**Nephrology
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Original Article

Comparison of continuous and intermittent renal replacement therapy for acute renal failure

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Abstract

Background. Mortality rates of critically ill patients with acute renal failure (ARF) requiring renal replacement therapy (RRT) are high. Intermittent and continuous RRT are available for these patients on the intensive care units (ICUs). It is unknown which technique is superior with respect to patient outcome.
Methods. We randomized 125 patients to treatment with either continuous venovenous haemodiafiltration (CVVHDF) or intermittent haemodialysis (IHD) from a total of 191 patients with ARF in a tertiary-care university hospital ICU. The primary end-point was ICU and in-hospital mortality, while recovery of renal function and hospital length of stay were secondary end-points.
Results. During 30 months, no patient escaped randomization for medical reasons. Sixty-six patients were not randomized for non-medical reasons. Of the 125 randomized patients, 70 were treated with CVVHDF and 55 with IHD. The two groups were comparable at the start of RRT with respect to age (62 ± 15 *vs* 62 ± 15 years, CVVHDF *vs* IHD), gender (66 *vs* 73% male sex), number of failed organ systems (2.4 ± 1.5 *vs* 2.5 ± 1.6), Simplified Acute Physiology Scores (57 ± 17 *vs* 58 ± 23), septicaemia (43 *vs* 51%), shock (59 *vs* 58%) or previous surgery (53 *vs* 45%). Mortality rates in the hospital (47 *vs* 51%, CVVHDF *vs* IHD, $P = 0.72$) or in the ICU (34 *vs* 38%, $P = 0.71$) were independent of the technique of RRT applied. Hospital length of stay in the survivors was comparable in patients on CVVHDF [median (range) 20 (6–71) days, $n = 36$] and in those on IHD [30 (2–89) days, $n = 27$, $P = 0.25$]. The duration of RRT required was the same in both groups.

Conclusion. The present investigation provides no evidence for a survival benefit of continuous *vs* intermittent RRT in ICU patients with ARF.

Keywords: acute renal failure; haemodiafiltration; haemodialysis; organ failure; randomized clinical trial

Introduction

Before new drugs are introduced onto the market, an array of prerequisites have to be fulfilled including prospective controlled trials comparing the efficacy of the new xenobiotic with that of the traditionally prescribed drug. Interestingly, legal obligations appear to be far less demanding when new therapeutic interventions other than pharmacotherapeutic agents are marketed. This liberal attitude towards innovation in the field of therapeutic devices probably best explains why the worldwide standard for renal replacement therapy (RRT) in patients with acute renal failure, intermittent haemodialysis (IHD), has not been compared with the later developed continuous RRT [1] in prospective controlled trials focusing on final therapeutic objectives, such as patient survival, length of hospital stay or recovery of renal function in patients with acute renal failure (ARF) until recently. Mehta *et al.* [2] reported on a multicentre trial performed between 1991 and 1995 in southern California. In that trial, after exclusion of 208 patients mainly for haemodynamic reasons or refusal of the treating physician to include a given patient in the study, 166 patients were randomized to either IHD or continuous arteriovenous haemodiafiltration during the first 2 years of the trial or to continuous venovenous haemodiafiltration (CVVHDF) for the rest of the study period. As indicated by the authors, there were significant differences between the groups in several covariates independently associated with mortality,

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including gender, hepatic failure and severity of illness scores, in each instance biased in favour of the intermittent dialysis group [2]. Thus, the observation of the continuous therapy-associated increase in intensive care unit (ICU) and in-hospital mortality relative to IHD was difficult to interpret. In addition, most probably due to the multicentre approach, no uniform strategy for clinical decisions, including timing of initiation of dialysis or nutrition or haemodynamic support, was possible.

To test the hypothesis that CVVHD reduces in-hospital mortality, length of hospital stay or recovery of renal function, when compared with IHD, we performed a randomized controlled trial comparing IHD with CVVHDF in the ICU in a single centre. The single-centre approach was chosen for the following reasons: (i) to minimize a randomization bias; (ii) to avoid exclusion of patients from randomization for medical reasons; (iii) to ensure a constant dialysis approach during the study; and (iv) to control other clinical decisions, such as timing of initiation and dose of dialysis, nutrition and haemodynamic support.

Patients and methods

Patients

All patients admitted to the ICUs at the University Hospital of Berne, who were scheduled for RRT for ARF as defined by serum creatinine levels >350 μmol/l (>4.0 mg/dl) and/or urine output <20 ml/h between June 1998 and December 2000, were screened for this study. Patients with pre-existing chronic renal failure (CRF) treated by RRT or patients who needed a specific RRT for intoxication were excluded from this study.

All screened patients were randomized immediately before the need for RRT except for the following logistic situations: (i) all CVVHDF machines were in use at the time of randomization; and (ii) the patients were hospitalized in the one out of the five ICU wards that did not have the staff trained for CVVHDF. Non-randomized patients were treated by IHD and were excluded from further analyses.

Baseline vital signs, haemodynamic and laboratory data were recorded for the first ICU day and every day from the time of nephrology consultation. Simplified Acute Physiology Scores (SAPS) were computed at admission to the ICU to assess the severity of the illness [3]. The number of organ system failures was based on the criteria described by Metha et al. [2]. Patients were randomized to IHD or CVVHDF by a computer random number generator using a 'biased coin randomization' procedure [4]. This procedure was chosen since a restricted number of CVVHDF devices, but an unrestricted number of machines for IHD, were available. When two CVVHDF devices were available, the probability was 2:1 in favour of CVVHDF and when only one CVVHDF device was available, randomization was 2:1 in favour of IHD. When all CVVHDF devices were engaged, no randomization occurred. The study was approved by the ethics committee of the University of Berne in 1995. At that time, intermittent or continuous RRT for ARF was used at our institution depending on the availability of the devices and on personal preference because no evidence for the superiority of one of the two methods was available [1].

Furthermore, no additional clinical data were recorded or blood samples taken for this study. Therefore, it was agreed with the ethics committee that no informed consent needed to be asked for in participants in this study.

Once randomized, patients continued treatment with the assigned form of RRT until discharge from the ICU, when all patients still requiring RRT were switched to IHD. No crossover from one to the other form of RRT was allowed during the stay. The possibility of such a crossover would have (i) invalidated the basic concept of this study that each patient could be randomized (see above); and (ii) compromised the interpretation of the outcome results [2]. None of the patients was actually switched from one to the other form of RRT treatment during the study.

A sample size of 100 patients per group was estimated to allow the detection of a mortality difference of 20% between the two groups with a power of 90% assuming an overall mortality of 75% [5]. The same sample size would still have provided a sufficient power of 80% with a substantially lower overall mortality of ~50% [5]. The investigation was terminated prematurely after 30 months when it became increasingly more difficult to guarantee that no patient escaped randomization for medical reasons. No intermediate data analysis was done prior to the end of the study.

Renal replacement techniques

Vascular access was obtained in all patients by insertion of a Mahurkar double-lumen haemodialysis catheter (Sherwood Medical Company, St Louis, MO) into the subclavian, internal jugular or femoral vein by standard Seldinger technique. Biocompatible polysulfone membranes were used in IHD while acetonitrile membranes (AN69) were used in CVVHDF. Daily supplements of trace elements and vitamins or additional potassium chloride and sodium-hydrogen phosphate were given as required. Also, supplemental bicarbonate was administered during the study period when necessary.

CVVHDF

CVVHDF was performed with the HOSPAL-Prisma device (Gambro Healthcare, Lakewood, CO) using the proprietary sets, including standard tubing and AN69 high-flux haemo-filters. The filter was initially rinsed with 1l of normal saline including 5000 IU of heparin for at least 30 min. The system was then connected to the patient. Either a loading dose of 1500 IU of heparin followed by an individual patient-adjusted anticoagulation regimen or no anticoagulation was used. Blood flow ranged from 100 to 180 ml/min. A standard lactate-buffered fluid was used as dialysate and substituate at a combined rate of 2000 ml/h. Fluids were rewarmed to 37°C by a heating device when appropriate, and pre-dilution was used for fluid substitution. This procedure yields urea and creatinine clearances of ~30 ml/min.

IHD

IHD was performed using a standard haemodialysis device (MiroClav, Baxter GmbH, Germany) and standard blood lines. A high-flux polysulfone haemodialysis filter (Fresenius

GmbH, Bad Homburg, Germany) was used, starting the first session with a small surface area filter (F50) and increasing the filter size (F60 or F80) on further sessions. Initial heparin rinsing and circuit anticoagulation did not differ from CVVHDF. Blood flow ranged from 150 to 350 ml/min. A bicarbonate-buffered dialysate was used during IHD. Ultrafiltration rate was 250–1000 ml/h to achieve a negative fluid balance that approximately matched the fluid intake minus estimated fluids lost by other routes. In addition to fluid balance considerations, the frequency and duration of IHD sessions were determined by taking into account electrolyte or acid–base disturbances and an estimate of the catabolic state. The usual IHD session lasted from 3 to 4 h. This procedure yields urea and creatinine clearances of slightly less than 200 ml/min.

End-points and other variables

All-cause mortality in the ICU and in the hospital was the primary end-point of the trial. Secondary end-points were fluid and nutritional needs, vasopressor requirement and haemodynamic stability, control of azotaemia and volume overload, ICU and hospital days, and renal function recovery.

Blood pressure data on the ICU were recorded daily, and for each day the minimum and maximum diastolic, systolic and mean blood pressure were analysed. For each patient, the average mean arterial pressure (MAP) throughout the period on the ICU was calculated. Circulatory failure was defined as an average MAP ≤ 65 mmHg during the entire ICU period. The difference between daily maximum and minimum MAP was used to analyse haemodynamic stability, which was defined as an average cumulative daily variability of MAP <30 mmHg.

For the analysis of vasopressor requirement, nutritional needs and fluid balance, the type and rate of substances administered were analysed for differences in the two groups according to (i) the number of patients for each variable;

(ii) the number of patient-days of treatment; and (iii) the average dose or volume of substances received per 12 h computed for the days they were given.

Renal function recovery in survivors was assessed by serum creatinine values at discharge. Since some of the patients had pre-existing CRF at inclusion, defined as a stable increase in serum creatinine >150 μmol/l at least 3 months prior to randomization, full recovery was considered when baseline creatinine values $\pm 10\%$ were reached.

Statistical analysis

Between-group differences for continuous variables were analysed by the non-parametric Wilcoxon–Mann–Whitney test and by analysis of variance (ANOVA). Categorical variables were analysed by Fisher's exact test. A multiple logistic regression analysis was used to adjust for binary end-points. Analyses were performed with the SYSTAT 9.0 software (SPSS, Chicago, IL). All statistical tests were two-sided. Results are given as means $\pm$ SD or median and range.

Results

Study participants and randomization

During the 30 months of the trial, a total of 191 patients were scheduled for RRT because of ARF (Figure 1). Sixty-two patients (32%) were not randomized for the logistic reasons described in Patients and methods. No patient escaped randomization for medical reasons or refusal to be randomized. Four patients were excluded immediately after therapy was instituted for violation of the randomization procedure.

Figure 1 shows the breakdown of all randomized patients qualifying for RRT. Of the 125 randomized
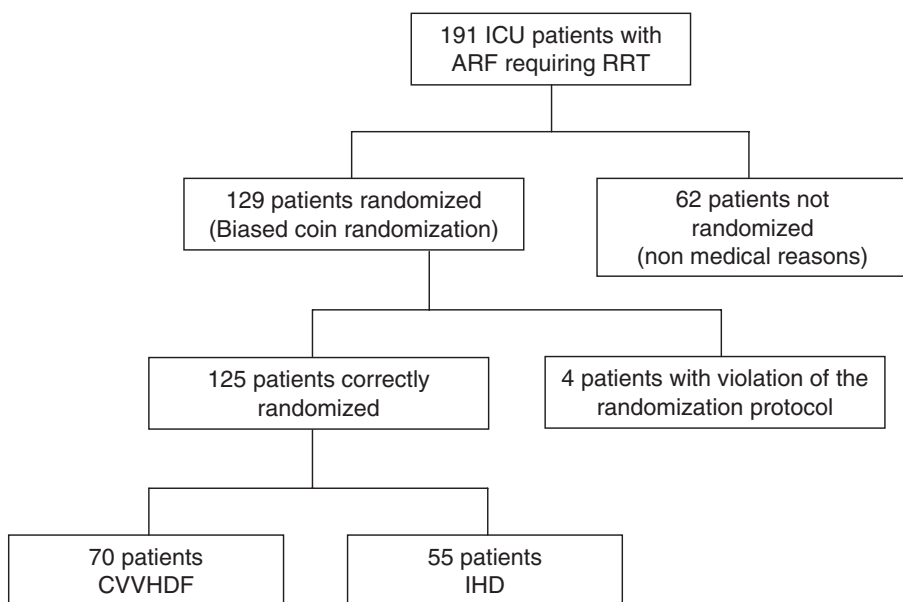
Fig. 1. Trial profile and distribution of randomized patients.

Table 1. Characteristics of patients assigned to continuous (CVVHDF) or intermittent (IHD) renal replacement therapy for acute renal failure

Characteristics	CVVHDF (n = 70)	IHD (n = 55)	P-value
Patients' demographics			
Age (years)	67 (19–84)	66 (18–85)	0.89
Male sex	46 (66)	40 (73)	0.44
Surgical	36 (51)	26 (45)	0.47
Septicaemia	30 (43)	28 (51)	0.47
Pre-existing CRF	16 (23)	11 (20)	0.82
Oliguric	45 (64)	34 (62)	0.85
Mechanical ventilation	55 (76)	42 (77)	0.83
Catecholamine therapy	58 (80)	38 (70)	0.29
Aetiological factors for ARF			
Ischaemic	41 (59)	32 (58)	0.91
Nephrotoxic	8 (11)	4 (7)	0.55
Multisystem disease	0 (0)	3 (5)	0.08
Unknown	21 (30)	16 (29)	0.87
Severity of illness scores			
SAPS	55 (21–103)	55 (21–110)	0.67
Number of organs failing	3 (1–6)	3 (1–6)	0.64
Renal function markers			
Urine output (ml/h)	9 (0–158)	10 (0–237)	0.14
Serum urea (µmol/l)	25.4 (8.7–39.9)	30.1 (6.3–57.6)	0.41
Serum creatinine (µmol/l)	342 (137–646)	335 (62–1037)	0.22

Values given are the number (%) or median (range).
Pre-existing chronic renal failure (CRF): serum creatinine >150 µmol/l at least 3 months before randomization.

Table 2. Continuous (CVVHDF) vs intermittent (IHD) renal replacement therapy for acute renal failure: prediction of in-hospital mortality

Variable	Parameter	n	% mortality	OR	P-value
RRT group	CVVHDF	70	47.1	1.00	–
	IHD	55	50.9	1.16	0.36
Gender	Male	86	45.3	1.00	–
	Female	39	53.8	1.41	0.39
Pre-existing CRF	No	98	44.9	1.00	–
	Yes	27	63.0	2.09	0.45
Age	<60	40	47.5	1.00	–
	60–70	41	51.2	1.16	0.82
	>70	44	45.5	0.92	1.00
No. of organs failing	1–2	55	43.6	1.00	–
	3	34	50.0	1.29	0.66
	≥4	36	52.7	1.44	0.52
Liver failure	No	93	47.3	1.00	–
	Yes	32	50.0	1.11	0.41
SAPS	<50	48	35.4	1.00	–
	50–70	44	52.3	1.99	0.14
	>70	33	60.6	2.81	0.04
Surgical	No	63	41.3	1.00	–
	Yes	62	56.7	1.75	0.15
Sepsis	No	66	40.9	1.00	–
	Yes	60	55.0	1.73	0.15
Shock	No	51	37.2	1.00	–
	Yes	74	55.4	2.09	0.07
Catecholamines	No	30	23.3	1.00	–
	Yes	95	56.8	4.3	0.002

OR = odds ratio; CRF = chronic renal failure (serum creatinine >150 µmol/l).

patients, 70 were treated with CVVDHF and 55 with IHD. No patient was lost from the trial because of incomplete follow-up. Table 1 compares the baseline clinical characteristics of the two treatment groups. There were no between-group differences with respect to key variables. Of the 62 surgical patients, 36 underwent cardiovascular surgery (CVVHDF vs IHD, 26 vs 10), 20 abdominal surgery (CVVHDF vs IHD, 8 vs 12) and 6 other surgeries (3 in each group). In the non-surgical patient group, there were 17 patients with heart diseases (CVVHDF vs IHD, 11 vs 6), 16 with respiratory diseases (CVVHDF vs IHD, 7 vs 9), 9 with malignancy (CVVHDF vs IHD, 5 vs 4) and 21 with miscellaneous disorders (CVVHDF vs IHD, 10 vs 11).

ICU and in-hospital mortality, co-morbid conditions and severity of illness

The overall ICU and in-hospital mortalities for both treatments were 36 and 49%, respectively. ICU mortality was similar in patients treated with CVVHDF and IHD [34 vs 38%, odds ratio (OR) 1.16, P = 0.71]. Similarly, in-hospital mortality was not different between patients treated with CVVHD (47%) and those treated with IHD (51%, OR 1.18, P = 0.72). Male gender, age, presence or absence of antecedent surgical procedures or liver failure were not associated with an increased ICU (results not given) and in-hospital mortality (Table 2). Pre-existing

CRF, defined as a serum creatinine >150 µmol/l at least 3 months before admission, tended to predict an increased mortality. When patients were stratified into tertiles based on their SAPS scores at the time of admission to the ICU, overall mortality was directly related to the degree of severity of illness. The number of organs failing did not predict mortality (Table 2). The presence of shock and treatment with catecholamines were strong predictors of mortality (Table 2).

Retrospective chart analysis of the 62 patients who could not be randomized for logistic reasons and who were treated by IHD revealed that 21 patients (34%) died during the course of hospitalization. The tendency for a slightly lower mortality in the non-randomized patients compared with the randomized patients did not reach statistical significance (P = 0.14).

Fluids and nutrition

In total, there were 965 RRT treatment days on the ICU (CVVHDF 510 days, IHD 455 days) (Table 3). The type and rate of fluids and nutrition administered were analysed for differences between the two groups according to the number of patients for each variable, the number of patient-days of treatment and the average dose or volume of substances received, computed for the days they were administered (Table 3).

Table 3. Fluids and nutrition in patients assigned to continuous (CVVHDF) or intermittent (IHD) renal replacement therapy for acute renal failure

Characteristics	CVVHDF (n = 70)	IHD (n = 55)	P-value
Cumulative treatment days	510	455	
Fluids			
Crystalloids			
No. of patients (%)	70 (100)	55 (100)	1.00
No. of patient-days (%)	510 (100)	455 (100)	
Volume (ml/12 h)	425 (20–4300)	425 (15–3080)	0.25
Colloids			
No. of patients (%)	58 (83)	46 (84)	1.00
No. of patient-days (%)	163 (32)	150 (33)	
Volume (ml/12 h)	500 (8–11200)	560 (50–3700)	< 0.01
Blood			
No. of patients (%)	48 (69)	39 (71)	0.85
No. of patient-days (%)	96 (19)	78 (17)	
Volume (ml/12 h)	300 (100–7150)	275 (100–2760)	0.83
Nutrition			
Enteral			
No. of patients (%)	69 (99)	54 (98)	1.00
No. of patient-days (%)	350 (68)	320 (70)	
Volume (ml/12 h)	300 (17–1950)	340 (20–1400)	0.41
Parenteral			
No. of patients (%)	40 (57)	36 (65)	0.36
No. of patient-days (%)	217 (42)	184 (41)	
Volume (ml/12 h)	600 (21–1450)	650 (60–1700)	0.16

Values given are the number (%) or median (range).

Table 4. Catecholamines in patients assigned to continuous (CVVHDF) or intermittent (IHD) renal replacement therapy for acute renal failure

Characteristics	CVVHDF (n = 70)	IHD (n = 55)	P-value
Cumulative treatment days	510	455	
Adrenaline			
No. of patients (%)	31 (44)	15 (27)	0.06
No. of patient-days (%)	87 (17)	21 (5)	
Dose (μg/12 h)	4070 (2–56 750)	7350 (2–80 500)	0.13
Noadrenaline			
No. of patients (%)	38 (54)	28 (51)	0.72
No. of patient-days (%)	155 (30)	129 (28)	
Dose (μg/12 h)	4300 (10–143 500)	3300 (47–161 350)	0.21
Dopamine			
No. of patients (%)	5 (7)	7 (13)	0.37
No. of patient-days (%)	11 (2)	13 (3)	
Dose (mg/12 h)	21 (2–156)	33 (1–485)	0.13
Dobutamine			
No. of patients (%)	31 (44)	19 (35)	0.36
No. of patient-days (%)	150 (29)	76 (17)	
Dose (mg/12 h)	32 (1–835)	24 (12–425)	<0.001

Values given are the number (%) or median (range).

There were no between-group differences in the number of patients receiving fluids in the form of crystalloids or blood and nutrition, either enteral or parenteral. Patients in the IHD group received a slightly higher amount of colloids. The rate at which these fluids were administered and the cumulative number of patient-days administered was comparable in the two groups.

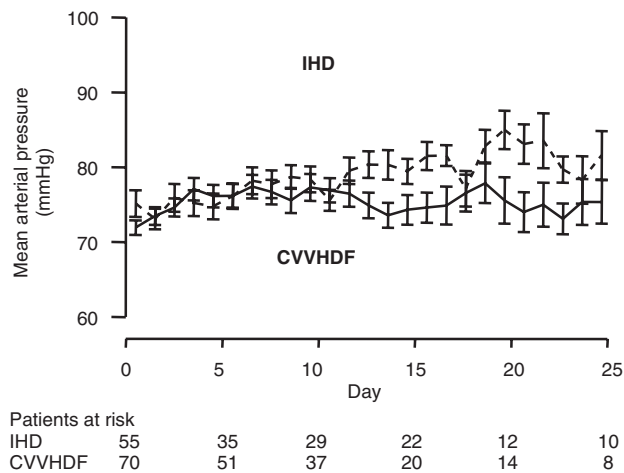*Vasopressor agents and hemodynamic stability*

There was no difference in the number of patients or the rate of adrenaline, noradrenaline or dopamine used in the two groups (Table 4). Patients in the CVVHDF group received on average slightly more dobutamine than those on IHD (Table 4).

The average MAP for the first 25 days from the beginning of RRT in the two groups of patients is reported in Figure 2. The incidence of circulatory failure, as assessed by an average daily MAP ≤ 65 mmHg throughout the entire ICU period, did not differ between the CVVHDF (15 patients, 21%) and IHD group (eight patients, 15%, $P = 0.36$). All these patients were on vasopressor agents and there was a 78% mortality among patients with circulatory failure (CVVHDF *vs* IHD, 81 *vs* 71%, $P = 0.62$). Haemodynamic instability, defined as the average variability between maximum and minimum daily MAP, was also similar in CVVHDF (20 subjects, 29%) and IHD (22 subjects, 40%, $P = 0.13$) groups.

Fig. 2. Average daily mean arterial pressure values during therapy with CVVHDF (solid line) and IHD (dashed line) for the first 25 days (mean ± SEM).

Quality of dialysis, control of azotaemia and volume overload

Data on the quality of RRT was available from 121 patients, because 4 patients (3 in the CVVHDF group and 1 in the IHD group) died after randomization before RRT could be started. Mean blood flow was lower with CVVHDF than with IHD (159 ± 18 *vs* 231 ± 56 ml/min, $P < 0.0001$), while the average daily duration of RRT was 20.5 ± 6.2 h in the CVVHDF group and 3.0 ± 0.4 h in the IHD group ($P < 0.0001$) (Figure 3). Achieved urea clearances during RRT
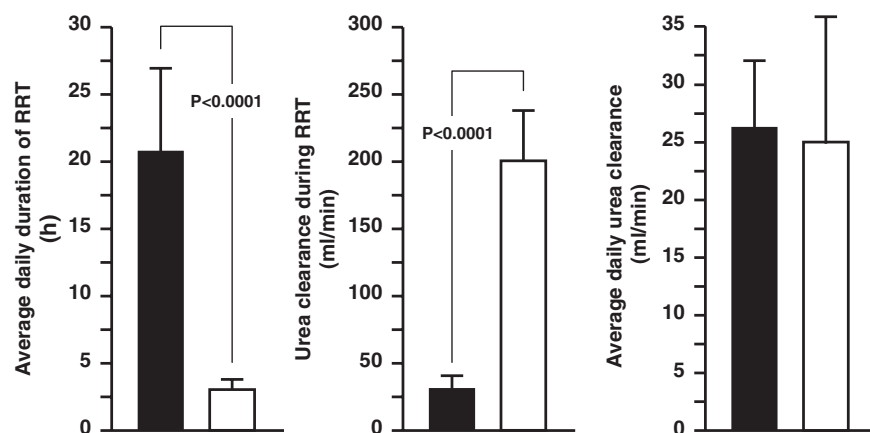
Fig. 3. Average daily duration of RRT, urea clearances during RRT and average daily urea clearances in the CVVHDF (solid bars) and IHD (open bars) groups (mean ± SD).

averaged 30 ± 4 ml/min with CVVHDF and 198 ± 39 ml/min with IHD ($P < 0.0001$). Thus, the average daily small solute clearance was comparable between the CVVHDF and IHD groups (25.9 ± 5.9 vs 24.8 ± 11.3 ml/min, $P = 0.34$) (Figure 3). However, the percentage of patients with an RRT clearance >20 ml/min was higher in the CVVHDF (84%) than in the IHD group (57%, OR 3.9, $P < 0.001$). Mortality was similar in patients whose dose of RRT was <20 ml/min or ≥ 20 ml/min (48 vs 46%, $P = 0.89$).

The amount of fluid removed daily by RRT did not differ between the two groups (CVVHDF 1170 ± 1285 vs IHD 1307 ± 1018 ml/day). Average fluid balance was $+211 \pm 1351$ ml/12 h in CVVHDF patients and $+230 \pm 1264$ ml/12 h in IHD patients ($P = 0.66$). A total of 97 (75%) patients were on assisted ventilation during RRT [CVVHDF vs IHD, 55 (79%) vs 42 (76%), $P = 0.98$]. Ventilator-associated parameters in the two groups were comparable, FiO_2 was $48.7 \pm 19.4\%$ in CVVHDF and $46.4 \pm 19.2\%$ in IHD patients ($P = 0.09$), and PEEP was 6.4 ± 2.7 mmHg in CVVHDF and 6.4 ± 2.5 mmHg in IHD patients ($P = 0.87$).

Duration of RRT and length of stay

Duration of RRT did not differ between CVVHDF [6.0 (1–49) days] and IHD patients [7.0 (1–50) days, $P = 0.99$]. There was no significant difference in the duration of RRT in the 64 survivors of the CVVHDF [6.0 (1–38) days, $n = 37$] compared with those in the IHD group [6.0 (1–49) days, $n = 27$, $P = 1.00$]. The length of stay in the hospital was calculated from the time of randomization. Hospital length of stay did not differ significantly between CVVHDF and IHD survivors [20.5 (6–71) vs 30 (2–89) days, $P = 0.25$].

Renal recovery

Of the 64 patients who survived, 62 (97%) had complete or partial recovery of renal function.

One patient in each RRT group remained on dialysis. The percentage of patients with full recovery of renal function was 50% in the CVVHDF and 42% in the IHD group ($P = 0.61$). Serum creatinine concentration at hospital discharge was similar in patients randomized to CVVHDF [121 (72–242) μmol/l, $n = 36$] and to IHD [153 (59–496) μmol/l, $n = 26$, $P = 0.17$] and was not related to the presence of initial oliguria [non-oliguric, $n = 23$, 142 (60–496) μmol/l vs oliguric, $n = 39$, 147 (59–443) μmol/l, $P = 0.41$] or the presence of chronic renal insufficiency [non-CRF, $n = 53$, 125 (59–496) μmol/l vs CRF, $n = 9$, 208 (85–411) μmol/l, $P = 0.11$]. Multiple regression analysis with type of RRT, presence of pre-existing CRF, haemodynamic stability, use of vasopressor agents and therapy with aminoglycosides as independent variables revealed that pre-existing CRF was an independent predictor of renal recovery as measured by serum creatinine at discharge (F-ratio 4.509, $P = 0.038$). In the 53 survivors without pre-existing CRF, serum creatinine at hospital discharge was 117 (72–242) μmol/l in the CVVHDF group ($n = 30$) and 143 (59–496) μmol/l in the IHD group ($n = 23$, $P = 0.40$).

Discussion

Since the introduction of continuous haemofiltration and continuous haemodialysis, these techniques with several modifications have turned out to be efficient and safe [1]. Despite the conceptual advantages of continuous forms of RRT, including improved haemodynamics, easier fluid removal and flexibility with parenteral nutrition [1], continuous therapies exhibit some potential drawbacks such as access-related complications, bleeding and increased manpower or financial investments when highly sophisticated treatment devices are used [1]. Whether these peculiar features of the IHD and CVVHD methods are relevant for the outcome of critically ill patients with ARF can only be established in prospective controlled studies. A large multicentre trial failed

to answer this question appropriately because of inconsistencies in the randomization protocol [2]. Although the quality of RRT for patients with ARF has improved steadily during the last decade, no evidence with respect to survival rate suggests that continuous RRT is superior to intermittent RRT [1]. The present investigation provides information from a prospective, controlled trial about the effect of the unrestricted application of either IHD or CVVHD to all patients without any inclusion restrictions related to the underlying disease entity or physician's preference, a design mimicking reality in many institutions around the world where systematically either an IHD or a continuous method for RRT is prescribed in the ICU setting.

The worldwide standard care for ARF requiring dialysis in the ICU is IHD, as recently mentioned by Metha *et al.* [2]. Whereas this statement holds for many institutions in the USA, it is not the case in other countries such as, for instance, Australia, where continuous RRT is applied to >97% of the patients in the ICU by critical care physicians with restricted input from nephrologists [6]. These differences in physicians' preferences in the therapeutic approach for RRT in the ICU are by and large not evidence based, only partly understood, and probably best explained by local availability of devices for continuous or intermittent treatment, reimbursement system, training of physicians and their variable desire for interdisciplinary work or adherence to recommendations given by their professional groups. Besides these arguments accounting for the physicians' preferences, four aspects of potential benefit for the patient would argue in favour of the potentially more physiological continuous RRT.

Haemodynamic stability. Haemodynamic instability accounts for a substantial number of ICU patients with ARF given primarily a continuous method of RRT rather then IHD. In a recently published multi-centre study, 21% were not randomized for haemo-dynamic instability defined as an MAP <70 mmHg [2]. In the present investigation, patients were equally randomized regardless of the initial haemodynamic status. Moreover, the incidence of low blood pressure (MAP $\leq$65 mmHg) and the average variability between maximum and minimum daily MAP throughout the entire ICU period were similar in patients treated with CVVHD and IHD, indicating no therapy-induced enhanced instability. Patients treated with IHD received slightly higher amounts of colloids. Since the use of fluids and nutrition was not controlled during this study, we do not know if the higher amounts of colloids administered during IHD were given to counteract real or to prevent expected episodes of haemodynamic instability.

In order to avoid or to enhance pre-existing haemodynamic instability, the therapeutic maneouvre of IHD was started gently with a blood flow of 150 ml/min, using a low surface area filter of $0.5 \, \text{m}^2$ for a short duration of 2–3 h, removing small amounts of fluid (0–500 ml/h). Such gentle procedures resulted in daily IHD sessions for the majority of patients during the first days of RRT. The median frequency of IHD sessions over the whole period of RRT was five per week. The results would certainly have been different if we had not chosen to let haemodynamic stability guide our treatment prescriptions but rather had tried to minimize the number of intermittent treatments to three per week.

Removal of cytokines. It appears *a priori* reasonable to remove continuously and not intermittently inflammatory mediators including cytokines in critically ill patients with sepsis [7,8]. Mass-balance considerations revealed, however, that only insignificant numbers of these mediators are removed in comparison with endogenous clearance [8,9]. Furthermore, it is unknown whether the clearance of pro-inflammatory endobiotics by the extracorporeal therapy is not outweighed by a similar or even more pronounced removal of their natural antagonists [8]. On the other hand, dialysis procedures are pro-inflammatory by themselves as a consequence of blood–membrane contact [10–12]. Thus, it is conceivable that a shorter duration of blood–membrane contact as in IHD might diminish the overall exposure of the patients to inflammatory mediators.

Total parenteral nutrition. Total parenteral nutrition requires large amounts of fluid dispensed daily, and in patients with ARF can only be achieved when net fluid is removed. Therefore, one might anticipate a shorter duration or lower dose of parenteral nutrition assigned to patients on IHD than in those on CVVHD. Interestingly, no such difference was found between the two groups. This is best explained by the fact that in our institution the need for nutrition and supplementation of blood constituents dictate the amount of dialysis therapy delivered and not vice versa.

Delivered dose of dialysis. With increasing haemo-dialysis, dose mortality rates decrease in chronic haemodialysis patients in the out-patient environment [13,14] and in patients with ARF treated with venovenous haemofiltration in the ICU [15,16]. Such a dose–response relationship has been clearly observed when the low dose range was considered for both patients with CRF on IHD and patients with ARF on venovenous haemofiltration or IHD. However, this dose–response relationship has not been shown so far in patients on chronic IHD [14] and was absent in patients with ARF on venovenous haemofiltration [15], when an intensive treatment strategy such as that for both groups of patients in the present investigation was applied. Thus, it appears that even when a high dose of dialysis is delivered with IHD or CVVHDF to patients with ARF in the ICU, their outcome with respect to survival is not dependent on the type of RRT chosen, provided an adequate dose of dialysis is delivered which allows azotaemic control with full nutritional support, volume, electrolyte and acid–base balance [17]. These targets can only be reached of

course with IHD when treatment sessions occur daily whenever required [16].

The present study has limitations. The open design which cannot be avoided for this type of therapeutic interventions might have influenced the outcome of the patients. The power of the study is lower than originally predicted due to the pre-terminal end and the smaller than expected number of patients included. The studied number of 55 and 70 patients, respectively, would only have allowed the detection of a mortality difference of 25% between the two therapies with a power of 80% [5]. The tendency for a slightly lower mortality observed in the non-randomized patients treated by IHD precludes a bias towards a healthier patient population in the randomized patients treated by IHD. More than two-thirds of the participants were white men. Subgroup analyses were not possible and thus it is conceivable that a potential benefit of CVVHDF might be present in other racial groups or females, or patients with a specific disease state. Furthermore, some patients with multiorgan failure are so severely ill that they will die regardless of any form of therapy delivered. Others are well enough to survive any form of RRT. It is conceivable that the observations at the two extremes of the severity of illness spectrum have blunted any discrete advantages of one over the other form of RRT.

The conclusion that IHD and continuous treatment yield equal dialysis efficiency with respect to the final therapeutic end-point of survival is probably only valid for institutions where for both treatment modalities so-called biocompatible dialysis membranes [18–20] and machines which allow accurate automated volume/pressure control are applied by staff equally trained to provide a tailored treatment for both methods according to the patient's need.

In summary, CVVHDF as compared with IHD applied to medically unselected patients in a tertiary-care university hospital does not reduce mortality, nor does it influence length of stay, haemodynamic instability or recovery of renal function.

Conflict of interest statement. None declared.

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