7%) died in the CVVH group compared with 15 (55.5%) in the

TABLE 2
Indications for starting continuous renal replacement therapy

Indication	CVVH (n=94)	CVVHDF (n=59)
AKI with reduced urine output	70 (74.47)	41 (69.49)
Acidosis* and AKI	6 (6.38)	5 (8.47)
Abdominal compartment syndrome	2 (2.13)	0 (0.00)
Salicylate toxicity	1 (1.06)	0 (0.00)
Pulmonary odema	6 (6.38)	9 (15.25)
Thrombotic thrombocytopenic purpura	1 (1.06)	0 (0.00)
Oliguria†	4 (4.26)	0 (0.00)
Rhabdomyolysis‡ with AKI	1 (1.06)	0 (0.00)
Uremia	3 (3.19)	3 (5.08)
Not clear	0 (0.00)	1 (1.69)

Data presented as n (%). *ph <7.2 with acute kidney injury (AKI); †Oliguria Urine output <500 mL/24 h; ‡Elevated creatine kinase level and associated AKI not responsive to fluid management. CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration

CVVHDF group (OR 1.08 [95% CI 0.4 to 2.90]; P=0.87). Mortality at 30 days, ICU and hospital length of stay were similar in both groups (Table 5). Multiple regression analysis adjusting for variables such as sex, pre-existing ischemic heart disease and APACHE II score yielded similar results (Table 5).

DISCUSSION

In the present retrospective study, we did not find any differences in hospital or 30-day mortality when comparing CVVH with CVVHDF. The present study included a wide spectrum of critically ill patients admitted to the neurotrauma, medical and cardiac surgery ICUs. Baseline APACHE II scores were high, which reflect a high predicted mortality at baseline (Table 1). Hence, hospital mortality was high but consistent with the recent literature (1). Fifty-eight percent of patients died in the CVVH group compared with 64% in the CVVHDF group and, although the results were numerically different, multivariate logistic regression analysis did not yield a statistically significant difference. ICU length of stay was similar in both groups; however, there was a trend toward reduction in hospital length of stay in the CVVH group. Although the difference could be due to chance, we cannot rule out other factors that could explain this observation.

Some studies have suggested that CRRT increases clearance of beneficial hormones such as thyroid-stimulating hormone, parathyroid hormone, cortisol, aldosterone, insulin and, possibly, testosterone (24,25). The clinical implication of this observation is unknown. In our study, we did not measure the clearance of any hormones but we described the proportion of patients who received thyroid replacement and glucocorticoids; the use of both hormones was higher in the CVVHDF group and the difference was statistically significant (P=0.01) (Table 4). It is possible that the temporal nature of the interventions influenced the observed results. CVVHDF was used in our institution before 2008, in which glucocorticoids were also more frequently prescribed to critically ill patients with septic shock than over the past few years. We cannot draw any firm conclusions based on these observations, but it may generate hypotheses to be validated in future studies. Moreover, we observed lower serum lactate and creatinine levels with CVVH at 48 h but the difference was not statistically significant (Table 4). Although a firm conclusion cannot be drawn, this may be an indirect measure of the efficiency of CVVH.

We hypothesized that postcardiac surgery patients will have more benefit with convective therapy using CVVH because these patients carry high risk for death in the context of AKI requiring dialysis postoperatively (21). However, subgroup analysis did not reveal any difference between the groups in all clinical and biochemical outcomes.

Over the past few years, CVVH has become widely used in ICU settings (20). This is possibly related to the theoretical advantage of

TABLE 3
Primary outcomes: Univariate and multivariate regression analysis

Outcome	CVVH	CVVHDF	Univariate analysis	Multivariate analysis*
Mortality at 30 days, n/n (%)	54/94 (57)	32/59 (54)	OR [†] 1.14 (95% CI 0.59 to 2.19); P=0.70	OR 1.35 (95% CI 0.62 to 2.95); P=0.45
Hospital mortality, n/n (%)	55/94 (59)	37/58 (64)	OR 0.80 (95% CI 0.41 to 1.57); P=0.52	OR 0.85 (95% CI 0.38 to 1.89); P=0.69
ICU length of stay, days, mean	19.35	46.84	MD [‡] -27.5 (95% CI -59.46 to 4.43); P=0.09	MD -28.22 (95% CI -65.26 to 8.81); P=0.14
Hospital stay, days, mean	28.53	62.85	MD -34.32 (95% CI -68.03 to -0.60); P=0.05	MD -34.14 (95% CI -72.92 to 4.65); P=0.08

*All models were adjusted for sex, ischemic heart disease, liver disease, hypertension, Acute Physiology and Chronic Health Evaluation score, pre-central venous pressure, 24 h urine output and pre-continuous renal replacement therapy, which were identified by comparing the group balance. Backward stepwise regressions were used for variable; [†]OR from logistic model; [‡]MD Mean difference from linear regression model. CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration; ICU Intensive care unit

TABLE 4
Secondary outcomes

Outcome	CVVH (n=94)	CVVHDF (n=59)	P*
Glucocorticoids, n (%)	34 (36)	34 (58)	<0.01
Lactate clearance, mmol/L, mean ± SD			
Day 1	-0.86±5.52	-1.43±4.23	0.52
Day 2	-2.19±6.09	-1.24±4.04	0.33
Thyroid replacement, n (%)	16 (17)	23 (39)	<0.01

* χ^2 test for categorical data and two-group t test for continuous data. CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration

increased clearance of higher molecular weight molecules and inflammatory cytokines, especially in septic patients (14,26,27). There are no large randomized controlled trials comparing the two modalities. Recently, a multicentre Canadian pilot study (OMAKI [28]) compared the two modalities in critically ill patients and showed that mortality (54% CVVH; 55% CVVHD) and dialysis dependence in survivors (24% CVVH; 19% CVVHD) at 60 days were similar. However, a larger randomized controlled trial is needed in this area.

The strengths of our review include using standardized case report forms for data abstraction; the use of robust statistical methods to test our hypothesis; and examining the effect of interventions on important patient outcomes and laboratory markers. However, a few limitations are

worth mentioning. Our study was perhaps underpowered to detect a mortality difference (if a difference truly exists); this is mainly related to the small sample size. Similar to other retrospective cohort studies, our review was subject to biases, especially in outcome assessment because it is challenging to acquire verifiable data based on retrospective data collection. Patient selection (selection bias) may play a role in choosing the dialysis mode in which sicker patients received CVVH; this is suggested by the difference in baseline characteristics in both groups (Table 1). Data regarding delivered dose of dialysis were not collected, although high doses (35 mL/kg/h) were prescribed. It is challenging to ascertain whether the delivered dose was similar to the prescribed dose. Data regarding eight patients were missing and they were not included in the analysis (Figure 1). Although we used multivariable analysis adjusting for different confounding variables, it is challenging and sometimes impossible to control for all confounding variables in a nonrandomized study design.

CONCLUSION

The present retrospective review suggests that the use of CVVH is not associated with improved survival when compared with CVVHDF. Although the use of CVVH was associated with shorter hospital stay, the difference was not statistically significant. A large randomized controlled trial is warranted before we can draw any firm conclusions. Future research should examine the clinical consequences of hormonal and other biomarkers clearance.

TABLE 5
Univariate and multivariate analyses for cardiovascular intensive care unit (ICU) patient outcomes

Outcome	CVVH	CVVHDF	Univariate analysis	Multivariate analysis*
Mortality at 30 days, n/n (%)	23/40 (57)	15/27 (55)	OR [†] 1.08 (95% CI 0.40 to 2.90); P=0.87	OR 0.90 (95% CI 0.28 to 2.88); P=0.86
Hospital mortality, n/n (%)	23/40 (58)	17/27 (63)	OR 0.72 (95% CI 0.26 to 1.99); P=0.52	OR 0.53 (95% CI 0.16 to 1.78); P=0.30
ICU length of stay, days, mean	17.8	40.48	MD [‡] -2.66 (95% CI -10.91 to 5.60); P=0.53	MD -4.87 (95% CI -13.94 to 4.20); P=0.29
Hospital stay, days, mean	28.2	30.7	MD -2.52 (95% CI -14.46 to 9.43); P=0.68	MD -4.13 (95% CI -17.73 to 9.46); P=0.55

*All models were adjusted for sex, ischemic heart disease, liver disease, hypertension, Acute Physiology and Chronic Health Evaluation score, pre-central venous pressure, 24 h urine output and pre-continuous renal replacement therapy, which were identified by comparing the group balance. Backward stepwise regressions were used for variable; [†]OR from logistic model; [‡]MD Mean difference from linear regression model. CVVH Continuous venovenous hemofiltration; CVVHDF Continuous venovenous hemodiafiltration

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