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Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure

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Acute renal failure (ARF) in critically ill patients is associated with high mortality. Optimal method and dose of continuous renal replacement therapy could improve survival in these patients. We studied the hypothesis that an increase in dialysis dose obtained by continuous veno-venous hemodiafiltration (CVVHDF) is associated with a better survival than continuous veno-venous hemofiltration (CVVH) among critically ill patients with ARF. In a prospective randomized trial, these two methods were compared in patients undergoing renal replacement therapy in two intensive care units (ICUs). The patients had either CVVH (1–2.5 l/h replacement fluid) or continuous CVVHDF (1–2.5 l/h replacement fluid + 1–1.5 l/h dialysate) according to their body weight. 28- and 90-day mortalities, renal recovery, and duration of ICU stay were the main outcome measures. Two hundred and six patients were randomized from October 2000 to December 2003. Twenty-eight-day survivals (%) were, respectively, 39 and 59 ($P = 0.03$) in the CVVH and CVVHDF groups. Three months survivals (%) were, respectively, 34 and 59 ($P = 0.0005$) in the CVVH and CVVHDF groups. Apache II score, age, baseline blood urea nitrogen, and hemodiafiltration (hazard ratio 0.59, 95% confidence interval 0.40–0.87; $P = 0.008$) were independent predictors of survival at 90 days. Renal recovery rate among survivors (71 versus 78% in the CVVH and CVVHDF groups respectively, $P = 0.62$) was not affected by the type of renal replacement therapy. These results suggest that increasing the dialysis dose especially for low molecular weight solutes confers a better survival in severely ill patients with ARF.

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Acute renal failure (ARF) occurs frequently in intensive care unit (ICU) patients and critically ill patients with ARF present an overall mortality ranging from 37 to 70%.[1,2] Intermittent hemodialysis was the main renal replacement therapy until the end of the 1970s when continuous renal replacement therapies (CRRTs) (continuous hemofiltration and hemodialysis) were introduced.[2] Despite the necessity of permanent anticoagulation and subsequently increased risk of bleeding, these continuous treatments have been gaining popularity among nephrologists and intensive care specialists as there is less treatment-induced cardiovascular instability than with intermittent hemodialysis. Solute removal occurs in continuous therapies by convection, diffusion, and adsorption.[3] Continuous veno-venous hemofiltration (CVVH) works by convection, meaning that a proportion of plasma water and solutes are carried across the membrane by a hydrostatic pressure gradient. Convection is particularly efficient in removing middle molecular weight solutes. Continuous veno-venous hemodialysis (CVVHD) works mainly by diffusion. The dialysate flow runs countercurrently through the filter and diffusive solute removal results in decreased solute concentration in the blood compartment along the length of the hemodialyser. Diffusion is more efficient for removing small molecular weight solutes. When both mechanisms are combined, CRRT is labelled continuous veno-venous hemodiafiltration (CVVHDF). This therapy is particularly advocated for highly catabolic patients as it is assumed that improved small molecules clearance is of greater benefit to the patient.[3] There is some evidence that mortality is inversely correlated to the dialysis dose[4] and that a Kt/V higher than 1.0 per session has a significant impact on the mortality.[5] Recently, a randomized prospective study demonstrated that the survival rate in patients with ARF and treated by CVVH was enhanced by increasing the ultrafiltration rate from 25 to 35 ml/kg/h.[6] Although these results were not confirmed in another trial,[7] one may question whether this positive effect on mortality is due to a better removal of inflammatory mediators by increased clearance of medium-sized molecules or simply to a better overall dialysis dose. Adding a dialysis compartment to CVVH will mainly increase the small solutes clearance without affecting the removal of middle molecules such as inflammatory mediators. We therefore undertook a study to determine whether

increasing the dialysis dose by adding a dialysis flow rate to CVVH for intensive care patients with ARF will affect their prognosis.

RESULTS

Patient characteristics

Between October 2000 and December 2003, 371 patients with ARF were treated by CRRTs in our institution. Two hundred and six patients (56%) were enrolled. The plan of the study is shown in Figure 1. The seven patients who were not treated because of rapid improvement of their renal function ($n=3$) or death before implementation of treatment ($n=4$) and 19 patients who died within the first 24 h of the intervention were included in the intent-to-treat analysis.

Demographics and clinical characteristics are shown in Table 1. The two groups did not differ in their baseline characteristics, except for mean pre-treatment plasma creatinine level, which was significantly higher in the CVVHDF group. One hundred and forty-three (69%) patients were recruited in the medical ICU. Sixty-eight (33%) patients were known to have chronic renal failure before the present insult, 51% were known to have a normal serum creatinine before this hospitalization, and 16% were thought to have normal renal function (based on their age and/or absence of known comorbidities) before this episode of acute renal injury.

Procedural data

Within the first 24 h, most of the treatment prescribed was delivered to the patients in both groups (Table 2). At 48 h after implementation of CRRT, mean urea reduction ratio in the CVVH and CVVHDF groups was 40 and 50%, respectively ($P<0.009$). Mean creatinine reduction ratios were 38 and 46% for the CVVH and CVVHDF groups, respectively ($P<0.014$).

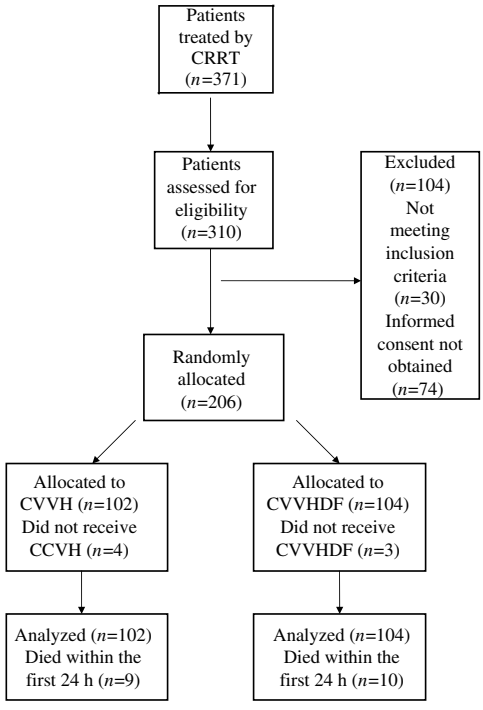

Figure 1 | Trial profile.

Patient outcomes

Survival at 28 days was, respectively, 39 and 59% ($P=0.03$) in the CVVH and CVVHDF groups. Survival at 90 days was, respectively, 34 and 59% ($P=0.0005$) in the CVVH and CVVHDF groups (see Figure 2).

Excluding the 26 untreated or moribund patients, survival at 28 days was, respectively, 44 and 64% ($P=0.003$) in the CVVH and CVVHDF groups. Survival at 90 days was, respectively, 38 and 64% ($P=0.0004$) in the CVVH and CVVHDF groups.

Between days 28 and 90, five patients died in the CVVH group, whereas no deaths were noted in the CVVHDF group. Causes of death were: intractable heart failure in a heart transplant patient, sudden death occurring after complete renal recovery in one patient, multiorgan failure in one patient, and dialysis withdrawal for palliative care in two patients. Of these five patients, two were still treated by CRRT at the time of death and two had previous chronic renal impairment before the acute renal injury.

At 28 days, Apache II score (hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.02–1.08), age (HR 1.02, 95% CI 1.00–1.04), baseline blood urea nitrogen (BUN) (HR 0.98,

Table 1 | Clinical and laboratory characteristics of patients at baseline

	CVVH group (n=102)	CVVHDF group (n=104)
Age (years)	65±12	62±15
Male gender (%)	65	57
Weight (kg)	73±15	73±20
Diagnosis of renal failure (medical/trauma/surgical)	66/11/25	77/5/22
Specific etiologies of renal failure (n)		
Sepsis	34	37
Volume depletion or intraoperative ischemia	16	20
Cardiogenic shock or cardiac arrest	20	12
Nephrotoxic drugs/contrast media	5	8
Rhabdomyolysis	1	2
Malignant hypertension	1	4
Myeloma kidney	1	—
Multifactorial	24	21
APACHE II score	26±9	24±9
SOFA score	10±5	9±5
Sepsis (%)	56	64
Oliguria (%)	33	41
Creatinine (μmol/l)	388±170	468±318*
BUN (μmol/l)	29±14	30±14

BUN, blood urea nitrogen; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; SOFA, sequential organ failure assessment.
Data are given in mean±s.d.
*$P<0.03$.

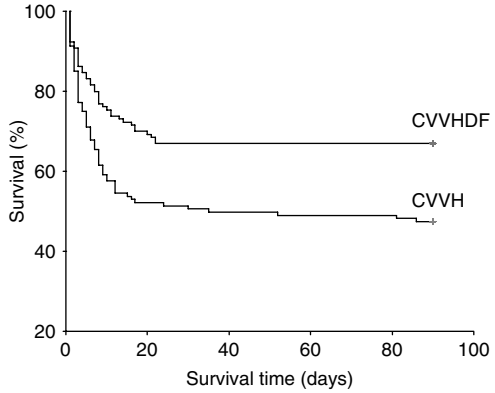

Figure 2 | Kaplan–Meier analysis of survival rates in the two groups.

(95% CI 0.97–0.99), and hemodiafiltration (HR = 0.65 (95% CI 0.43–0.96)) were independent predictors of death in a Cox multivariate analysis model. With baseline serum creatinine instead of baseline BUN, hemodiafiltration was just not statistically significant (HR = 0.71 (95% CI: 0.48–1.06)).

At 90 days, Apache II score (HR = 1.06 (95% CI: 1.03–1.08)), age (HR = 1.02 (95% CI 1.0–1.04)), baseline BUN (HR 0.98, (95% CI 0.97–0.99)), and hemodiafiltration (HR = 0.59 (95% CI 0.40–0.87)) remained independent predictors of survival (Table 3). When baseline BUN was replaced by baseline serum creatinine in the model, hemodiafiltration remained a significant predictive factor (HR = 0.59 (95% CI 0.38–0.93)).

Of the 101 patients who were still alive at 28 days, 12% remained on dialysis, of whom three were still treated in an ICU setting by CRRT and nine by intermittent hemodialysis. Of the 95 patients who survived at 90 days, 75% had recovered their previous renal function. Among those with permanent chronic renal impairment at 90 days, four (two in each group) remained on dialysis.

Type of renal replacement therapy did not affect significantly the rate of renal recovery at 90 days among survivors (71 versus 78% in the CVVH and CVVHDF groups, respectively, $P = 0.62$). The only finding which differentiated between those who recovered renal function from those with persistent renal impairment was the prevalence of previous CRF, which was significantly lower in the former group (33 versus 68%, $P = 0.006$).

Duration of the ICU stay was longer in the CVVHDF group (Table 3), although this was not statistically significant ($P = 0.06$). This difference did not persist when the analysis was restricted to survivors (data not shown), and this reflected likely the lower early mortality in the patients treated by CVVHDF.

Side effects

CRRT was well tolerated in our patients.

Occurrence of CRRT-associated complications such as bleeding was similar between the two groups, with only one major episode of bleeding in each group.

Table 2 | Intervention data

	CVVH group (n=102)	CVVHDF group (n=104)
Mean prescribed ultrafiltration dose (ml/kg/h)	25 ± 5	24 ± 6
Mean prescribed dialysis dose (ml/kg/h)	—	18 ± 5
Bicarbonate replacement fluid (%)	58	52
Delivered dose during first 24 h (%)	87 ± 11	83 ± 16
T° after 24 h CRRT	36.6 ± 0.7	36.7 ± 0.7
CRRT-free days at day 28 (days)	22 (9)	23 (7)
Mechanical ventilation-free days at day 28 (days)	19 (10)	21 (9)
Cumulative NA dose (mg)	35 (1–172)	11 (0–107)
Duration of ICU stay (days)	6 (2–10)	8 (4–16)

CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodiafiltration; ICU, intensive care unit; NA, noradrenaline; T°, temperature.

Table 3 | Results of Cox's proportional hazards model (90-day survival)

Variable	Unadjusted HR	P-value	Adjusted HR	P-value
Age	1.01 (0.99–1.03)	0.07	1.02 (1.00–1.04)	0.01
Gender	0.80 (0.54–1.18)	0.26	0.70 (0.44–1.09)	0.12
Weight	1.00 (0.99–1.01)	0.91	1.0 (0.99–1.01)	0.71
Diagnosis				
Surgical	1	0.32	1	0.12
Trauma	1.48 (0.68–3.19)	0.43	1.88 (0.84–4.19)	0.19
Medical	1.21 (0.76–1.92)		1.40 (0.85–2.29)	
Sepsis	1.53 (1.02–2.30)	0.04	1.30 (0.50–1.20)	0.24
Baseline BUN	0.98 (0.97–0.99)	0.02	0.98 (0.97–0.99)	0.008
CVVHDF vs CVVH	0.40 (0.31–0.73)	0.001	0.59 (0.40–0.87)	0.008
APACHE II score	1.07 (1.04–1.09)	0.001	1.06 (1.03–1.08)	0.001

BUN, blood urea nitrogen; CI, confidence interval; CVVHDF, continuous venovenous hemodiafiltration; CVVH, continuous venovenous hemofiltration; HR, hazard ratio. Data are given with 95% CI.

Filter clotting (filter lasting less than 24 h) did not differ between the two groups (1.1 ± 1.7 versus 1.3 ± 2.5 filter/person/day, $P = 0.97$).

DISCUSSION

Our results showed that adding a dialysis dose to CVVH had an impact on mortality in critically ill patients with ARF. At 28 days, survival was 59% in the CVVHDF group compared to the 39% observed in the CVVH group and this difference remained highly significant at 90 days. ARF occurs commonly in critically ill patients and is associated with high mortality ranging from 37 to 70%.[2,8] Patients with sepsis are especially prone to develop ARF in the context of multiorgan failure and the mortality may be as high as 80–90%.[9,10] Thus, it is important to find the optimal renal replacement therapy for these patients. The use of biocompatible membranes, daily intermittent hemodailysis, and continuous hemofiltration with an ultrafiltration rate of $\geqslant$35 ml/kg/h have been shown in randomized trials to reduce the mortality of ARF patients.[6,11–13] Although there is no consensus as to the

optimal dose of dialysis, better control of uremia was shown to be beneficial in these patients.[8] However, no difference in the survival of patients with ARF was found in another trial, where early implementation of treatment and high volume hemofiltration (median 48 ml/kg/h) was compared with late treatment and low volume filtration (median 19 ml/kg/h).[7] These conflicting results are probably explained by a difference in patients populations. Although our population had more sepsis, and with a probably later implementation of CRRT (as judged by its baseline BUN level) than in the study conducted by Ronco *et al*., we also noted an improvement in patients who received a higher dose of dialysis. Most of the difference in survival between the two groups occurred in the first 20 days and an improved control of aezotemia in the early course of their renal insufficiency in critically ill patients may be primordial. Adding ultrafiltration and dialysis flow rates provided a mean 'ultrafiltration' dose of approximately 42 ml/kg/h in the CVVHDF group, which should be comparable to the higher ultrafiltration rates used within the two previous trials.[6,7] The main difference with these trials was the method of CRRT. Instead of increasing the ultrafiltration rate, we chose to improve the clearance of small molecules by adding dialysis solution. Indeed, improved control of aezotemia may explain this decrease in mortality. Previously, in a prospective cohort of patients with severe ARF, high-volume hemofiltration up to 100 l/day was associated with a lower death rate than expected.[14] high-volume hemofiltration (8 l/h) during 4 h has been shown to reverse intractable septic shock in some patients.[15] Removal of toxic mediators owing to the high membrane permeability and the ultrafiltration flow may explain this positive effect on survival. However, the increment of dialysis in our group treated by CVVHDF was due to the addition of dialysis flow, which increased mainly the clearance of small molecules such as urea and has a negligible effect on middle molecules clearance.[16]

Other techniques such as daily intermittent hemodialysis and slow extended dialysis have been used successfully in ICU patients with ARF.[12,17] These methods also had a negligible effect on the clearance of middle molecules. Slow extended dialysis seems to be associated with equivalent cardiovascular stability and solute control as CRRT.[18]

A faster resolution of renal impairment was noted among patients treated with daily dialysis compared with intermittent dialysis.[12] Renal recovery did not differ among survivors in our two groups, but owing to our sample size, a type I error can not be excluded. Further trials powered for that particular issue are necessary to determine whether a beneficial effect on renal recovery is observed with increased dose of CRRT. Duration of ICU stay did not differ in our two groups.

Our trial has some limitations. At randomization, a slightly higher (but not statistically significant) Apache II score in the CVVH group may contribute to the poorer survival seen in this group. Although the difference was not statistically significant, more patients with cardiogenic shock or cardiac arrest were randomized to the CVVH group and patients with this diagnosis are known to have a particularly ominous prognosis. Excluding these patients does, however, not change the results of our survival analysis. It is improbable that the higher baseline creatinine in the CVVHDF group, which may reflect a more profound renal impairment, could also have contributed to this difference in the survival. Serum creatinine is a poor marker of ARF in ARF[10] and when it was used instead of baseline BUN in our multivariate model, the results did not change substantially. Effectively received dialysis treatments are usually lower than those prescribed in ICU patients.[19] During the first 24 h, received dialysis and ultrafiltration doses were above 80% of what was prescribed in both groups and we have to assume that ultrafiltration and dialysis daily doses were similar throughout the whole ICU stay. One may argue that our CVVH group had a high mortality owing to underdialysis but the mean prescribed 25 ml/kg/h is a usual dose prescribed previously in our unit and as well widely throughout the ICU.[19] Heat loss is known to occur in patients treated with CRRT and that may contribute to mortality.[20] We could not find a difference in body temperature between the groups after the first treatment day (see Table 3). For logistic reasons, there was no treatment blinding, but it is unlikely that the method of RRT may have biased our colleagues in the ICUs. Lastly, we did not compare diuretic use in our two groups and diuretic use was found to be detrimental in a cohort study of critically ill patients.[21] This observation was however, not confirmed in a recently published randomized trial studying the use of diuretics in patients with ARF.[22]

In summary, these results suggest that patients treated with CRRT may benefit of an increased dialysis dose, especially for low molecular weight solutes. This translates in a better survival in severely ill patients with ARF.

MATERIALS AND METHODS

Patients

Our study population comprised patients treated in the medical and surgical ICUs of Geneva University Hospitals. They were eligible for extra-renal replacement therapy if they fulfilled the following inclusion criteria: oliguria (urine output <200 ml/12 h) despite fluid resuscitation and intravenous diuretic treatment, and/or aezotemia (BUN >30 mmol/l) with urine output <1500 ml/12 h.

Exclusion criteria were the following: prerenal failure (reversibility of oliguria/uremia with fluid administration or with improvement of cardiac output), postrenal failure (on renal ultrasound examination and/or antegrade or retrograde contrast studies if high clinical suspicion), suspicion of glomerular disease (if high clinical suspicion and compatible urinalysis and/or serologic tests), end-stage renal failure (baseline serum creatinine $>300\,\mu$mol/l or creatinine clearance <20 ml/min), and patients on angiotensin-converting enzyme inhibitors (24 h temporary exclusion owing to possibility of ACE inhibitors induced anaphylactoid reaction with the polyacrylonitrile AN69 filter). The severity of illness was determined on the day of the first renal replacement treatment with the help of sequential organ failure assessment and APACHE II scores.

At enrolment, demographic data, APACHE II score, and etiology of renal failure were recorded. Causes of renal failure were simplified as medical, surgical, and trauma for the purposes of statistical analysis. Diagnosis of sepsis was made by the ICU team according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[23]

Previous chronic renal failure was diagnosed if the patients were known to have an abnormal serum creatinine level (>88 and $>106\,\mu$mol/l for women and men, respectively) before the present hospitalization.

To be eligible, patients have fulfilled the inclusion criteria. They or their relatives were asked for their consent to participate in the trial. The study protocol was approved by the Geneva University Hospitals Ethics Committee.

Study design: Patients were randomized to either CVVH or CVVHDF. A randomization list was generated by computer, in random blocks of four and six patients, and corresponding treatment allocation cards were placed in consecutively numbered opaque envelopes. Each time a patient was enrolled in the study, the next available envelope was opened by the nephrologist on call, and the allocated treatment option was communicated to the treatment team. Blinding was impossible for logistic reasons.

Intervention

A dual lumen venous catheter was inserted through a central vein. Renal replacement therapy was initiated and continued for 48 h, and then followed by 24 h observation if clinically possible. On account of increasing BUN and/or persisting oliguria, renal replacement therapy was resumed for another 48 h. Inotropic support was prescribed when mean arterial pressure was <60 mm Hg and cardiac index was <2.5 l/min/m^2.

Dialysis treatment was performed by pump-driven machines (Prisma, Hospal-Gambro) with fluid balance systems and multiflow 100 polyacrylonitrile, 0.9 m^2 AN 69 membrane (Hospal-Gambro). Replacement fluid was administered in the predilution mode. Blood flow was maintained between 100 and 125 ml/min. Bicarbonate replacement fluid was provided for patients with severe liver impairment, hyperlactacidemia, or severe hemodynamic instability. Otherwise, lactate replacement fluid was used.

CVVH: Ultrafiltration flow rate (1–2.5 l/h) was determined according to patient's estimated urea distribution volume (60% of their body weight at enrolment), so that this estimated volume could be cleared within 24 h, for example, a 80-kg patient will have an ultrafiltration flow rate of 2 l/h. For the purposes of simplification, hourly ultrafiltration flow rate was rounded off to the upper 500 ml level within the interval from 1 to 2.5 l.

CVVHDF: In addition to the ultrafiltration rate, dialysate flow rate was added between 1 and 1.5 l/h for patients weighing less or more than 70 kg. Owing to the effluent bag capacity, 2.5 l was the maximum hourly ultrafiltration rate if patients were randomized in the CVVHDF group and received also 1.5 l/h of dialysate. Heparin was administered during renal replacement therapy in the absence of bleeding, severe thrombocytopenia, or impaired liver function. In which case, heparin was replaced by periodic flushing with saline. Any bleeding episodes were recorded. Invasive monitoring was requested if patients required inotropic support.

The filter was changed daily during the first 48 h. Protein-rich (>2g/kg per day) and energy-rich (30–35 kcal/day) nutritional support was provided. Recovery of renal function was based on assessment of urine output and biochemical data to determine whether the patient needed further renal replacement therapy (absence of all criteria for implementing CRRT, urine output $=1$ ml/kg/h over 24 h, neutral fluid balance).

Renal replacement therapy was stopped when there was extreme hypotension unresponsive to inotropic support or irreversible severe lactic acidosis.

Statistical analysis

The primary outcomes were survival at 28 and 90 days. Analysis was performed using the intent-to-treat approach. Analyses that excluded untreated patients and those who died within the 24 h after onset of CRRT were also performed.

The secondary outcomes were: renal recovery (mean duration of ARF) and length of ICU stay.

Parametric and non-parametric tests were used to check for significant differences between demographic and baseline characteristics of study groups. Significant P-values were <0.05.

Survival and renal recovery were assessed with the Kaplan–Meier method and a Cox's proportional hazards model was used for controlling for possible pre-randomization confounding factors. The variables analyzed in this model were similar to those analyzed in the trial by Ronco *et al.*[6] (age, weight, gender, cause of renal failure, APACHE II score, presence of sepsis, BUN at start of CRRT, and method of CRRT).

Sample size: With an expected death rate of 60% in this population and assuming a 25% decrease in mortality, 90 patients per group were required to have a 80% power with an $\alpha<0.05$.

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