Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial

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Summary

Background Continuous veno-venous haemofiltration is increasingly used to treat acute renal failure in critically ill patients, but a clear definition of an adequate treatment dose has not been established. We undertook a prospective randomised study of the impact different ultrafiltration doses in continuous renal replacement therapy on survival.

Methods We enrolled 425 patients, with a mean age of 61 years, in intensive care who had acute renal failure. Patients were randomly assigned ultrafiltration at 20 mL h^{-1} kg^{-1} (group 1, n=146), 35 mL h^{-1} kg^{-1} (group 2, n=139), or 45 mL h^{-1} kg^{-1} (group 3, n=140). The primary endpoint was survival at 15 days after stopping haemofiltration. We also assessed recovery of renal function and frequency of complications during treatment. Analysis was by intention to treat.

Results Survival in group 1 was significantly lower than in groups 2 (p=0·0007) and 3 (p=0·0013). Survival in groups 2 and 3 did not differ significantly (p=0·87). Adjustment for possible confounding factors did not change the pattern of differences among the groups. Survivors in all groups had lower concentrations of blood urea nitrogen before continuous haemofiltration was started than non-survivors. 95%, 92%, and 90% of survivors in groups 1, 2, and 3, respectively, had full recovery of renal function. The frequency of complications was similarly low in all groups.

Interpretation Mortality among these critically ill patients was high, but increase in the rate of ultrafiltration improved survival significantly. We recommend that ultrafiltration should be prescribed according to patient's bodyweight and should reach at least 35 mL h^{-1} kg^{-1}.

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Introduction

Acute renal failure occurs frequently in critically ill patients in intensive care.[1] The disorder is defined as a sudden sustained decline in glomerular filtration rate, generally associated with azotaemia and a fall in urine output. The diagnosis of acute renal failure based on a change in urine output, blood urea nitrogen, or creatinine concentration alone should be made cautiously. Several disorders may lead to such disturbances, the most frequent being volume depletion.[1] Blood urea nitrogen concentrations might be raised in patients who have gastrointestinal haemorrhages, severe catabolism, low urine flow rate, intravascular volume depletion, and after administration of drugs. Creatinine can be raised in the absence of acute renal failure in patients who have high muscle mass, or after traumatic muscle injury. For all these reasons, a complete clinical assessment is normally done before the diagnosis is made. Whatever the underlying cause of acute renal failure, ischaemic or toxic injuries to the kidneys represent the final common pathways leading to acute tubular necrosis.[1]

Acute renal failure, however, is frequently only one of several organ system failures that are present in intensive-care patients, and is generally seen as part of multiple-organ dysfunction syndrome. Such patients are critically ill, and receive various pharmacological and life-support treaments. The primary aim of renal replacement therapy in these circumstances is to achieve adequate correction of homoeostatic disorders with good clinical tolerance. Intermittent renal replacement and peritoneal dialysis have some limitations in efficiency and clinical tolerance.[2–4] Continuous renal replacement therapy is increasingly being used to treat acute renal failure in critically ill patients.[5] The advantages of continuous treatments are steady biochemical correction, slow continuous fluid removal, and excellent cardiovascular stability,[4–6] and they are the most popular forms of renal replacement for critically ill patients in Europe and Australia.[7] In the USA, there is still some resistance to wider application of these treatments, supported by claims that outcomes better than with other approaches have never been shown.[8–9] Even in countries where continuous treatments are widely used, however, there are substantial differences between facilities, and standards in procedures have not yet been achieved. Furthermore, there is no consensus on an adequate treatment dose[9] or on the impact of dose delivery on outcome.[10]

In St Bartolo Hospital, Vicenza, Italy, continuous veno-venous haemofiltration has been the sole form of first-line renal replacement therapy in patients who have acute renal failure, in intensive care, since 1980. The long-term clinical experience led us to undertake a prospective randomised trial of the effects of different treatment doses on the survival of patients with acute renal failure treated by continuous haemofiltration. The study also assessed recovery of renal function and treatment complications.

Methods

Patients

We enrolled patients from two different intensive-care units of the same institution. Criteria for inclusion were admission to the intensive-care unit and the presence of acute renal failure, defined by abnormal concentrations of serum blood urea nitrogen and creatinine, and urine output of less than 200 mL in the preceding 12 h, despite fluid resuscitation and furosemide administration.[1–11] Fluid resuscitation was done, according to each intensive-care-unit's protocol, to maintain blood pressure and to ensure that serum abnormalities and oliguria were not related to volume depletion. In most patients, we monitored haemodynamic disorders by indwelling Swan-Ganz catheter. Oliguria was taken to be refractory to diuretic treatment when minimum or no response was induced by diuretic infusion (500 mg furosemide) in the 12 h before the start of renal replacement therapy. At enrolment, we recorded the underlying clinical disorder, biochemical variables, and results of acute physiology and chronic health assessment (APACHE II) to measure of the severity of illness.[12,13]

Study design

Enrolment started in 1994, and the last patient was recruited in September, 1999. Once the decision had been made to proceed with renal replacement therapy, a double-lumen catheter was inserted in the internal jugular vein and continuous haemofiltration was started. Blood flow rate was maintained at between 120 mL/min and 240 mL/min, according to blood-access function and required ultrafiltration rate. We used polysulfone hollow-fibre haemofilters with surface areas of 0·7–1·3 m^2. Heparin was infused at an initial rate of 8 IU kg^{-1} h^{-1} and adjusted every 6 h according to activated partial thromboplastin time (target 30–40% above normal).

Patients were randomly assigned treatment at one of three doses (we used the prescribed amount of ultrafiltration as a proxy for treatment dose): 20 mL h^{-1} kg^{-1} (group 1); 35 mL h^{-1} kg^{-1} (group 2); or 45 mL h^{-1} kg^{-1} (group 3, figure 1). In continuous veno-venous haemofiltration, solute transport is achieved by pure convection. The solute flux across the membrane is proportional to the ultrafiltration rate (Qf) and the ratio between the concentration of the solute in the ultrafiltrate and in plasma water (sieving coefficient S). For solutes freely crossing the membrane, sieving coefficients are equal or close to 1. Since clearance is calculated from the product Qf×S, when S is proximal to 1, as for urea, clearance is assumed to equal Qf, provided that replacement solution is infused with dilution occurring after passing through the filter. Therefore, since ultrafiltration rate corresponds to clearance in continuous haemofiltration, it can be used as a surrogate of treatment dose.

The treatment dose in group 1 was chosen based on the average dose delivered in routine clinical practice and reported in studies at the time of the start of our study.[14–17] We chose the doses in groups 2 and 3 by stepwise, clinically relevant, increase of ultrafiltration rate and according to technical feasibility.

We used lactate-based replacement solutions to maintain fluid balance, infused after passing through the filter. Different machines were used for the study but all were equipped with calibrated peristaltic blood pumps and fluid balance systems (with calibrated scales) capable of providing an accurate balance of ultrafiltration rate and reinfusion rate. End-to-end pressure drop in the haemofilter was monitored continuously for early detection of fibre clotting or filter malfunction. Haemofilters were changed at least every 24 h to prevent decay in membrane permeability and loss of ultrafiltration capacity. Cumulative ultrafiltration rate was measured every hour from the machine display and by measurement of the ultrafiltrate volume on a separate scale at every bag exchange. 1 kg was taken to equal 1 L.

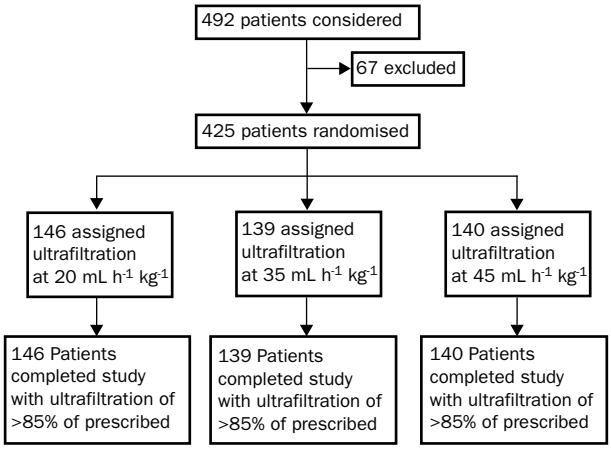

Figure 1: **Trial profile**

Doses were prescribed according to the patient's bodyweight. Some patients had haematomas or substantial fluid overload. We therefore did not use actual bodyweight to prescribe dose, but used each patient's weight before admission to intensive care. We obtained information on weight from personal health-care records, relatives, or records from previous hospital admissions.

The primary outcome measure was survival at 15 days after discontinuation of treatment. We calculated values of ultrafiltration achieved from true cumulative ultrafiltration volumes, measured directly as effluent, and totalled by the software incorporated in the machines. Interruptions in treatment for radiological assessment or other necessary diagnostic procedures on specified days were not taken as failure to reach the prescribed dose during that day. Prescription of treatment was incremented in the subsequent hours to compensate and to match the target in the next 24 h.

The secondary outcome measure was the recovery of renal function 15 days after continuous renal replacement therapy had been stopped. We assessed renal function by urine output, creatinine clearance, and concentrations of serum creatinine and blood urea nitrogen. Full recovery was restoration of diuresis, creatinine clearance within normal ranges, and normal concentrations of serum creatinine and blood urea nitrogen. Partial recovery in patients no longer requiring renal replacement therapy was defined by restored diuresis and improvement towards normalisation of creatinine clearance, but with serum concentrations of creatinine and blood urea nitrogen remaining abnormal. Failure of recovery of renal function was defined by requirement of further renal replacement therapy (mostly intermittent haemodialysis) after discontinuation of continuous veno-venous haemofiltration.

We also studied possible differences in complications between dose groups. We recorded technical complications, such as filter clotting or vascular-access malfunction, in all patients. Repeated filter clotting was reported if the filter life-span was less than 24 h on 2 consecutive days and had

Characteristics	Group 1 (n=146)	Group 2 (n=139)	Group 3 (n=140)
Demography			
Mean (SD) bodyweight (kg)	68 (11)	69 (8)	67 (9)
Sex (F/M)	65 (44·5%)/ 81 (55·5%)	62 (44·6%)/ 77 (55·4%)	60 (42·9%)/ 80 (57·1%)
Mean (SD) age (years)	61 (10)	59 (9)*	63 (12)
Causes of acute renal failure			
Surgical	112 (77%)	159 (74%)	105 (75%)
Medical	15 (10%)	19 (14%)	21 (15%)
Trauma	19 (13%)	17 (12%)	14 (10%)
Clinical characteristics			
Presence of sepsis	20 (14%)	17 (12%)	15 (11%)
Mean (SD) blood urea nitrogen (mmol/L)	18·2 (4·3)	17·9 (3·9)	19·3 (4·3)
Mean (SD) serum creatinine (μmol/L)	309·4 (132·6)	327·1 (141·4)	318·2 (185·6)
Mean (SD) APACHE II score	22 (3)†	24 (4)*	22 (4)
Mean prescribed ultrafiltration (L/24 h)	32·4 (5·3)	57·6 (7·1)	71·9 (9·2)

*p<0·017 group 1 *vs* group 2. †p<0·017 group 2 *vs* group 3.

Table 1: **Characteristics of patients at start of continuous haemofiltration**

to be changed because of increased drop in end-to-end pressure or unwanted reduction of ultrafiltration at a given transmembrane pressure, despite increased heparin infusion. Vascular-access malfunction was the inability of the catheter to deliver the prescribed blood flow. Clinical complications, such as bleeding or fluid-balance errors (difference from the prescribed balance >500 mL in 24 h) were also assessed as secondary outcome measures.

The institutional review board approved the study and we obtained informed consent from all patients participating in the study or their next of kin.

Statistical analysis

We based calculation of the sample size on a power analysis that assumed an expected improvement in survival of 20% in groups 2 and 3, compared with group 1. Analysis was done by intention to treat, according to prescribed ultrafiltration rates.

We compared dose groups for baseline characteristics by χ^2 test for categorical variables (eg, sex) or by one-way ANOVA for continuous variables (eg, APACHE II score). Univariate comparisons of survival were done by Kaplan-Meier estimation and long-rank tests. Subsequently, multivariate models of survival were analysed by Cox's proportional hazards regression to find out whether differences remained after adjustment for possible confounding factors. We set the level of significance for multiple comparisons with use of the Bonferroni

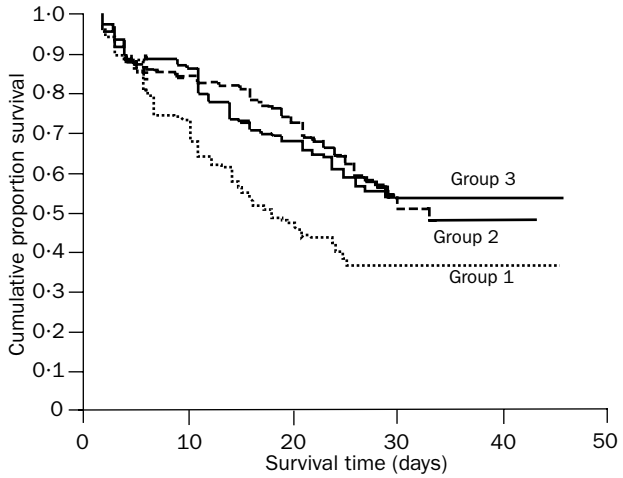

Figure 2: **Kaplan Meier estimation of survival rates in the three groups**

Variable	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Sex (female)	0·90 (0·69–1·19)	0·89 (0·66–1·20)
Weight	1·01 (0·99–1·03)	1·00 (0·99–1·02)
Age	1·00 (0·98–1·01)	1·00 (0·98–1·01)
Causes of acute renal failure		
Surgical	1·0	1·0
Medical	0·483 (0·28–0·82)	0·82 (0·46–1·46)
Trauma	1·384 (0·93–2·06)	1·09 (0·72–1·64)
Presence of sepsis	1·71 (1·20–2·44)	0·55 (0·34–0·89)
BUN at start of continuous haemofiltration	1·06 (1·05–1·07)	1·05 (1·04–1·07)
APACHE II score	1·13 (1·09–1·18)	1·11 (1·04–1·19)
Trial groups		
Group 1	1·0	1·0
Group 2	0·55 (0·40–0·77)	0·51 (0·36–0·72)
Group 3	0·57 (0·41–0·78)	0·49 (0·35–0·69)

BUN=blood urea nitrogen.

Table 2: **Results of Cox's proportional hazards regression**

Trial group	No sepsis (%)	Sepsis (%)	p
Group 1	55/126 (44%)	5/20 (25%)	0·90
Group 2	76/122 (62%)	3/17 (18%)	0·001
Group 3	74/125 (59%)	7/15 (47%)	0·256

Table 3: **Survival rates stratified by trial group and presence of sepsis**

adjustment. For all other statistical tests α=0·05. All analyses were on SPSS version 10.0 and SAS version 7.0.

Results

Of the 492 patients considered for the study, 67 did not fit the entry criteria or refused to give their consent. Therefore, 425 patients (187 women, 238 men) were enrolled (figure 1). The origin of acute renal failure was mostly postsurgical, but in some patients causes were medical and trauma-related. Sepsis was present in 14%, 12%, and 11% of patients in groups 1, 2, and 3, respectively.

Small but significant differences were present for age, APACHE II score, and serum concentrations of blood urea nitrogen at baseline (table 1). All patients reached values of ultrafiltration of at least 85% of prescribed dose (384 [90·4%] reached ultrafiltration rates higher than 90%). For patients in whom ultrafiltration delivery was between 85% and 90% of the prescribed dose (15 in group 1, 13 in group 2, and 13 in group 3), blood-flow limitation was the main technical complication.

Survival in the three groups was 41%, 57%, and 58% in groups 1, 2, and 3, respectively. Kaplan-Meier survival curves are shown in figure 2. Median survival was 19·0 days for group 1 (95% CI 14·70–23·30), which was significantly shorter than in the other two groups (group 2, 33·0 days, p=0·0007; group 3 had 53% alive at day 46, p=0·0013). Survival in groups 2 and 3 did not differ significantly from one another (p=0·87). The differences remained when patients who received less than 90% of the prescribed ultrafiltration dose were excluded from analyses.

Since differences were found among the groups on some of the baseline measurements, Cox's proportional-hazards regression was used to control for confounding factors. Patients in groups 2 and 3 were significantly less likely than those in group 1 to die, after adjustment for all other factors in the model (table 2). APACHE II score, concentration of blood urea nitrogen at start of continuous haemofiltration, and presence of sepsis were also significantly associated with mortality.

The hazard ratio for sepsis changed from being more than 1·0 in the univariate model to being less than 1·0 in the multivariate model. Additional model exploration showed that trial group, APACHE II score, and concentration of

	Group 1	Group 2	Group 3
Mean (SD) delivered ultrafiltration (L/24 h)	30·9 (6·2)	55·7 (8·2)	68·2 (9·3)
Mean (SD) effective blood flow (mL/min)	145 (14)	171 (20)	207 (27)
Mean (SD) duration of replacement treatment (days)	11 (6)	13 (8)	12 (7)
Bleeding	5%	6%	4%
Repeated filter clotting	3%	2%	2%
Vascular-access malfunction	10%	11%	12%
Fluid-balance errors	4%	6%	7%

Table 4: **Surgery parameters and complications**

blood urea nitrogen at start of continuous haemofiltration all seemed to act as moderator variables for presence of sepsis. Adjustment for these variables in the multivariate model changed the direction of the hazard ratio for sepsis, whereas dropping them from the model restored the hazard rate for sepsis to a value similar to that in the univariate model. There is, therefore, a possible interaction between these four variables. The interaction of trial group with presence of sepsis in particular, indicates that patients who have sepsis might benefit from a higher dose of blood replacement (table 3), since the rate of survival among the sepsis patients in group 3 was higher in than among those in the other two groups. This interaction was not significant in a proportional-hazards model, however (p=0·23).

The frequency of complications was low despite the severity of illness (table 4). Among survivors, 95%, 92%, and 90% in groups 1, 2, and 3, respectively, had full recovery of renal function 15 days after continuous haemofiltration was stopped. Among the non-survivors, 20%, 19%, and 20% had full recovery of renal function before death. Patients in all three groups who survived started treatment with lower concentrations of blood urea nitrogen than non-survivors (16·1 [4·3] *vs* 20·0 mmol/L [3·9] in group 1; 16·1 [3·2] *vs* 56 20·0 mmol/L [3·2] in group 2; 17·1 [3·2] *vs* 22·49 [3·9] in group 3).

Discussion

In chronic haemodialysis patients, haemodialysis dose might affect morbidity and mortality.[17] A similar correlation between outcome and dose of treatment in acute renal failure has been suggested.[18] In previous analyses, the increase in ultrafiltration was significant, but maximum treatment dose was still low. We compared three medium to high doses of ultrafiltration volume.

The difficulty of doing this type of study on critically ill patients is the definition of criteria for severity of illness and recruiting a sufficient number of patients. We used the APACHE II scoring system to measure severity of illness, although its adequacy in patients with acute renal failure is questionable.[19] In multicentre studies, the accurate matching of treatment prescription and delivered dose is difficult, since procedures and treatment delivery vary between centres. All patients in our study received at least 85% of the prescribed dose, which is remarkable given that some patients received treatment for more than 2 weeks.

Despite a high degree of accuracy in treatment delivery, we encountered some difficulties in patients who were scheduled to receive high filtration doses. Transmembrane pressure gradient had to be progressively increased during treatment because of a decrease in membrane permeability and ultrafiltration. This complication was seen mainly in patients who had low blood flows. When the filtration fraction (the ratio between ultrafiltration and plasma flow) exceeds 30%, filter function must be monitored carefully, since membrane fouling is likely to occur. This complication might encourage use of predilution, especially in larger patients or for treatment with high filtration rates. The infusion of the replacement solution before passage through the filter may lead to better performance of the filter and to a lower filtration fraction. However, dilution of solutes before passage through the filter might slightly reduce efficiency compared with dilution after passage through the filter at similar ultrafiltration volumes.

Our results suggests that, once other factors are normalised, treatment dose may have an impact on survival of patients in intensive care who have acute renal failure. This effect is seen up to a certain degree of clearance, beyond which further improvements cannot be obtained by increasing the treatment dose, and other issues must be considered.[19–22]

Based on our results, in an average 70 kg patient with acute renal failure, multiple-organ failure, or both, in intensive care, we recommend starting continuous haemofiltration early, at 2 L per h or more. Continuous treatments remove solutes better than intermittent approaches. Rapid removal of plasma solute during intermittent treatment, with a lag phase while equilibrium is regained from the total body pool, lowers concentration gradients across dialysers and, therefore, treatment efficiency. The efficiency is preserved in continuous treatments.[23,24] High treatment doses might be difficult or impossible to achieve with use of intermittent haemodialysis—very aggressive therapy might be necessary, with possible risks of severe clinical intolerance. Intermittent approaches are, therefore, greatly limited as a treatment option for patients in intensive care with acute renal failure.

In our population, the early start of treatment seemed to have a positive impact on outcomes. Early start of treatment might, therefore, contribute to maintaining a stable condition and prevent development of additional and more severe disorders.

The rate of complications in our study was low, probably because continuous veno-venous haemofiltration is a routine treatment in our institution and nurses are fully trained to solve technical complications quickly and effectively. The accurate monitoring of coagulation variables and patients' vital signs are other important features that contribute to the treatment being administered safely and smoothly. However, although the rate of complications did not differ greatly between the three groups, we strongly suggest careful monitoring when a high volume of fluid is exchanged daily. New machines for continuous renal replacement therapy are invaluable, since they are equipped with systems to control ultrafiltration and record fluid balance over a long period of time. Many technical and clinical factors may interfere with the effective treatment delivery and, therefore, careful controls must be used to ensure that the prescribed dose is delivered.

Once adequate dose delivery has been achieved, other factors must be taken into account to improve survival in critically ill patients with acute renal failure, including the control of sepsis, appropriate and timely surgical interventions, and rapid correction of metabolic disorders. Adequate renal replacement therapy is probably one of the several factors affecting outcome of acute renal failure in the critically ill patient.

Contributors

Guiseppe La Greca coordinated the study, and Claudio Ronco was the principal investigator and designed the project. Rinaldo Bellomo contributed to the study design and advised on data collections and analysis. Alessandra Brendolan was in charge of treatment procedures and monitoring of continuous renal replacement therapy. Maurizio Dan and Pasquale Piccinni assisted in the recruitment of patients and established severity indices. Peter Homel provided independent analysis of data and did the statistical analysis of results.

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