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ORIGINAL

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial

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Abstract *Purpose:* Septic shock is a leading cause of death among critically ill patients, in particular when complicated by acute kidney injury (AKI). Small experimental and human clinical studies have suggested that high-volume haemofiltration (HVHF) may improve haemodynamic profile and mortality. We sought to determine the impact of HVHF on 28-day mortality in critically ill patients with septic shock and AKI. *Methods:* This was a prospective, randomized, open, multicentre clinical trial conducted at 18 intensive care units in France, Belgium and the Netherlands. A total of 140 critically ill patients with septic shock and AKI for less than 24 h were enrolled from October 2005 through March 2010. Patients were randomized to either HVHF at 70 mL/kg/h or standard-volume haemofiltration (SVHF) at 35 mL/kg/h, for a 96-h period. *Results:* Primary endpoint was 28-day mortality. The trial was stopped prematurely after enrolment of 140 patients because of slow patient accrual and resources no longer being available. A total of 137 patients were analysed (two withdrew consent, one was excluded); 66 patients in the HVHF group and 71 in the SVHF group. Mortality at 28 days was lower than expected but not different between groups (HVHF 37.9 % vs. SVHF 40.8 %, log-rank test $p = 0.94$). There were no statistically significant differences in any of the secondary endpoints between treatment groups. *Conclusions:* In the IVOIRE trial, there was no evidence that HVHF at 70 mL/kg/h, when compared with contemporary SVHF at 35 mL/kg/h, leads to a reduction of 28-day mortality or contributes to early improvements in haemodynamic profile or organ function. HVHF, as applied in this trial, cannot be recommended for treatment of septic shock complicated by AKI.

Keywords Acute kidney injury · Renal replacement therapy · High volume hemofiltration · Blood purification · Septic shock

Introduction

Septic shock is common, increasingly encountered and an important attributable cause of death (30–45 %) [1], in particular when complicated by acute kidney injury (AKI) [2]. While numerous innovative therapies have been tried in recent years, the majority, such as recombinant human activated protein C, toll-like receptor-4 antagonist and tight glycaemic control, have shown either no efficacy or harm [3–5].

High-volume haemofiltration (HVHF) for critically ill patients with septic shock and AKI is an appealing strategy for maintaining azotaemic, acid–base and fluid homeostasis, along with having the potential to modulate the immune system response to sepsis by removal of toxins and other inflammatory mediators that contribute to organ injury and dysfunction [6–10]. Indeed, experimental studies have shown HVHF can improve myocardial performance and systemic haemodynamics while also removing inflammatory cytokines [11–15]. Human clinical studies, mostly conducted in refractory septic shock, have also shown that HVHF can improve systemic haemodynamics and contribute to lower than expected mortality [16–22].

While observational data suggest that HVHF is frequently utilized [23, 24], the available data are clearly suboptimal because of limitations in study design (i.e. non-randomized case series, retrospective cohort studies, no control group), variability in technique applied (i.e. duration of therapy, dose of therapy, haemofilter type) and failure to evaluate the breadth of potential adverse consequences associated with HVHF (i.e. excessive loss of micronutrients [25, 26], antimicrobial clearance [27]). Additionally, there are limited data to support evidence of significant serum clearance of inflammatory mediators with HVHF [28–30].

Accordingly, in response to the need for higher quality data on this issue, we performed a multicentre randomized controlled trial of HVHF in critically ill patients with septic shock and AKI. Our primary objective was to compare the efficacy of high-volume (70 mL/kg/h) compared with standard-volume (35 mL/kg/h) haemofiltration in the management of critically ill patients with septic shock complicated by AKI on 28-day survival.

Methods

Human research ethics review and approval were obtained from the Human Research Ethics Committee for South-West France and Overseas Departments (CPP SOOM III, approval number 05-01), from each participating institution's human ethics committee for those centres from outside France and from the French National Agency for the Safety of Health Products (AFSSAPS) prior to study commencement.

The trial protocol was registered on ClinicalTrials.gov (identifier: NCT00241228). The trial had an independent Data Safety and Monitoring Committee (DSMC) that examined the description of severe adverse events data and was intended to interpret the planned interim analysis and provide advice on the overall conduct of the trial. The trial enrolment period was from October 2005 through March 2010.

Trial design

The IVOIRE (hIgh VOlume in Intensive caRE) trial was a prospective randomized clinical trial conducted at 18 ICUs in France, Belgium and the Netherlands. The primary objective was to evaluate whether the application of high-volume haemofiltration (HVHF, 70 mL/kg/h), compared with routine standard-volume haemofiltration (SVHF, 35 mL/kg/h) for 96 h in critically ill patients with septic shock for less than 24 h and AKI was associated with a reduction in 28-day mortality.

Participants

Written informed consent was obtained from each participant or next of kin prior to enrolment. In selected circumstances (i.e. urgent need for renal replacement therapy (RRT), next of kin immediately unavailable) participants were enrolled by deferred consent, where written informed consent was obtained from either the participant or next of kin as soon as possible. This practice is consistent with the French law and European regulations for clinical research and was approved by the ethics committee.

The inclusion criteria were (1) patient age $\geq$18 years, (2) admission to ICU, (3) presence of septic shock, defined according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee [31], for a period of no more than 24 h, and (4) presence of AKI fulfilling the INJURY category or greater according to the Risk, Injury, Failure, Loss, End-Stage Kidney Disease (ESKD) (RIFLE) classification scheme, by either the serum creatinine and/or urine output criteria [32]. Presence of any of the following exclusion criteria resulted in ineligibility: (1) age $\geq$80 years, (2) estimated life expectancy of $\leq$3 months, (3) metastatic cancer, (4) decompensated cirrhosis, (5) acute necrotizing pancreatitis, (6) prior diagnosis of ESKD, (7) confirmed pregnancy, (8) severe coagulopathy (defined as international normalized ratio (INR) >3 and/or platelet count <20,000 cells/mL), and (9) lack of commitment to full medical support.

In addition to the allocated haemofiltration therapy, all the patients received therapy for septic shock consistent with best contemporary practice and consensus guideline recommendations [Surviving Sepsis Campaign, recommendations for septic shock patients from the French Intensive Care Society (SFAR + SRLF)] [33].

We dosed all antibiotics during 5 days in the Bordeaux centre (45 patients) for an ancillary study planned before the start of the IVOIRE study (see protocol on ClinicalTrial.gov). All antibiotics were given at a standard dosage used in non-AKI patients (i.e. 16 g per day for piperacillin or 2 g per day for ceftriaxone) and at the same dosage in the two groups to avoid bias as recommended by the external reviewers at study acceptance by the authorities.

Study endpoints

The primary endpoint was 28-day mortality. The secondary endpoints included (1) change in haemodynamic profile (i.e. arterial blood pressure cardiac output, systemic vascular resistance, vasopressor dose and dependence) during the 96-h study intervention, (2) changes in Sequential Organ Failure Assessment (SOFA) score (components and composite) [34] and Simplified Acute Physiology Score II (SAPS II) [35] during the 96-h study intervention and at day 10 and day 28, (3) duration of mechanical ventilation, (4) duration of RRT and recovery of renal function, defined as independence from RRT at ICU discharge or death, (5) duration of stay in ICU and hospital, (6) mortality at 60 and 90 days after enrolment, and (7) adverse events attributable to haemofiltration therapy up to 28 days after enrolment.

Randomization

The allocation sequence was computer-generated by the clinical trials unit (CTU)'s statistician (SAS® software v. 9.1.3, SAS Institute Inc., Cary, NC, USA). The randomization ratio was 1:1. Randomization was stratified by centre, using blocks of four for centres with expected enrolment below 30, and random blocks of four or six for centres with an expected enrolment greater than 30. The allocation process was centralized and the allocation group was concealed until it was implemented. When a patient was eligible, the investigator logged on to the

secure CTU website (http://usmr.isped.u-bordeaux2.fr/) to obtain the treatment group allocated to the patient: continuous RRT (CRRT) at a total effluent dose of either 70 or 35 mL/kg/h for 96 h. As a result of feasibility issues, investigators and attending physicians were not blinded to the treatment assignment.

Procedure

In each centre, treatment was initiated and monitored by the attending physician responsible for the participant. A 14-French coaxial double lumen haemofiltration catheter was percutaneously inserted in the right internal jugular or femoral vein by applying the Seldinger technique. For all the patients, haemofiltration was performed with an Aquarius® haemofiltration circuit (Edwards Life Sciences) equipped with a 1.9 m^2 Aquamax® polyethersulfone filter (Edwards Life Sciences; molecular weight cut-off approximately 35,000 Da; low adsorption capacity). The same circuit and haemofilter were applied for all the participants to avoid bias.

Every haemofiltration was delivered in the continuous veno-venous haemofiltration (CVVH) mode. In the HVHF group, CVVH was prescribed at a dose of 70 mL/kg/h for 96 h. The blood flow rate was modified in order to maintain a filtration fraction ≤25 %, with average blood flow rates ranging between 200 and 320 mL/min. In the SVHF group, CVVH was prescribed at a dose of 35 mL/kg/h, which was in accordance with contemporary best practice recommendations at the time [21]. In both groups, target transmembrane pressure was maintained between 100 and 300 mmHg. All patients received unfractionated heparin for extracorporeal circuit anticoagulation, delivered by an electrically operated syringe driver, and titrated to maintain an activated clotting time (ACT) between 1.5 and 2 times that of the control test. Ultrafiltration rate (i.e. fluid removal) was adapted to the needs of the patient. The haemofilter was changed every 48 h. Replacement solution was divided in a 1/3–2/3 proportion between pre- and post-haemofilter dilution. Replacement solutions were commercially prepared from Baxter or Hospal and all contained bicarbonate buffer with virtually identical compositions [see Electronic Supplemental Material (ESM)]. For those participants still requiring RRT after the 96-h intervention, any form of renal support modality could be applied as necessary; however, treating physicians were instructed to prescribe a dose not above 35 mL/kg/h. Decisions regarding discontinuation of renal support were at the discretion of the treating physicians.

Data collection

Clinical data were recorded at baseline, every 12 h for haemodynamic parameters and every 24 h for biological parameters, all during 96 h. Severity of illness scores (SOFA score [34]; SAPS II [35]) were recorded at baseline, following the intervention period at 96 h and at days 10 and 28. The dosages of vasoactive/vasopressor agents were expressed as the inotropic score [36, 37], a dimensionless variable calculated as (dopamine dosage × 1) + (dobutamine dosage × 1) + (adrenaline dosage × 100) + (noradrenaline dosage × 100), wherein all dosages are expressed as micrograms per kilogram per minute. This score has also been referred to as the vasopressor score [38] or catecholamine index [39]. In clinical practice, the vasopressor dose is titrated periodically according to the mean arterial pressure (MAP). Thus, a dose–response relationship between vasopressor dose and MAP was used as another surrogate for the degree of haemodynamic impairment. This relationship was expressed as the vasopressor dependency index (VDI) by Cruz et al. [40], which is calculated as the ratio of inotropic score to MAP; the higher the score, the greater the vasopressor requirement. All data were captured by trained research coordinators and/or investigators on standardized electronic case report forms accessible through a secured website managed by the CTU of Bordeaux University Hospital (USMR, http://usmr.isped.u-bordeaux2.fr/).

Data and statistical analysis

Sample size estimation

The anticipated control (SVHF) group mortality was difficult to estimate because of the wide variability, between 40 and 80 %, reported in the literature [41–43]. In two prior pilot studies of HVHF for refractory septic shock, observed 28-day mortality was between 46 and 55 %, despite predicted mortality between 70 and 80 %, respectively [16, 17]. Accordingly, we hypothesized that 28-day mortality would be 46 % in the HVHF group and 61 % in the SVHF group. One interim analysis of the primary endpoint had been planned and the type I error adjusted to 2.9 % [44]. To detect this 15 % absolute reduction in 28-day mortality with an 85 % power, a sample size of 230 patients per group (a total 460) was required. Unfortunately, because of slow participant accrual, the trial was prematurely terminated and the decision was taken to keep only one final analysis, despite the possible lower power than expected and the higher risk of β error.

Data analysis

Analysis was performed by intention-to-treat. However, according to clinical research regulations, patients who withdrew consent were not taken into account for analysis. Discrete variables were described as numbers and

percentages and compared using chi-squared tests. Quantitative parameters were described by medians and interquartile ranges (IQR), and compared by Wilcoxon tests. Survival functions were estimated using the non-parametric Kaplan–Meier method and survival times were compared between treatment groups using the log-rank test. Day 0 (D0) was defined as the day of randomization. A Cox proportional hazards model regression analysis was carried out to adjust the effect of allocated treatment on prognostic factors of mortality, regardless of possible imbalances between groups [45]. The complete model included fluid volumes infused during the 12-h pre-inclusion period (crystalloids, synthetic colloids, albumin and packed red cells) and baseline values of PaO_2/FiO_2, SAPS II score, RIFLE stage, VDI and aspartate aminotransferase (ASAT). The Cox model assumptions were systematically checked. When the proportional hazards assumption was not fulfilled, the effect of treatment was modelled for different periods of time. When the linearity assumption was not fulfilled for continuous variables, transformations were used. No selection of variables was carried out, as the aim was to obtain the best-adjusted estimation of the effect of haemofiltration treatment. The evolution of secondary endpoints between day 0 and day 4 was assessed by mixed linear regression models including a random time effect.

Results

In total, 140 participants were randomized (66 to HVHF and 71 to SVHF). Of those randomized, three patients were excluded from analysis: two withdrew consent and one was excluded by the steering committee for major ineligibility criteria (Fig. 1). The median (IQR) duration in ICU prior to enrolment was 19 h (8–40).

Table 1 shows the demographic and baseline clinical characteristics stratified by treatment group. Participants were representative of critically ill patients with septic shock and AKI: median (IQR) age was 68.1 (58.4–75.1); 60.6 % were male; median (IQR) SAPS II score was 65 (57–75); and 97 % received mechanical ventilation.

Type of infection and identified causative microorganisms were not significantly different between groups. The most common sources of sepsis were gastrointestinal (ca. 50 %) and pulmonary (ca. 25 %), and the most common organisms were gram negative bacteria (ca. 66 %) (see tables in ESM).

Primary outcome

In a crude analysis, mortality at 28 days was not significantly different between treatment groups (HVHF: 25 deaths, 37.9 % vs. SVHF: 29 deaths, 40.8 %; log-rank test = 0.94) (Fig. 2). In the Cox model, the hazard ratio (HR) of death was not constant over the 28-day period. To comply with the assumption of hazard proportionality, two periods of treatment were therefore defined, based on visual inspection. Crude mortality was not significantly different between treatment groups during either period: from day 0 to day 1, there were five deaths in the HVHF group and one death in the SVHF group [HR 5.52; 95 % CI (0.65–47.28), $p = 0.12$]; from day 2 to day 28, there were 20 deaths in the HVHF group and 28 deaths in the SVHF group [HR 0.817; 95 % CI (0.46–1.45), $p = 0.49$]. In adjusted analysis, there was no significant difference between treatment groups in mortality at 28 days (Table 2). The only variables independently associated with an increased risk of death at 28 days were higher SAPS II score and lower PaO_2/FiO_2 ratio at baseline (Table 2).

Secondary outcomes

There were no statistically significant differences in any of the secondary endpoints between treatment groups, including 60- and 90-day mortality, duration of mechanical ventilation, duration of RRT, renal recovery, or ICU and hospital length of stay (Tables 3, 4). There were no statistically significant differences in temporal trends in illness severity, organ dysfunction or in any secondary physiologic or organ failure endpoint between treatment groups. Acid–base balance similarly improved for both groups and disturbances present at inclusion were well corrected after 96 h (Tables 3, 4). Moreover, the evolution of variables between day 0 and day 4, as assessed by mixed regression models, was not significantly different between the treatment groups (p values ranging from 0.13 to 0.92, data not shown).

Adverse events

There was no difference in the occurrence of serious adverse events between the groups. In total, three serious adverse events that had been defined as unexpected in the usual course of a septic shock (one myocardial infarction, one acute embolic stroke and one episode of major post-operative bleeding) occurred in three participants (one in HVHF and two in SVHF). Each event was independently adjudicated by the Hospital Pharmacovigilance Unit and found not be related to the study intervention.

We showed that all antibiotics were easily filtered, mean sieving coefficients were from 38.70 to 96.70 %. The mean elimination half-life of all the agents in the HVHF group (from 1.29 to 28.54 h) was significantly shorter than that reported in the SVHF group (from 1.51 to 33.85 h).

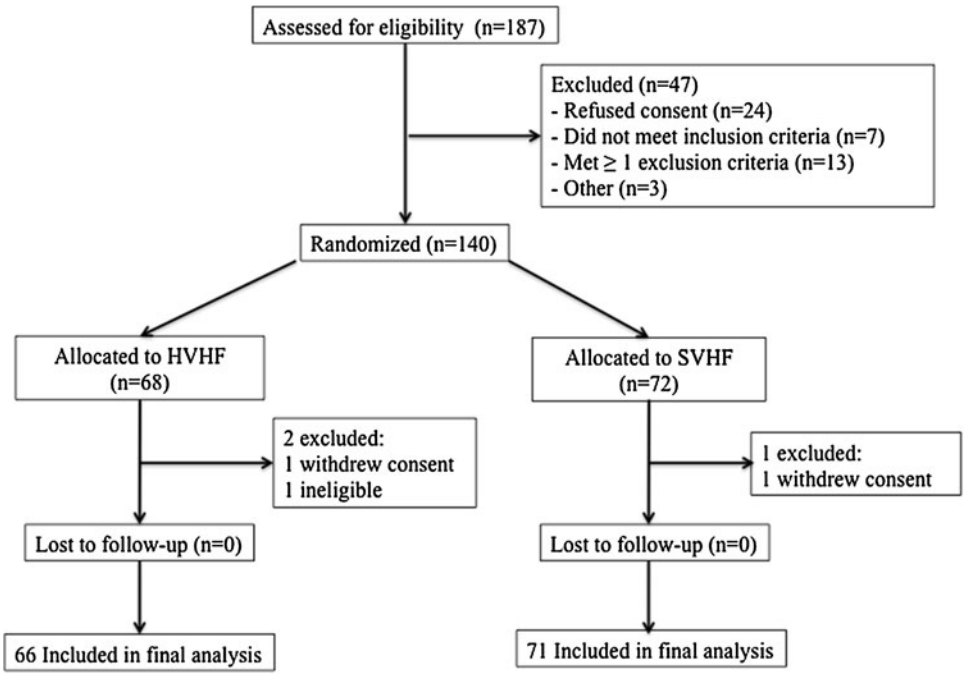

Fig. 1 Patient flow diagram

Additional adverse events were mostly limited to electrolyte disturbances with a trend for a higher number of events in the HVHF group—specifically hypokalaemia [30 % in HVHF vs. 20 % in SVHF ($p = 0.1$) (Table 3)] and hypophosphatemia [HVHF: 97 events, 88 % ($n = 32$) vs. SVHF: 43 events, 38 % ($n = 34$) ($p < 0.01$)] despite intravenous supplementation (hypophosphatemia was not recorded in the original database and was collected and analysed retrospectively; most data were available only after August 2008).

Discussion

To our knowledge, the IVOIRE study is the largest multicentre randomized controlled trial performed to date evaluating the impact of HVHF compared with SVHF on survival in critically ill patients with septic shock and AKI. This trial found no significant difference in the primary endpoint of 28-day mortality between those allocated to 96 h of protocolized HVHF compared with SVHF.

Unfortunately, the IVOIRE study was stopped prematurely on the basis of the trial steering committee's recommendation with support from the DSMC, primarily because of a lower than anticipated primary endpoint event rate, slower than anticipated participant accrual and for reasons related to limited resources. As a consequence, the trial had insufficient statistical power to detect a 15 % absolute reduction (25 % relative reduction) in 28-day mortality.

Despite this, we believe there are a number of important findings from this study that have implications for clinical practice that warrant discussion. The protocolized delivery of 96 h of HVHF was not associated with significant differences in survival at 90 days; renal recovery of dialysis dependence at 90 days; reductions in health resource utilization (i.e. duration of mechanical ventilation, duration of RRT, duration of ICU or hospital stay); or clinically important improvements in key physiologic and organ failure assessment outcomes. However, HVHF was associated with greater clearance of antibiotics and electrolytes as compared with SVHF.

The IVOIRE trial aimed to enrol critically ill patients with catecholamine-dependent septic shock, AKI and high acuity of illness. This population is generally characterized by an unacceptably high attributable mortality and utilizes a considerable breadth of health resources. There has been continued interest in the immune system modulating potential of HVHF. Recent data suggest that HVHF is applied in up to 11–22 % of critically ill septic patients [23, 24]. Numerous small clinical studies, many with important methodological limitations, had suggested encouraging clinical benefit with HVHF [16–19, 21]; however, the high-quality IVOIRE trial failed to confirm these findings. While the statistical power of the IVOIRE study was lower than expected, there was no trend of a clinical benefit across any of the primary and secondary outcomes of interest. In addition, a recent single-centre randomized study by Zhang et al., comparing HVHF (50 mL/kg/h) and very high-volume haemofiltration (85 mL/kg/h) on septic patients with AKI failed to show any difference [46]. Moreover, the mortality at 28 days

Table 1 Baseline patient characteristics according to the randomization group

Characteristics	High-volume HF group ($n = 66$)	Standard-volume HF group ($n = 71$)
Age, years	68 (58–77)	70 (58–75)
Male sex (n, %)	45 (68)	38 (54)
Weight (kg)	79 (65–90)	72 (66–85)
SAPS II score	68 (59–78)	64 (52–74)
SOFA score	12 (11–14)	12 (10–14)
Mean arterial pressure (mmHg)	78 (68–88)	80 (71–89)
Cardiac index (L/min)	3.5 (2.9–4.1)	3.3 (2.6–3.8)
SVRI (dyn s^{-1} cm^{-5})	1,277 (880–1,661)	1,333 (967–1,795)
PaO_2/FiO_2 (mmHg)	139 (87–243)	180 (93–243)
Urea (mmol/L)	19.0 (13.3–29.3)	18.5 (11.0–24.3)
Creatinine (μmol/L)	227 (159–319)	210 (159–276)
RIFLE injury/failure	46/20 (70/30)	57/14 (80/20)
Bilirubin (μmol/L)	18 (9–32)	20 (10–39)
ASAT (U/L)	64 (31–172)	105 (47–253)
pH	7.23 (7.13–7.29)	7.25 (7.17–7.32)
Bicarbonate (mmol/L)	17.15 (14.2–19.0)	18.2 (15.0–21.0)
Sodium, Na^+ (mmol/L)	139 (135–143)	137.5 (135–141)
Potassium, K^+ (mmol/L)	4.5 (4.1–5.2)	4.3 (3.9–4.8)
Lactate, arterial (mmol/L)	3.75 (2.12–6.80)	3.80 (2.47–6.40)
Mechanical ventilation	64 (97)	69 (97)
Noradrenaline (μg/kg/min)	0.87 (0.39–1.20)	0.80 (0.40–1.20)
Inotropic score	86.5 (40–125)	81.9 (41–130)
Vasopressor dependency index ($mmHg^{-1}$)	10.9 (4.8–18.6)	10.9 (5.3–16.0)
RRT prior to enrolment	0	0
Days in ICU prior to enrolment (days[a])	2.44 (0–5.31)	1.87 (1.1–2.64)
Surgical procedure/operative (n, %)	34 (51.5)	35 (49.3)
Corticosteroids (n, %)	36 (54.6)	39 (54.9)
Activated protein C (n, %)	7 (10.6)	6 (8.5)
Fluid therapy (mL/kg)[a]	29.9 (24–35.7)	33.8 (26–41.7)
Crystalloids (mL/kg)[a]	13.6 (10.2–16.9)	17.8 (11.7–23.9)
Synthetic colloids (mL/kg)[a]	9.2 (6.7–11.6)	9.8 (7–12.6)
Albumin (mL/kg)[a]	4.2 (2.2–6.2)	4.3 (3–5.7)
Red cells transfusion (mL/kg)[a]	2.9 (1.6–4.2)	1.9 (0.9–2.9)

Data are reported as median (1st–3rd quartile) for quantitative variables or number (%) for qualitative variables, unless otherwise indicated. Fluid therapy and components were fluids received in the 12 h prior to randomization. See "Methods" section for formulas for inotropic score and vasopressor dependency index

SAPS II Simplified Acute Physiology Score II, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, *SOFA* Sequential Organ Failure Assessment, *SVRI* systemic vascular resistance index, *ASAT* aspartate aminotransferase

[a] Expressed as mean (95 % CI)

(58 %) was markedly higher than in the IVOIRE trial (39 %) with lower overall illness severity (septic shock ca. 50 %; APACHE II score ca. 21).

Over a decade of clinical investigation in order to optimize RRT for critically ill septic patients provided a strong rationale for the IVOIRE trial. Ronco and colleagues were the first to describe the potential improved survival associated with higher total effluent volumes (>45 mL/kg/h) for patients with septic AKI [47]. In a small randomized trial, Boussekey and colleagues later found that HVHF was associated with an improved haemodynamic profile; however, there was no significant impact on organ dysfunction or survival [22]. Recently, two large multicentre randomized trials, the RENAL and ATN studies, found no added benefit of higher compared with standard intensity of RRT in heterogeneous cohorts of critically ill patients with AKI [48, 49], and there was no suggestion of improved outcome amongst the subgroups with sepsis. However, a recent post hoc analysis from the RENAL study showed that patients with acidosis had greater improvements in MAP and catecholamine requirement with higher intensity RRT (40 mL/kg/h) [50]. In the IVOIRE study, SVHF patients were already treated at 35 mL/kg/h and showed similar haemodynamic improvements to those receiving HVHF. This may be explained by a possible plateau effect for haemodynamic improvement at a haemofiltration dose of 35–40 mL/kg/h.

Furthermore, there is growing concern about the negative consequences of HVHF, in terms of the potential harm associated with excessive clearance of electrolytes, micronutrients, and essential drugs (i.e. antimicrobials, antiepileptics). Similar to the findings in the IVOIRE study, the RENAL and ATN trials along with additional smaller studies all found a higher incidence of hypophosphatemia and hypokalaemia in those receiving higher

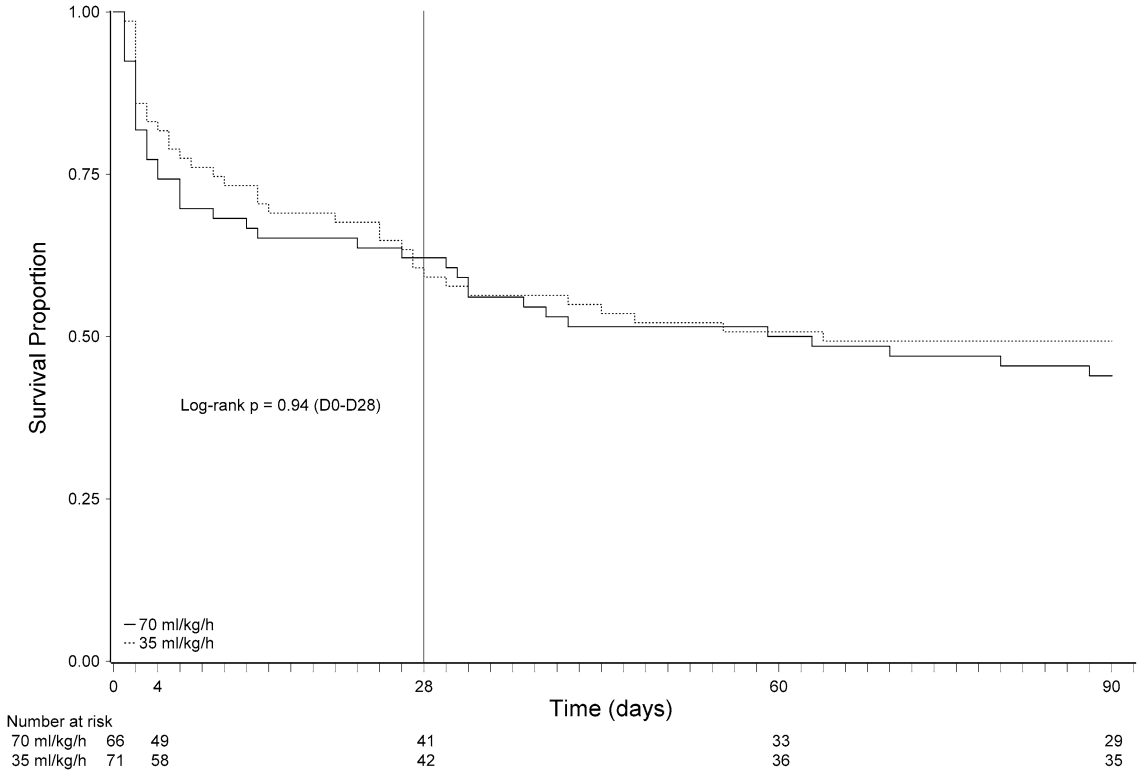

Fig. 2 Survival of participants in the IVOIRE (hIgh VOlume in Intensive caRE) trial. Participants in the HVHF group and SVHF group underwent haemofiltration at 70 mL/kg/h and 35 mL/kg/h of fluid exchange for 96 h, respectively

Table 2 Multivariate Cox model: adjusted effect of treatment (high-volume vs. standard-volume haemofiltration) and baseline prognostic factors on 28-day mortality

	Hazard ratio	95 % CI	*p*
Treatment[a] (haemofiltration 70 vs. 35 mL/kg/h)			0.23
From day 0 to day 1	3.404	0.39–29.95	0.27
From day 2 to day 28	0.665	0.36–1.24	0.20
$(SAPS\ II)^2/100$[b,c] (i.e. for additional 10 units on SAPS II)	1.024	1.01–1.04	0.0003
PaO_2/FiO_2 (mmHg)/100[c] (i.e. for additional 100 units on PaO_2/FiO_2)	0.628	0.44–0.90	0.012
Log (vasopressor dependency index)[b]	1.005	0.99–1.02	0.50
RIFLE (failure vs. injury)	1.667	0.90–3.10	0.11
ASAT (≥400 vs. <400 IU/L)	1.647	0.82–3.32	0.16
Fluid therapy 12 h before inclusion (mL/kg)	1.001	0.99–1.01	0.83

Day 0 date of randomization, *CI* confidence interval, *SAPS II* Simplified Acute Physiology Score II, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen, *ASAT* aspartate aminotransferase

[a] Two periods of treatment were defined to comply with the assumption of hazard proportionality

[b] Variable transformations to comply with Cox model log-linearity assumption

[c] Scale change for the sake of hazard ratios precision and interpretation

intensity RRT, despite protocolized replacement [48, 49, 51]. Importantly, there are some concerns regarding therapeutic failure due to the wide variability in achieving target concentrations of antimicrobials for patients receiving HVHF. In our study, clearances of all the agents were significantly higher in HVHF group, but patients were underdosed in the two groups for the most removed antibiotics such as β-lactam (i.e. total clearance for imipenem or piperacillin in the HVHF group was twice that in the SVHF group). This is comparable with the result of ancillary study on antibiotics removal in 24 patients from the RENAL study [52]. Those potential side effects may be highlighted by the higher mortality shown in Zhang et al.'s study [46] that used very high-volume haemofiltration and possibly increased the removal of some beneficial compounds.

Table 3 Comparison of patients' characteristics at different times after randomization (day 0) in the IVOIRE trial, according to randomization group

Variables	HVHF group ($n = 66$)	SVHF group ($n = 71$)	p
Prescribed dose (mL/kg/h)	70	35	
Treatment delivered (day 0–day 4 %)	93.8 (57.3–96.9)	94.8 (82.3–97.9)	0.29
Delivered dose (mL/kg/h)	65.6 (40–67.9)	33.2 (28.7–33.6)	
MAP at day 4 (mmHg)	92 (81–104) ($n = 48$)	92 (81–103) ($n = 56$)	0.76
SVRI at day 4 (dyn s^{-1} cm^{-5})	1,670 (1,200–1,980) ($n = 33$)	1,498 (1,234–2,201) ($n = 28$)	0.73
Noradrenaline at day 4 (µg/kg/min)	0.19 (0.13–0.41) ($n = 21$)	0.2 (0.10–0.64) ($n = 32$)	0.20
Inotropic score at day 4 (µg/kg/min)	3.0 (0.0–18.0) ($n = 49$)	10.0 (0.0–26.0) ($n = 57$)	0.16
VDI at day 4	0.3 (0.0–2.1) ($n = 48$)	1.1 (0.0–3.1) ($n = 56$)	0.19
PaO_2/FiO_2 at day 4	220 (159–264) ($n = 47$)	233 (168–288) ($n = 53$)	0.23
Urea at day 4 (mmol/L)	4.3 (3.4–6.0) ($n = 48$)	8.1 (5.6–11.9) ($n = 56$)	<0.0001
Creatinine at day 4 (µmol/L)	57.0 (44.2–72.0) ($n = 49$)	88.4 (61.9–123.7) ($n = 57$)	<0.0001
Bilirubin at day 4 (µmol/L)	23.5 (14.0–38.0) ($n = 46$)	20.1 (8.5–48.5) ($n = 52$)	0.35
ASAT at day 4 (U/L)	43 (32–83) ($n = 47$)	57 (36–138) ($n = 53$)	0.19
pH	7.45 (7.4–7.48) ($n = 49$)	7.42 (7.38–7.46) ($n = 56$)	0.11
Bicarbonate (mmol/L)	26.5 (25–28) ($n = 49$)	25.9 (24.4–27.65) ($n = 57$)	0.19
Sodium, Na^+ (mmol/L)	137 (136–138) ($n = 49$)	137 (135.3–138) ($n = 57$)	1
Potassium, K^+ (mmol/L)	3.6 (3.4–4.0) ($n = 49$)	3.82 (3.6–4.1) ($n = 57$)	0.02
Lactate, arterial (mmol/L)	1.4 (1.13–2.13) ($n = 48$)	1.87 (1.4–2.4) ($n = 45$)	0.04

Data are reported as median (1st–3rd quartile) and compared by the Wilcoxon test for quantitative variables, or number (%) and compared by the chi-squared test for qualitative variables. See "Methods" section for determination of inotropic score and vasopressor dependency index

D0 date of randomization, *PaO_2* partial pressure of oxygen in arterial blood, *FiO_2* fraction of inspired oxygen, *SVRI* systemic vascular resistance index, *ASAT* aspartate aminotransferase, *VDI* vasopressor dependency index, *MAP* mean arterial pressure

Table 4 Comparison of patients' characteristics at different times after randomization (day 0) in the IVOIRE trial, according to randomization group

Variables	HVHF group ($n = 66$)	SVHF group ($n = 71$)	p
Mortality at day 60 (n, %)	33 (50)	35 (49.3)	0.93
Mortality at day 90 (n, %)	37 (56.1)	36 (50.7)	0.53
SOFA score at day 4	9.0 (6.5–13.5) ($n = 48$)	11.0 (6.0–14.0) ($n = 57$)	0.54
SOFA score at day 28	3 (2.0–8.0) ($n = 19$)	3 (1.0–7.0) ($n = 25$)	0.47
SAPS II score at day 4	38.5 (31.5–49.0) ($n = 48$)	47.0 (35.0–56.0) ($n = 57$)	0.07
SAPS II score at day 28	36.0 (26.0–54.0) ($n = 19$)	32.0 (28.0–45.0) ($n = 25$)	0.78
Catecholamine-free days (day 28), days	23 (19–25)	22 (18–25)	0.32
RRT dependency at day 90	0	1	0.95
RRT-free days (day 90), days	84 (78–86)	83 (74–85)	0.22
MV-free days (day 90), days	82 (72–86)	79 (63–85)	0.36
ICU-free days (day 90), days	75 (59–86)	74 (59–83)	0.46
Hospital-free days (day 90), days	61 (34–86)	60 (26–81)	0.51

Data are reported as median (1st–3rd quartile) and compared by the Wilcoxon test for quantitative variables, or number (%) and compared by the chi-squared test for qualitative variables

SAPS II Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment, *RRT* renal replacement therapy, *MV* mechanical ventilation

Likewise, there are additional logistical challenges to be considered with the provision of HVHF, including increased nursing workload, added resource implications, along with greater risks for introduction of error. Given the absence of clear efficacy for improved survival and/or physiologic benefits to mitigate these potential risks, HVHF should not be a routinely recommended as an adjuvant therapy for septic shock.

Several important limitations must be also considered when evaluating these data. Firstly, the study was underpowered due to a lower than expected participant accrual and primary outcome event rate, resulting in early termination of the trial because of a lack of further available resources. Secondly, the study intervention was not blinded owing to practical limitations. Lastly, our study was pragmatic and focused on patient-centred outcomes; accordingly, we did not have data on the clearance of inflammatory mediators. Prior data have inconsistently shown differences in circulating inflammatory mediators by treatment modality. Furthermore, a small randomized trial of early SVHF in septic patients without AKI compared with conventional support found worse organ

dysfunction in those receiving haemofiltration over the first 14 days, with no significant impact of circulating cytokine removal [53].

However, the IVOIRE trial is the largest multicentre randomized trial of HVHF in septic shock patients with AKI performed to date and is strengthened by its high-quality design implying strong internal validity, along with being generalizable and applicable. We believe the findings of the IVOIRE study are of clinical importance to better inform current best practice, in particular when considering that HVHF is commonly applied to these patients and may lack efficacy and be associated with harm. Future studies of RRT should ideally focus on the evaluation of optimal timing for starting RRT and on novel adsorption techniques to further decrease the high attributable mortality in septic shock complicated by AKI.

Conclusion

In the IVOIRE trial, there was no evidence that HVHF at 70 mL/kg/h, when compared with contemporary SVHF at 35 mL/kg/h, leads to a reduction of 28-day mortality or contributes to early improvements in haemodynamic profile or organ function. Accordingly, on the basis of these data, HVHF, as applied in this trial, cannot be recommended as adjuvant treatment for critically ill septic shock patients with AKI and should not be provided outside of further clinical trials.

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Appendix: Participating centres and investigators

University Hospital of Bordeaux, Hopital Haut-Lévèque (France): Joannes-Boyau, Fleureau, Dewitte, Coquin, Rozé, Janvier, Ouattara; St-Pierre Para-University Hospital (Belgium): Honoré; Hopital R. Boulin, Libourne (France): Grand, Gauche; University Hospital of Liege (Belgium): Canivet, Wiesen, Dubois; Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Lyon (France): Flamens, Bastien; Clinique Bordeaux Nord Aquitaine, Bordeaux (France): Pujol, Perdrix, Clement; Hopital Européen Georges Pompidou (HEGP), Paris (France): Journois; Albert Michallon Hospital, Grenoble (France): Broux, Robin, Durand; Hôpital de Cavale Blanche, CHU de Brest (France): Floch; Hôpital Tivoli, Université Libre de Bruxelles, La Louvière (Belgium): Franck, Bouckaert; Cliniques de l'Europe-Site St Michel, Brussels (Belgium): Collin.

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