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Intermittent high-volume predilution on-line haemofiltration versus standard intermittent haemodialysis in critically ill patients with acute kidney injury: a prospective randomized study

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Abstract

Background. The optimal modality of dialysis treatment in critically ill patients with acute kidney injury (AKI) remains unclear. Intermittent high-volume predilution on-line haemofiltration (HF) is not a well-established dialysis modality. The purpose of the study was to compare clinical outcomes between HF and standard intermittent haemodialysis (HD) in this specific population.

Methods. In this prospective, randomized, controlled single-centre clinical study, we compared mortality and recovery of kidney function between HF and HD in critically ill adult patients with AKI. The primary study outcome was 60-day all-cause mortality. Secondary study outcomes included 30-day and in-hospital all-cause mortality along with recovery of kidney function. Time to kidney function recovery and the number of required dialysis procedures were analyzed in the subgroup of patients with in-hospital recovery of kidney function.

Results. Baseline characteristics of the 273 patients in the two study groups were similar. All-cause mortality by Day 60 was 65.0% in the HF group and 65.5% in the HD group (hazard ratio, 0.98; 95% confidence interval, 0.71–1.33; P = 0.87). There were also no significant differences between the two groups in 30-day and in-hospital all-cause mortality or recovery of kidney function. Time to kidney function recovery and the number of required dialysis procedures were similar between the HF and the HD subgroup of patients with in-hospital recovery of kidney function.

Conclusions. Dialysis treatment with intermittent high-volume predilution on-line HF in critically ill patients with AKI did not decrease mortality, improve recovery of kidney function or reduce the need for dialysis support compared to standard intermittent HD.

Keywords: acute kidney injury; critically ill patients; intermittent haemodialysis; intermittent high-volume predilution on-line haemofiltration; mortality

Introduction

Acute kidney injury (AKI) develops in more than one-third of critically ill patients treated in intensive care units (ICUs) [1], predominantly due to acute tubular necrosis (ATN) and as part of multiple organ failure (MOF). Essential supporting treatment of severe AKI is acute dialysis support, which is required in 5–6% of critically ill ICU patients [1, 2]. As a result of development and widespread use of dialysis treatment, complications of AKI are nowadays uncommon cause of death. Even so, AKI represents an important risk factor of morbidity and mortality [3] and AKI as part of MOF is still associated with high in-hospital mortality rates of 50–80% [1–6]. Although >60 years have passed since the first successful clinical use of dialysis in AKI, many fundamental issues concerning the optimal approach to dialysis management of AKI in critically ill patients with MOF, including the selection of dialysis modality, are still controversial [7–9].

In this specific population, different dialysis modalities have been introduced and some are already well-established. However, despite long-term clinical experiences and numerous studies, there is no consistent evidence that any particular modality has advantage over the others due to better clinical outcomes [10–15]. Standard and most commonly prescribed dialysis modality is intermittent haemodialysis (HD). Haemofiltration (HF) has been established mainly as continuous modality [2, 9], while intermittent high-volume predilution on-line HF is relatively new and rarely applied in everyday clinical practice. Intermittent HF is presently well-established in chronic dialysis patients, in whom various studies proved important advantages of chronic HF compared to HD [16–19].

In AKI as part of MOF, high-volume HF is supposed to confer beneficial effects particularly in critically ill patients with sepsis or other systemic inflammatory response syndromes, owing to higher convective clearances for middle/high-molecular-weight humoural mediators involved in the development of MOF [20–22]. There

are several small, observational non-randomized studies in severely ill ICU patients with advanced MOF that suggested improved patient outcomes when intermittent high-volume HF [23–26] or haemodiafiltration [27] was applied, but no relevant randomized controlled study has been published yet.

We performed a randomized controlled study to test the hypothesis that dialysis treatment with intermittent high-volume predilution on-line HF in critically ill patients with AKI can improve clinical outcomes, i.e. decrease mortality, increase recovery of kidney function and reduce the need for dialysis support compared to standard intermittent HD.

Materials and methods

Study design, setting and patients

This prospective, randomized single-centre clinical study comparing patient outcomes between intermittent high-volume predilution on-line HF and standard intermittent HD in critically ill ICU patients with AKI as part of MOF was undertaken at the Department of Nephrology, University Medical Centre Ljubljana, Slovenia.

Patients were eligible for enrolment if they were at least 18 years old, in ICU-treated critically ill patients, who had AKI due to ATN (based on clinical criteria) requiring acute dialysis support as well as a failure of at least one additional (non-renal) organ. Patients were excluded from the study if they had AKI due to other aetiology (not solely due to ATN), chronic kidney disease (baseline serum creatinine concentration ≥150 μmol/L), prior kidney or other organ transplantation, acute haematological or terminal stage malignancy, if they had received more than one intermittent or >24 h of continuous dialysis procedure prior to enrolment or if less than one study dialysis procedure was performed after enrolment (i.e. <50% of the first procedure due to patient death).

Patients were recruited from different ICUs of the University Medical Centre Ljubljana, Slovenia. Simple randomization was done. Eligible patients were randomly assigned to either the HF group or the HD group in 1:1 ratio according to randomization table by Fleiss [28]. The study group was written in closed numbered envelopes and thus blinded until enrolment of individual patient. In order to assess the adequacy of randomization, the following baseline patient characteristics at dialysis initiation were compared between the two modality groups: age, gender, weight, diuresis, serum concentration of creatinine, urea, potassium, bicarbonate and pH, presence of oliguria (diuresis < 400 mL/day), serum concentration of creatinine >300 μmol/L, urea >30 mmol/L, potassium >5.5 mmol/L, pH <7.2, fluid overload, mechanical ventilation, aetiological factors of AKI, number of failed non-renal organs and values of three different scoring systems, i.e. Acute Physiology and Chronic Health Evaluation II score (APACHE II) [29], Cleveland Clinic Foundation–Acute Renal Failure score [30] and Modified Organ System Failure score [31].

The study was performed in accordance with the ethical principles of the 'Declaration of Helsinki', and it was approved by The National Medical Ethics Committee of the Republic of Slovenia, which waived written patient informed consent for study enrolment. Due to the severity of the underlying critical illness and complications of AKI, patients were not legally competent and written informed consent could not be obtained from them. A decision about patient's enrolment was left to the discretion of the treating physicians taking into consideration the assumed patient's will according to opinion and principal consent from patient's relatives or legal representatives.

The study was registered in The Cochrane Renal Group registry (CRG030600055).

Interventions

Decision to initiate dialysis treatment was a specific inclusion criterion, so it had to be made ahead of patient's enrolment independently of the study. Indications for and the timing of dialysis initiation were not dictated by the study protocol but were determined in adherence to the generally accepted clinical practice. Dialysis modality was prescribed according to the assigned study group, i.e. either intermittent high-volume predilution on-line HF or intermittent HD. The modality assigned to individual patient at randomization was prescribed from the first dialysis procedure after enrolment to the last one.

General parameters of standard HD were not dictated by the protocol but were prescribed individually by the attending nephrologists with respect to temporary patient clinical characteristics and treatment goals. Several parameters of HF were dictated by the protocol, but others were prescribed individually. Further details of the prescribed parameters of intermittent HD and intermittent high-volume predilution on-line HF are described in the Appendix 1 and the Appendix 2, respectively. Special protocol for regional citrate anticoagulation for HF was designed and successfully applied in patients with increased bleeding risk [32]. Temporary untunnelled HD catheters were used as vascular access in all study patients [33].

Criteria for dialysis discontinuation were not dictated by the protocol but were the same as in regular practice, i.e. recovery of kidney function, patient death or withdrawal of life-sustaining therapy, including dialysis support. Recovery of kidney function was defined as improvement of kidney function to dialysis independence on the basis of clinical criteria. In patients with recovery of kidney function, time to recovery was considered to be equivalent to duration of dialysis treatment.

All study patients were followed up until the end of hospitalization, i.e. either until hospital discharge to home or death.

Study outcomes

The primary study outcome was mortality from any cause by Day 60 after randomization. Secondary outcomes included 30-day and in-hospital all-cause mortality along with 30-day and in-hospital recovery of kidney function. Time to kidney function recovery and the number of required dialysis procedures were analysed in the subgroup of patients with in-hospital recovery of kidney function.

Statistical analyses

Sample size calculation was based on the primary study outcome. To test the primary hypothesis, i.e. to detect a decrease in 60-day all-cause mortality from a priori estimated 65% (in the HD group) to 50% (in the HF group), at least 166 patients were required in each study group with an alpha risk set at 5% and a statistical power of at least 80%. Assuming a 10% dropout rate, we planned to enrol altogether 370 patients.

Because it was a single-centre study with a limited rate of patients' recruitment, interim assessments were performed in order to readjust the enrolment. When the number of the enroled patients had reached >80% of the required sample size, the interim analysis showed such a negligible difference in the primary study outcome between the two groups, that the detection of statistically significant difference could not be expected even if greater number of patients were enroled. For this reason, the investigators decided to end patients' recruitment prematurely.

All study outcomes were analysed according to the intention-to-treat principle. Normally distributed continuous variables were expressed as means ± SD and compared with the Student's *t*-test. Non-normally distributed variables were expressed as medians with interquartile ranges and compared with the non-parametric Mann–Whitney *U*-test. Proportions were compared with the chi-square test.

Rates of cumulative mortality and recovery of kidney function were calculated according to the Kaplan–Meier survival method. Comparisons of the Kaplan–Meier curves were performed with the log-rank test. Multivariate analyses of mortality and recovery of kidney function were performed using the Cox proportional hazard regression model, testing the effect of dialysis modality adjusted for the pre-specified variables considered to be of clinical significance, i.e. patient age, gender, APACHE II score, presence of oliguria, sepsis and major surgery. Additional subgroup analyses were performed with regard to the presence or absence of patient age >65 years, APACHE II score >25, oliguria and sepsis.

Two-sided P-value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using the SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL).

Results

Enrolment

Between December 2004 and January 2008, altogether 290 critically ill adult patients with AKI as part of MOF

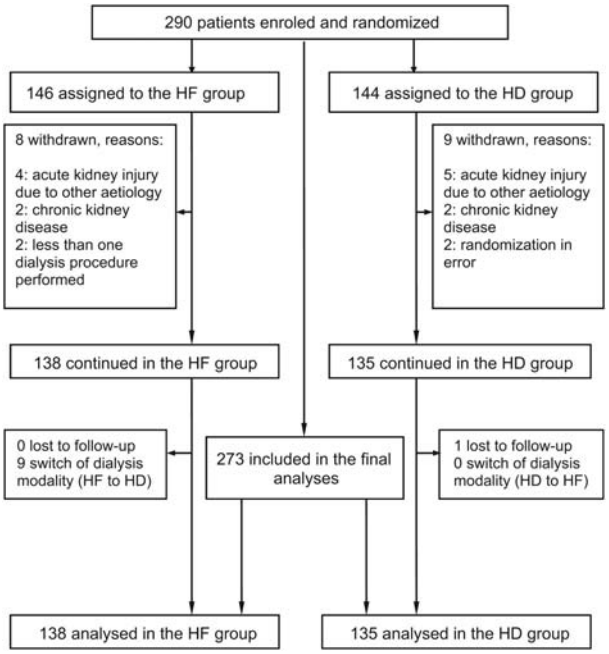


Fig. 1. Diagram showing enrolment, randomization and follow-up of study patients.

treated in eight different ICUs of the University Medical Centre Ljubljana were enroled in the study, 146 patients were randomly assigned to the HF group and 144 patients to the HD group (Figure 1). A total of 17 (5.9%) patients (9 in the HD and 8 in the HF group) were withdrawn after randomization because they were subsequently found to be ineligible for the study. Finally, 273 patients (138 patients in the HF group and 135 patients in the HD group) continued the study and were included in the final analyses. Only one patient in the HD group was lost to follow-up, all other patients were followed up until the end of hospitalization (overall until the end of May 2008).

Baseline characteristics

As shown in Table 1, baseline characteristics were similar between the two study groups, except for myoglobinuria, which was more frequent cause of AKI in the HD group. The mean (±SD) age was 68.7 ± 12.5 years, 66.3% of patients were male, 42.1% had oliguria and 75.1% required mechanical ventilation. AKI was most frequently attributed to sepsis (80.6%), ischaemia (69.2%) and major operation (39.2%). Other common aetiological factors were nephrotoxic antibiotics, myoglobinuria and

Table 1. Baseline characteristics of study patients[a]

Characteristic	Overall ($N = 273$)	HF group ($N = 138$)	HD group ($N = 135$)	P-value
Age (years)	68.7 ± 12.5	67.9 ± 12.2	69.5 ± 12.8	0.30
Male gender	181 (66.3)	91 (65.9)	90 (66.7)	0.90
Weight (kg)	79.7 ± 15	81.3 ± 14.1	77.8 ± 16.4	0.19
Urine output (mL/day)				
Mean ± SD	1135 ± 1176	1151 ± 1246	1118 ± 1094	0.83
<400	115 (42.1)	58 (42.0)	57 (42.2)	0.97
Creatinine (μmol/L)				
Mean ± SD	472 ± 165	481 ± 158	463 ± 171	0.37
>300	237 (86.8)	124 (89.8)	113 (83.7)	0.22
Urea (mmol/L)				
Mean ± SD	40.9 ± 15.5	39.4 ± 14.8	42.3 ± 16.1	0.14
>30	187 (68.5)	92 (66.7)	95 (70.4)	0.55
Potassium (mmol/L)				
Mean ± SD	4.9 ± 1.1	4.8 ± 0.9	5.0 ± 1.2	0.09
>5.5	66 (24.2)	28 (20.3)	38 (28.1)	0.10
pH				
Mean ± SD	7.29 ± 0.11	7.29 ± 0.11	7.29 ± 0.12	0.86
<7.20	49 (17.9)	27 (19.6)	22 (16.3)	0.54
Bicarbonate (mmol/L)	20.8 ± 5.4	20.5 ± 4.8	21.2 ± 6.1	0.36
Fluid overload				
Yes	145 (53.1)	75 (54.3)	70 (51.9)	0.73
Mechanical ventilation	205 (75.1)	107 (77.5)	98 (72.6)	0.33
Cause of ATN				
Sepsis	220 (80.6)	109 (79.0)	111 (82.2)	0.50
Ischaemia	189 (69.2)	90 (65.2)	99 (73.3)	0.15
Major surgery	107 (39.2)	53 (38.4)	54 (40.0)	0.79
Nephrotoxic antibiotics	94 (34.4)	44 (31.9)	50 (37.0)	0.37
Myoglobinuria	68 (24.9)	26 (18.8)	42 (31.1)	0.03
Radiocontrast agents	58 (21.2)	33 (23.9)	25 (18.5)	0.28
Other	23 (8.4)	13 (9.4)	10 (7.4)	0.55
Number of failed non-renal organs	3.3 ± 1.1	3.4 ± 1.1	3.2 ± 1.2	0.28
Severity of illness scoring system				
APACHE II score	31.1 ± 7.1	31.4 ± 7.6	30.9 ± 6.7	0.56
CCF–ARF score	10.6 ± 3.3	10.9 ± 3.1	10.3 ± 3.4	0.15
MOSF score	8.7 ± 2.5	8.8 ± 2.3	8.5 ± 2.7	0.27

[a]Data are presented as means ± SD or as total numbers (percentages). CCF–ARF score, Cleveland Clinic Foundation–Acute Renal Failure score; MOSF score, Modified Organ System Failure Score.

radiocontrast agents. Multiple potential causes of AKI were present in 84.6% of patients.

Management of study dialysis treatment

In the HF group, 129 (93.5%) patients received the assigned dialysis modality in >85% of all performed dialysis procedures. In nine patients (6.5%), HF was either switched to HD in all or was performed in <25% of all procedures. The most common reasons for the switch of HF to HD were technical problems, protocol violations and transfer of the patients from the University Medical Centre Ljubljana to another hospital. In the HD group, all patients received the assigned modality in all performed procedures.

Characteristics of study dialysis treatment and patients' follow-up are presented in Table 2. The number of dialysis procedures performed and the mean duration of dialysis treatment were similar between the two study groups, although the mean duration of the procedure was significantly longer in the HF group (4.8 versus 4.0 h; $P < 0.001$). The mean volume of infusate in the HF group was 81 ± 15 L, corresponding to the prescribed volume. Regional citrate anticoagulation was used in 33.7% of all procedures, more frequently in the HF group.

Study outcomes

Total all-cause mortality by Day 60 was 65.3% and was similar between the HF and the HD study group (65.0 versus 65.5%, $P = 0.94$) (Figure 2A). Multivariate analysis adjusted for the pre-specified variables confirmed that dialysis treatment with HF was not significantly associated with 60-day mortality (hazard ratio, 0.98; 95% confidence interval, 0.71–1.33; $P = 0.87$) (Table 3). Mortality by Day 60 was also not significantly different between the two study groups regarding all pre-specified subgroups (Figure 2B).

Total 30-day and in-hospital all-cause mortality was 51.2 and 70.7%, respectively. Total 30-day and in-hospital recovery of kidney function was 60.6 and 45.4%, respectively. Multivariate analyses showed no significant differences in any of the secondary outcomes between both modality groups (Table 3).

Kidney function has recovered during hospitalization in 124 (45.4%) patients, which is in all hospital survivors as well as in 44 (22.8%) hospital non-survivors. There was a trend towards fewer required dialysis procedures and faster recovery of kidney function in the HF subgroup compared to the HD subgroup of patients with in-hospital recovery of kidney function; however, these differences were non-significant (Table 4).

Complications of dialysis treatment

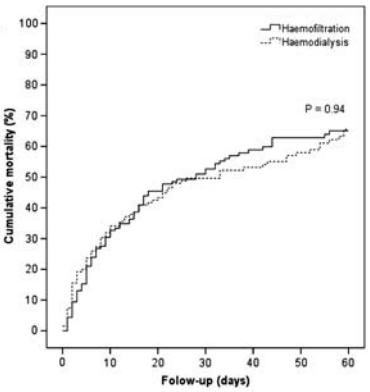
Hypotension, defined as an intratreatment reduction in mean arterial blood pressure of >20% from the pre-treatment value in at least one study dialysis procedure, was reported in altogether 124 patients (45.4%), among whom 73 patients (26.7%) had hypotension that required intratreatment introduction or escalation of vasopressors. Hypotension developed in lower proportion of patients receiving HF treatment (40.6%) than HD treatment (50.4%); however, the difference was not statistically significant (Table 5). Hypokalaemia (at least one measurement of serum potassium <3.8 mmol/L) was detected in 42.8% of patients in the HF group as compared with

Table 2. Characteristics of study dialysis treatment and follow-up of study patients[a]

Characteristic of study dialysis treatment	Overall ($N = 273$)	HF group ($N = 138$)	HD group ($N = 135$)
Dialysis procedures performed (number)	2679	1321	1358
Dialysis procedures/patient (number)			
Mean ± SD	9.8 ± 13.7	9.6 ± 13.8	10.0 ± 13.6
Median (interquartile ranges)	4 (2–13)	4 (2–13)	4 (2–13)
Duration of dialysis treatment (days)			
Mean ± SD	17.5 ± 30.7	17.0 ± 34.3	18.1 ± 26.7
Median (interquartile range)	7 (2–21)	7 (2–18)	7 (1–23)
Duration of dialysis procedure (hours)			
Mean ± SD	4.4 ± 0.94	4.8 ± 0.8	4.0 ± 0.9
Median (interquartile range)	4.5 (4.0–5.0)	5.0 (4.5–5.5)	4.0 (3.5–4.5)
Blood flow rate (mL/min)	294 ± 48	316 ± 51	271 ± 31
Dialysate flow rate (mL/min)	NA	NA	500
Volume of infusate (L)			
Mean ± SD	NA	81 ± 15	NA
Median (interquartile range)	NA	80 (72–96)	NA
Anticoagulation (%)			
None	4.8	0	9.6
Heparin	61.5	58.7	64.5
Citrate	33.7	41.3	25.9
Surrogate markers of dialysis dose			
Daily plasma urea (mmol/L)[b]	29.1 ± 8.6	28.5 ± 8.3	29.8 ± 8.9
Daily serum creatinine (μmol/L)[b]	327 ± 117	321 ± 116	332 ± 120
Follow-up of study patients (days)			
Median (interquartile range)	22 (7–56)	21 (7–54)	23 (6–58)

[a]Data are presented as total numbers, percentages, means ± SD or as medians (interquartile ranges). NA, not applicable.
[b]Concentrations were measured in routine morning blood samples.

A



B

Baseline characteristic	No. of patients	HF group (N=138)	HD group (N=135)	Hazard ratio for mortality by Day 60 (95% confidence interval)
Overall	273	50.5	49.5	0.98 (0.71 – 1.33)
Age				
≤ 65 years	85	34.1	28.1	1.04 (0.57 – 1.90)
> 65 years	188	65.9	71.9	0.94 (0.64 – 1.36)
APACHE II score				
≤ 25	60	22.5	21.5	1.37 (0.60 – 3.13)
> 25	213	77.5	78.5	0.91 (0.65 – 1.28)
Oliguria				
no	158	58.0	57.8	1.24 (0.79 – 1.94)
yes	115	42.0	42.2	0.77 (0.50 – 1.21)
Sepsis				
no	53	21.0	17.8	1.91 (0.81 – 4.50)
yes	220	79.0	82.2	0.85 (0.61 – 1.21)
				0.5 1.0 1.5 2.0
				HF better HD better

Fig. 2. Kaplan–Meier estimates of cumulative mortality (panel **A**) and hazard ratios for mortality by Day 60, according to baseline characteristics (panel **B**). Panel A shows the cumulative mortality from any cause in the HF and the HD study group. Panel B shows hazard ratios (and 95% confidence intervals) for mortality by Day 60 in the HF group as compared with the HD group. There was no significant interaction between dialysis modality and subgroup variables.

35.6% in the HD group (P = 0.22) and hypophosphataemia (at least one measurement of serum phosphate <0.8 mmol/L) in 10.1 and 7.4%, respectively (P = 0.43). The proportions of patients who underwent at least one episode of any serious adverse event requiring discontinuation of dialysis procedure were not significantly different between the two modality groups (Table 5).

Discussion

In this randomized, controlled single-centre clinical study, intermittent high-volume predilution on-line HF did not significantly decrease mortality of critically ill ICU patients with AKI as part of MOF compared to standard intermittent HD. There were also no significant differences in the rate of kidney function recovery or the need for dialysis support. Complications associated with dialysis treatment developed in similar proportions of patients in both modality groups.

Our results disagree with those from small, observational non-randomized studies that suggested improved clinical outcomes in severely ill ICU patients with advanced MOF, who were treated with intermittent high-volume HF [23–26] or haemodiafiltration [27]. However, no relevant randomized controlled study has been published beforehand. Mortality rate in the present study is higher than the rates reported in several other studies involving critically ill ICU patients with AKI as part of MOF [10, 34–39]. Higher values of prognostic scores and advanced MOF indicate worse prognosis of our study patients at enrolment compared to these studies. The main reason is probably the design of our study, namely non-requirement of written patient informed consent as inclusion criterion, which allowed more extensive and uniform enrolment of the most severely ill patients (including the patients requiring immediate initiation of dialysis) as well. Another study by Gastaldello *et al.* [40], which investigated the influence of different types of dialysis membranes on the clinical outcomes of AKI in critically ill ICU patients, used similar approach. Difficulties in acquiring written informed consent represent one of the major obstacles to recruitment of critically ill ICU patients. Studies have shown that in this particular population, restricting a study sample only to patients with obtained consent may lead to selection bias and thus limit generalizability of study results [41–43]. Time constraints associated with obtaining the consent disproportionately prevent from study enrolment mostly patients with the highest and the earliest mortality and may result in a 'death before consent' bias [41]. Avoiding such potential selective enrolment due to non-requirement of written consent has presumably contributed substantially to high mortality in our patient cohort but on the other hand enabled our study sample to be highly representative of the broad spectrum of critically ill patients with AKI as part of MOF. An additional reason for high mortality is sepsis, which was the most frequent cause of AKI (potentially contributing to development of AKI in 80.6% of all study patients) and is the leading cause of mortality in critically ill ICU patients [3, 6, 44].

Our results of kidney function recovery are comparable with those reported in previous studies, showing partial or complete recovery of kidney function following AKI as part of MOF in up to 95% of surviving as well as in up to 20% of non-surviving patients [10, 11, 35–37]. Kidney function has recovered in all our hospital survivors, which confirms a high potential for recovery of kidney function in case of 'de novo' AKI due to ATN also in critically ill patients with MOF, providing their survival and recovery from critical illness.

To our knowledge, this is the first randomized controlled study that compared clinical outcomes between intermittent high-volume predilution on-line HF and standard intermittent HD in critically ill ICU patients with AKI as part of MOF. Nevertheless, the lack of statistical power remains an important limitation of our study. Recruitment of study patients ended before the required

Table 3. Primary and secondary study outcomes

Outcome	Overall ($N = 273$)	HF group ($N = 138$)	HD group ($N = 135$)	Hazard ratio[a] (95% CI)	P-value
60-Day mortality[b]	65.3 (59.2–71.4)	65.0 (56.4–73.6)	65.5 (56.774.3)	0.98 (0.71–1.33)	0.87
30-Day mortality[b]	51.2 (45.1–57.3)	52.7 (44.3–61.1)	49.6 (41.0–58.2)	0.93 (0.66–1.31)	0.69
In-hospital mortality[c]	193 (70.7)	95 (68.8)	98 (72.6)	0.97 (0.72–1.29)	0.82
30-Day recovery of kidney function[b]	60.6 (52.6–68.6)	65.4 (54.0–76.8)	55.5 (43.9–67.1)	1.25 (0.84–1.85)	0.28
In-hospital recovery of kidney function[c]	124 (45.4)	65 (47.1)	59 (43.7)	1.12 (0.77–1.61)	0.56

[a]Hazard ratios (95% CI) in the HF group as compared with the HD group were calculated using the Cox proportional hazard regression model adjusted for the following pre-specified covariates: patient age, gender, APACHE II score, presence of oliguria, sepsis and major surgery. CI, confidence interval.
[b]Data are presented as percentages (95% CI); analysis with the Kaplan–Meier survival method.
[c]Data are presented as total numbers (percentages).

Table 4. Subgroup of patients with in-hospital recovery of kidney function[a]

Characteristic of study dialysis treatment	Overall ($N = 124$)	HF subgroup ($N = 65$)	HD subgroup ($N = 59$)	P-value
Dialysis procedures performed (number)	1227	517	710	NA
Dialysis procedures/patient (number)				
Mean ± SD	9.9 ± 12.2	8.0 ± 7.8	12.0 ± 15.6	0.06
Median (interquartile range)	5 (2–13)	4 (2–12)	7 (2–13)	0.38
Duration of dialysis treatment (days)				
Mean ± SD	17.7 ± 24.2	14.9 ± 21.3	20.7 ± 27.0	0.18
Median (interquartile range)	10 (3–24)	8 (3–20)	14 (3–30)	0.20

[a]Data are presented as total numbers, means ± SD or as medians (interquartile ranges). NA, not applicable.

Table 5. Summary of complications associated with study dialysis treatment[a]

Complication	Overall ($N = 273$)	HF group ($N = 138$)	HD group ($N = 135$)	P-value
Hypotension (>20% reduction in MAP)	124 (45.4)	56 (40.6)	68 (50.4)	0.13
Requiring introduction or escalation of vasopressors	73 (26.7)	32 (23.2)	41 (30.4)	0.18
Electrolyte disturbance[b]				
Hypokalaemia	107 (39.2)	59 (42.8)	48 (35.6)	0.22
Hypophosphataemia	24 (8.8)	14 (10.1)	10 (7.4)	0.43
Other serious adverse events[c]				
Arrhythmia causing haemodynamic instability	24 (9.5)	11 (8.0)	13 (9.6)	0.63
Bleeding	9 (3.3)	4 (2.9)	5 (3.7)	0.71
Filter clotting	11 (4.0)	7 (5.1)	4 (3.0)	0.38

[a]Data are presented as total numbers (percentages) of patients with at least one complication episode. MAP, mean arterial pressure.
[b]Concentrations were measured in routine morning blood samples.
[c]Requiring discontinuation of dialysis procedure.

sample size was reached; consequently, the study is underpowered to detect statistically significant reduction in mortality in the HF as compared with the HD group. Although our results cannot exclude the possibility that high-volume predilution on-line HF confers better clinical outcomes in critically ill patients with AKI as part of MOF, they imply that potential survival benefit, if present at all, would not be clinically relevant. In addition, our study is subject to several other limitations. Firstly, indications for and the timing of dialysis initiation were not dictated by the study protocol but were equal as in everyday clinical practice, based on broader patient clinical characteristics and trends of standard parameters, i.e. uraemia, hyperkalaemia, metabolic acidaemia, oliguria and/or fluid overload. There were no differences regarding these initiation criteria between the two groups. Except for emergency indications, clinical and biochemical parameters pointing to the optimal time to initiate dialysis support in critically ill patients with AKI as part of MOF remain undefined [45]. There are only few suitably designed high-quality studies, which have not confirmed better patient outcomes with ‘early’ versus ‘late’ dialysis initiation [37, 46, 47], therefore, we assume that the timing of initiation did not significantly influence our results. Secondly, dialysis dose or the intensity of dialysis treatment was not standardized in the protocol but was prescribed individually with respect to temporary treatment goals based on everyday patients’ assessment. Likewise, actual delivered dose was not estimated and compared between the two study groups by means of

standard parameters. However, the issue of dialysis dose and the validation of adequacy parameters are controversial in many aspects. Above all, critically ill patients with severe AKI differ substantially from stable chronic dialysis patients, in whom standard parameters were established and validated [48–51]. Furthermore, in contrast to guidelines concerning chronic dialysis (recommending high doses), there is no consensus on the optimal dialysis dose in this specific group of patients [48, 49]. Few earlier studies suggested superior clinical outcomes with higher doses [34–36], but many recent studies, including two multicentre, so far the largest randomized controlled studies among critically ill ICU patients with AKI as part of MOF, proved no significant improvements in survival or recovery of kidney function with higher compared to conventional doses, regardless of dialysis modality [37–39, 52, 53]. These studies present relatively firm evidence that in this population, increasing the intensity of dialysis support beyond the standard level provides no additional clinical benefit. Accordingly, we can assume that even though dialysis dose was possibly different between the two study groups, the intensity of dialysis treatment did not significantly affect our results. Mean daily urea and creatinine concentration as the main blood markers of uraemic retention/dialytic clearance were not significantly different between the HF and the HD groups, which suggests similar dialysis dose in both modality groups, although we agree with many other authors that concerning various complex problems in patients with AKI as part of MOF small solute clearance or surrogate markers alone cannot adequately reflect dialysis efficiency or cover the wide-ranging goals of dialysis support. Finally, patients with pre-existing chronic kidney disease were excluded from our study because they represent unique population with distinctively different prognosis (that is with both lower mortality and lower potential for kidney function recovery) compared to patients with 'de novo' AKI [54–56]. Still, patients with acute-on-chronic kidney injury constitute a considerable proportion of critically ill ICU patients requiring acute dialysis support. Because of their exclusion, our results cannot be generalized to such patients but are limited only to patients with true 'de novo' AKI due to ATN.

In critically ill patients with AKI as part of MOF, there is no consistent evidence that particular dialysis modality is superior to the others owing to better clinical outcomes, therefore, the selection of the optimal modality is still questionable. Although our study did not show improved clinical outcomes of intermittent high-volume predilution on-line HF compared to standard intermittent HD, it suggests that the application of high-volume on-line convective modality is feasible, safe and effective also in this specific population, in whom it is currently used only rarely in everyday clinical practice. Additional analyses addressing the technical issues, the workload required from dialysis staff and the costs are required to estimate whether this relatively novel dialysis modality could be added to the spectrum of modalities that are already established and applied routinely. In our dialysis centre, we have long-term clinical experiences with intermittent high-volume on-line HF in chronic dialysis patients, which is a valuable advantage. Very recently, Kron *et al.* [27] reported that having used the conventional on-line dialysis equipment already available in daily routine of dialysis facility (as it was in our study as well), the material costs per one intermittent high-volume on-line haemodiafiltration session were comparable to the costs per one standard HD session in chronic dialysis patient and thus much more cost-effective compared to conventional continuous modalities requiring expensive solution bags. We believe that the availability of larger choice of different modalities (diffusive and convective as well as intermittent and continuous), their exchange and combinations is beneficial because it facilitates more individual dialysis care, which might possibly be 'the best dialysis modality' or 'the best approach to dialysis treatment' in critically ill patients.

In conclusion, the present study indicates that dialysis treatment with intermittent high-volume predilution on-line HF in critically ill patients with AKI as part of MOF does not improve survival or recovery of kidney function compared to standard intermittent HD. Nevertheless, we have demonstrated that high-volume predilution on-line HF with individual reverse osmosis and regional citrate anticoagulation can be performed easily, safely and effectively also in the most severely ill ICU patients, which promises favourable options for further exploration of high-volume on-line convective modalities in the ICUs. The optimal approach to prescribe modality of dialysis treatment that could potentially improve the grave prognosis of these patients remains to be defined.

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Appendix 1. Prescribed parameters of intermittent HD

Dialysis monitor: Gambro AK-200 ULTRA S (Gambro, Lund, Sweden) with individual water treatment system WRO 300 (Gambro).

Haemodialyser: biocompatible synthetic highly permeable hollow-fibre membrane (Polyflux; Gambro or FX; Fresenius Medical Care, Bad Homburg, Germany) of different areas with respect to patient's body surface (body weight and height).

Blood flow rate: 250–300 mL/min.

Dialysate flow rate: 500 mL/min.

Composition of dialysate (electrolyte concentrations in mmol/L): sodium 140–150, potassium 2–4, calcium 1.25–1.75, magnesium 0.5, bicarbonate 26–40, glucose 5.5, chloride 108.0–109.5, acetate 3.

Temperature of dialysate: prescribed individually; 35–38°C.

Neto ultrafiltration: prescribed individually; 0–500 mL/h.

Procedure duration: prescribed individually; generally 3–5 h.

Procedure schedule: prescribed individually; generally every day or every alternate day.

Anticoagulation: prescribed individually; standard heparin, regional citrate anticoagulation, no anticoagulation (heparin-free).

Vascular access: temporary untunnelled HD catheter; insertion site and type prescribed individually; femoral, jugular or subclavian; single-lumen or double-lumen.

Appendix 2. Prescribed parameters of intermittent high-volume predilution on-line HF

Dialysis monitor: Gambro AK-200 ULTRA S (Gambro) with individual water treatment system WRO 300 (Gambro).

Haemofilter: biocompatible synthetic highly permeable hollow-fibre membrane, with an area of 2.4 m^2 (Polyflux 24S; Gambro) or 2.2 m^2 (FX 100; Fresenius Medical Care).

Blood flow rate: 250–400 mL/min.

Volume of infusate (replacement fluid): ∼1.3 times the dry body weight, i.e. 60 L at dry body weight <50 kg, 60–100 L at dry body weight of 50–80 kg and 100 L at dry body weight >80 kg.

Degree of predilution (infusate flow rate/blood flow rate ratio): 1–1.5.

Composition of infusate: equivalent to composition of dialysate.

Temperature of infusate: prescribed individually; 35–38°C.

Neto ultrafiltration: prescribed individually; 0–500 mL/h.

Procedure schedule: prescribed individually; generally every day or every alternate day.

Anticoagulation: prescribed individually; standard heparin, regional citrate anticoagulation.

Vascular access: temporary untunnelled HD catheter; insertion site and type prescribed individually; femoral, jugular or subclavian; single-lumen or double-lumen.

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