

Clinical Study

Comparison of Sustained Hemodiafiltration with Acetate-Free Dialysate and Continuous Venovenous Hemodiafiltration for the Treatment of Critically Ill Patients with Acute Kidney Injury

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We conducted a prospective, randomized study to compare conventional continuous venovenous hemodiafiltration (CVVHDF) with sustained hemodiafiltration (SHDF) using an acetate-free dialysate. Fifty critically ill patients with acute kidney injury (AKI) who required renal replacement therapy were treated with either CVVHDF or SHDF. CVVHDF was performed using a conventional dialysate with an effluent rate of $25 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and SHDF was performed using an acetate-free dialysate with a flow rate of 300–500 mL/min. The primary study outcome, 30 d survival rate was 76.0% in the CVVHDF arm and 88.0% in the SHDF arm (NS). Both the number of patients who showed renal recovery (40.0% and 68.0%, CVVHDF and SHDF, resp.; $P < .05$), and the hospital stay length (42.3 days and 33.7 days, CVVHDF and SHDF, resp.; $P < .05$), significantly differed between the two treatments. Although the total convective volumes did not significantly differ, the dialysate flow rate was higher and mean duration of daily treatment was shorter in the SHDF treatment arm. Our results suggest that compared with conventional CVVHDF, more intensive renal support in the form of post-dilution SHDF with acetate-free dialysate may accelerate renal recovery in critically ill patients with AKI.

1. Introduction

Despite improved medical care, the mortality rate in critically ill patients with acute kidney injury (AKI) who require renal replacement therapy (RRT) is still high (>50%) [1–5]. Whether or not more intensive RRT improves the outcomes of patients with AKI is an ongoing debate; several studies have reported the benefits of frequent dialyses and/or high-dose regimens [6, 7], while others have reported no such benefit [8, 9]. The multicenter, prospective, randomized US Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network study recently investigated this issue and is the largest trial in this field to date [10]. The study found no significant difference between the intensive and less-intensive treatment groups with regard to death

rate by day 60, duration of RRT, rate of recovery of kidney function, rate of nonrenal organ failure, or proportion of patients who developed hypotension that required the discontinuation of one or more RRT modalities. Thus, there were no significant differences in the benefits of intermittent hemodialysis (IHD), sustained low-efficiency dialysis (SLED), high-dose ($35 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) CVVHDF, and standard-dose ($20 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) CVVHDF.

We previously tested the hypothesis that more intensive RRT decreases mortality among critically ill patients with AKI to a greater extent than SLED or IHD [11]. In order to achieve clearance of small and medium molecular weight solutes, we tested a modified IHD protocol which we termed sustained hemodiafiltration (SHDF). SHDF is a form of

intermittent hemodiafiltration (IHDF) with extended (6–10 h) sessions, and regular blood and dialysate flow rates of 200 mL/min and 500 mL/min, respectively. In addition, the replacement fluid in SHDF is infused postfilter. The results of that study suggested that compared with conventional continuous RRT (CRRT) including high-dose CVVHDF, more intensive renal support in the form of postdilution SHDF could decrease mortality and accelerate renal recovery in critically ill patients with AKI.

The majority of maintenance hemodialysis (HD) patients in Japan are currently treated using an acetate-containing bicarbonate dialysate (acetate dialysate) with an acetate concentration of 48 to 60 mg/dL (8 to 10 mmol/L). Acetate may induce the production of cytokines and dilatation of vessels, but a small amount of acetate is necessary to maintain the pH of the dialysate at 7.1 to 7.6 to prevent precipitation of calcium and magnesium [12–14]. Although patients with acetate intolerance normally require acetate-free biofiltration, the standard dialysate still includes acetate. Therefore, critically ill patients with AKI who required acute RRT have been treated with acetate-containing dialysate. In the USA, although citrate dialysates (Citrasate® and DRYalysate®, Advanced Renal Technologies Co. Ltd, USA) may be used for maintenance of HD patients or critically ill RRT patients, those formulations still include a small amount of acetate [15]. Citrate dialysates are also commonly used as anticoagulants in cases when heparin cannot be utilized, such as in heparin-induced thrombocytopenia (HIT), high bleeding risk, trauma, and impending/postsurgical procedure, or in order to prevent the hemofilter clotting. Recently, the completely acetate-free bicarbonate dialysate Carbostar® (Ajinomoto Pharma, Tokyo, Japan) became available in Japan. However, as yet there are no reports which investigate the efficacy of acetate-free bicarbonate dialysate in critically ill patients with AKI.

In order to determine the impact of acute RRT strategies on patient outcomes, we conducted a prospective, randomized study comparing postdilution CVVHDF with an effluent rate of 20 to 25 mL·kg⁻¹·h⁻¹, with postdilution SHDF performed on a daily basis. Since there were no significant differences in the benefits afforded by high-dose (35 mL·kg⁻¹·h⁻¹) CVVHDF and standard-dose (20 mL·kg⁻¹·h⁻¹) CVVHDF in the largest previous ATN trial [10], CVVHDF was performed with the standard dose. CVVHDF was performed using acetate-containing dialysate and replacement fluid, and SHDF was performed using acetate-free dialysate.

2. Subjects and Methods

2.1. Study Design. This study was conducted in accordance with the Declaration of Helsinki (1996 amendment) and was performed at the Intensive Care Unit (ICU) of Nihon University Nerima Hikarigaoka Hospital, Tokyo, Japan, with the approval of the Clinical Research Ethics Committee of the same institution. All participants or their family members provided written informed consent prior to the commencement of the study. This study was designed

specifically for critically ill patients with AKI. All patients were admitted to the ICU of our hospital between April 2008 and October 2010. A total of 50 patients who had developed AKI that required RRT in the ICU were eligible for inclusion in this study. The main criterion for inclusion was a clinical diagnosis of AKI, defined by at least one of the following conditions: (1) volume overload despite diuretic administration, (2) oliguria (urine output <200 mL/12 h) in spite of fluid resuscitation and diuretic administration, (3) anuria (urine output <50 mL/12 h), (4) azotemia (blood urea nitrogen >80 mg/dL), (5) hyperkalemia (K value > 6.5 mEq/L), or (6) classification under the “R,” “I,” or “F” categories of the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) classification system [16]. The exclusion criteria for this study were the presence of end-stage renal disease requiring IHD, advanced chronic kidney disease (CKD) stages 4 and 5 (defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²) before admission, previous kidney transplant, an anticipated ICU stay of less than 48 h, or inability to provide informed consent. Severity of illness and hemodynamic instability were not used as exclusion criteria. All the patients were followed prospectively from the time of enrollment through discharge.

The type of treatment, effective duration of treatment, volume of ultrafiltrate and replacement fluid, episodes of hemofilter clotting, and number of episodes of catheter dysfunction were recorded for each treatment day. Acute Physiology and Chronic Health Evaluation (APACHE) II scores [17] and Sequential Organ Failure Assessment (SOFA) scores [18] were obtained at the time of initiation of RRT. The presence of pre-existing chronic kidney disease stage 3 was defined by a premorbid estimated glomerular filtration rate (eGFR) of 30–60 mL·min⁻¹·1.73 m⁻². The eGFR for Japanese patients was calculated using the following formula [19]: $eGFR \text{ (mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}) = 194 \times sCr^{-1.094} \times \text{Age}^{-0.287} (\times 0.739 \text{ for women})$, where sCr was the serum creatinine concentration. Pre-ICU sCr values were used to calculate the proportion of patients who fulfilled the RIFLE categories of risk, injury, and failure at the time of ICU admission. Sepsis was diagnosed clinically by the attending clinician using published consensus criteria [20]. The indicators of kidney function (sCr, serum urea nitrogen, and urine output) were documented on ICU admission, on study enrollment, and on ICU and hospital discharge.

2.2. Treatment Assignments. On the initiation of RRT, the patients were randomly assigned to the CVVHDF or SHDF treatment arms by a computer-generated adaptive randomization scheme. An independent investigator, who had neither treated nor was aware of the profile of the subjects before the commencement of the trial, monitored randomization in the order of the entry of the subjects; then the particulars of the assignments were immediately delivered to the individual investigators. To ensure balanced randomization, the treatment assignments were stratified by sepsis and oliguria, because both of these parameters are independent predictors of patient survival [1, 21]. We used

the following stratification categories: (1) sepsis + oliguria, (2) sepsis + nonoliguria, (3) nonsepsis + oliguria, and (4) nonsepsis + nonoliguria.

Each patient was treated for 2 or more consecutive days. Heparin or nafamostat mesilate was used as the anticoagulant in all patients at doses of 6–13 U·kg⁻¹·h⁻¹ and 0.4–0.6 mg·kg⁻¹·h⁻¹, respectively. Vascular access was obtained by placing temporary dual-lumen catheters in the femoral or internal jugular vein. Hemofilters with a 1.0 m² polymethylmethacrylate (PMMA; Hemofeel CH-1.0; Toray, Tokyo, Japan) or polyester-polymer alloy (PEPA; FDY-100GW; Nikkiso, Tokyo, Japan) membrane were used in both treatment arms.

All medications and nutrition were ordered and administered by the primary caregivers in the ICU, who did not actively participate in the study. Interventions to maintain hemodynamic stability, including adjustment of ultrafiltration, administration of saline flushes, cooling of the dialysate, and sodium modeling, were performed as required. The requirement of pressor support was determined according to the status of the patient during each RRT session.

2.3. CVVHDF. CVVHDF was performed using Asahi ACH-10 hemodiafiltration equipment (Asahi Kasei Medical Co., Tokyo, Japan). Hemodiafiltration was accomplished using blood flow rates of 80–200 mL/min and postdilution administration of replacement fluid. Sublood-BS[®] (Fuso Pharmaceutical Industries Ltd., Osaka, Japan), a sterile bicarbonate solution containing acetate, was used as the dialysate and replacement fluid for CVVHDF. The ultrafiltrate was adjusted to achieve fluid balance in each patient, and fluid replacement and net ultrafiltration rates varied with the clinical status of the patient. In the CVVHDF modality, the “total convective rate” represents the product of the convective components, that is, the sum of the replacement fluid rate and the fluid removal rate, and does not include the rate at which dialysate is spent. The “total convective volume” represents the sum of the replacement fluid volume and the fluid removal volume. The actual delivered dosage, or total effluent flow rate (mL/kg/h), is the sum of the replacement fluid rate, fluid removal rate, and dialysate flow rate. CVVHDF was prescribed to provide a total effluent flow rate of 25 mL·kg⁻¹·h⁻¹, based on the patient’s weight before the onset of acute illness. This dosage was adjusted for body weight changes and hemodynamic instabilities throughout the treatment period. Every attempt was made to divide the rate of flow of the sterile bicarbonate solution equally between the replacement fluid rate and dialysate flow rate. The total time of actual CVVHDF treatment (min/24 h) was recorded daily, along with time spent on treatment of clots, procedures, or other events. The hemofilters were replaced every 24 h. Arterial blood gas analysis was performed before (post) and after (pre) hemofilter replacement at each treatment session.

2.4. SHDF. SHDF was performed with the Nikkiso DBB-02 (Nikkiso Co., Tokyo, Japan). All patients underwent SHDF during the daytime in the ICU for 6–8 h. The acetate-free

TABLE 1: Renal replacement therapy procedures.

	CVVHDF	SHDF
RRT equipment	ACH-10	DBB-02
RO equipment	—	NRX-20P PURESYSTEM
Hemofilter	PMMA, PEPA	PMMA, PEPA
Dialysate	Sublood-BS [®]	Carbostar [®]
Replacement fluid	Sublood-BS [®]	Sublood-BS [®]
Blood flow rate (mL/min)	80–200	80–200
Dialysate flow rate (mL/h)	300–2000	300–500
Replacement fluid rate (mL/h)	300–3000	300–3000

CVVHDF: continuous venovenous hemodiafiltration; PEPA: polyester-polymer alloy; PMMA: polymethylmethacrylate; RO: reverse osmosis; RRT: renal replacement therapy; SHDF: sustained hemodiafiltration.

bicarbonate dialysate (Carbostar[®]) was prepared in the ICU using reverse osmosis equipment (NRX-20P PURESYSTEM; Daicn Membrane-Systems Ltd., Tokyo, Japan). SHDF was accomplished using blood flow rates of 80–200 mL/min and postdilution administration of replacement fluid. The initial dialysate flow rate was 300 mL/min, and if the patients were hemodynamically stable, this was increased to 500 mL/min. Sublood-BS[®] was used as the replacement fluid for SHDF. The ultrafiltrate was adjusted to achieve fluid balance in each patient, and the fluid replacement and net ultrafiltration rates varied with the clinical status of the patient. Target replacement fluid volume was set to greater than 14 L/session, and SHDF was performed until this target was achieved. In the SHDF modality, the “total convective rate” represents the product of the convective components, that is, the sum of the replacement fluid rate and the fluid removal rate. The “total convective volume” represents the sum of the replacement fluid volume and the fluid removal volume. The total SHDF treatment time was recorded daily, along with time spent on the treatment of clots, procedures, or other events. Arterial blood gas analysis was performed before (pre) and after (post) each treatment.

RRT procedures and composition of acetate-free dialysate (Carbostar[®]) and sterile bicarbonate solution (Sublood-BS[®]) are listed in Tables 1 and 2, respectively.

Patients in both treatment arms were transitioned to conventional IHD at the discretion of the treating nephrologists. This usually occurred when the patient was still dependent on dialysis but had been transferred from the ICU to the ward, or when the patient was being mobilized in the ICU. The dosage and timing of IHD were determined by the treating nephrologists. Renal recovery was defined on the basis of Cr clearance, measured by 6-hour timed urine collections when urine flow increased to more than 30 mL/h or when there was a spontaneous fall in the sCr level. RRT was continued if the Cr clearance was less than 12 mL/min and was discontinued if the Cr clearance was greater than 20 mL/min; decisions regarding discontinuation of RRT for subjects with intermediate values of Cr clearance were left to the investigator.

TABLE 2: Composition of acetate-free dialysate (Carbostar®) and sterile bicarbonate solution (Sublood-BS®).

	Acetate-free dialysate	Sterile bicarbonate solution
Sodium (mEq/L)	140	140
Chloride (mEq/L)	111	111.5
Calcium (mEq/L)	3	3.5
Magnesium (mEq/L)	1.0	1.0
Potassium (mEq/L)	2.0	2.0
Glucose (mg/dL)	150	100
Bicarbonate (mEq/L)	35	35
Acetate (mEq/L)	0	0.5
Citrate (mg/dL)	12.8	0
Final pH	7.5–8.0	7.2–7.4
Osmolarity (mOsm/kg)	298	298

2.5. Outcome Measurements. The primary outcome measure was survival until discharge from the ICU or for 30 d, whichever was earlier. Secondary end points included renal recovery at the time of discharge from the ICU, renal recovery at the time of discharge from the hospital, ICU survival, hospital survival, length of ICU stay, and length of hospital stay.

2.6. Statistical Analysis. Data were expressed as mean \pm SD. Analyses were performed on an intention-to-treat basis. The primary analysis was the comparison of the proportion of patients in each study arm who survived until discharge from the ICU or for 30 d, whichever was earlier. The proportions were compared using Pearson's χ^2 test, or Fisher's exact test when the χ^2 test was not valid. The secondary analysis was the comparison of the following parameters between the two study arms: proportion of patients who recovered renal function at the time of discharge from the ICU and hospital, ICU survival, hospital survival, and length of hospital stay. The methods used to perform these comparisons were similar to those used in the primary analysis. Baseline characteristics and outcome measures were compared using the two-group *t*-test or Wilcoxon's rank-sum test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables.

The Kaplan-Meier method was used to estimate the hospital survival for the prescribed RRT, and the log-rank test was used to compare the survival curves of the two therapies. All statistical tests were two sided and were performed using a significance level of $P < .05$.

3. Results

A total of 50 patients were enrolled in the study and were randomly assigned to each treatment arm. The demographic data and clinical characteristics of the patients in the two arms are presented in Table 3. The baseline characteristics did not significantly differ between the two arms. In all,

18 patients were included in the sepsis + oliguria stratum, 7 in the sepsis + nonoliguria stratum, 12 in the nonsepsis + oliguria stratum, and 13 in the nonsepsis + nonoliguria stratum. The proportion of patients with oliguria, sepsis, and preexisting chronic kidney disease (defined as premorbid eGFR $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was similar for both treatment arms.

The RRT parameters are described in Table 4. The number of treatments performed per patient was not significantly different between the two arms. The number of treatment hours per day was significantly less in the SHDF arm than in the CVVHDF arm. The dialysate flow rate and total dialysate volumes were significantly higher in the SHDF arm (dialysate volume, $9.6 \pm 1.6 \text{ L/session}$ in the CVVHDF arm versus $189 \pm 28 \text{ L/session}$ in the SHDF arm; $P < .0001$). The total convective rate was higher in the SHDF arm than in the CVVHDF arm; however, because the duration of SHDF treatment was shorter, the total convective volumes were not significantly different between the two groups. Accounting for the effect of postdilution fluid replacement on solute clearance, the mean actual delivered dosage was $26.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the CVVHDF arm. There were instances in which RRT was interrupted by hemofilter thrombosis and catheter dysfunction; interruptions were observed significantly more frequently during CVVHDF (30.1% of sessions) than during SHDF (12.6% of sessions; $P < .05$). In 20 of the 203 CVVHDF treatments (9.8%), hypotension occurred that required discontinuation of the treatment (versus 12 of the 170 SHDF treatments [7.1%], $P = .32$). In 26 of the CVVHDF treatments (12.8%), initiation of vasopressor support was required (versus 18 for SHDF [10.5%], $P = .48$), and in 63 of the CVVHDF treatments (31.0%), other interventions were required because of treatment-associated hypotension (versus 44 for SHDF [25.8%], $P = .19$). As shown in Figure 1, the pH and HCO_3^- concentration of arterial blood was significantly increased after treatment compared to pretreatment in both arms. However, comparing between the two arms, pH and HCO_3^- concentration were higher in the SHDF arm compared to the CVVHDF arm both before and after treatment.

Although the length of ICU stay was not significantly different between the two arms, the length of hospital stay was significantly shorter in the SHDF arm than the CVVHDF arm (Table 5). The primary study outcome, survival until discharge from the ICU or for 30 d, whichever was earlier, was 76.0% in the CVVHDF arm and 88.0% in the SHDF arm (no significant difference). There was no significant difference in the ICU survival rate and hospital survival rate between the two arms (Figure 2). However, the total number of patients who showed renal recovery was significantly higher in the SHDF arm than in the CVVHDF arm, and significant differences were detected in the number of surviving patients showing renal recovery at the time of discharge from the ICU or from the hospital (Table 5). In addition, 16% of patients in the CVVHDF arm and 8% of those in the SHDF arm were transitioned to IHD while in the ICU (no significant difference).

TABLE 3: Baseline characteristics of patients.

Characteristic	CVVHDF	SHDF	P value
No. of patients (male/female)	25 (17/8)	25 (16/9)	NS
Age (years)	65.3 ± 13.1	66.5 ± 12.1	NS
Cause of acute kidney injury (%)			NS
Nephrogenic	20	24	
Sepsis	52	48	
Cardiogenic	12	12	
Postsurgical	8	8	
Drug induced	0	4	
Hepatic failure	4	4	
Other	4	0	
Presence of CKD on admission (%)	40	44	NS
APACHE II score	19.6 ± 3.7	20.0 ± 4.3	NS
SOFA score	8.1 ± 2.0	8.2 ± 3.2	NS
RIFLE classification			
R (%)	20	20	NS
I (%)	44	40	NS
F (%)	36	40	NS
Mechanically ventilated (%)	36	32	NS
Oliguric (%)	60	60	NS
Baseline systolic blood pressure (mmHg)	107 ± 32	110 ± 29	NS
Required vasopressors (%)	28	24	NS
Renal parameters at RRT initiation			
Serum urea nitrogen (mg/dL)	69 ± 26	68 ± 24	NS
Serum creatinine (mg/dL)	4.6 ± 2.3	4.8 ± 2.1	NS
Days from ICU admission to RRT	2.1 ± 1.3	2.1 ± 1.5	NS

APACHE: acute physiology and chronic health evaluation; CKD: chronic kidney disease; CVVHDF: continuous venovenous hemodiafiltration; ICU: intensive care unit; RIFLE: Risk, Injury, and Failure with the outcome classes Loss and End-stage kidney disease classification system; RRT: renal replacement therapy; SOFA: sequential organ failure assessment; SHDF: sustained hemodiafiltration.

TABLE 4: RRT characteristics by treatment group.

Characteristic	CVVHDF	SHDF	P value
Total number of treatment days/sessions	203	170	—
Mean treatment times (days or sessions) per patient	8.1 ± 3.5	6.6 ± 2.6	NS
Mean duration of daily treatment (h)	15.2 ± 3.8	6.0 ± 1.0	<.0001
Dialysate flow rate (mL/min)	10.8 ± 2.8	471 ± 27	<.0001
Total dialysate flow volume (L/session)	9.6 ± 1.6	169 ± 28	<.0001
Total convective rate (mL/h)	683 ± 159	2006 ± 826	<.0001
replacement fluid rate (mL/h)	549 ± 127	1696 ± 819	<.0001
fluid removal rate (mL/h)	134 ± 58	310 ± 70	<.0001
Total convective volume (L/session)	15.0 ± 4.5	12.0 ± 5.1	NS
Actual delivered dosage (mL/kg/h)	26.6	—	—

CVVHDF: continuous venovenous hemodiafiltration; RRT: renal replacement therapy; SHDF: sustained hemodiafiltration.

4. Discussion

We propose that the acetate-free dialysate may have improved circulatory dynamics during RRT due to the differences in glucose and bicarbonate levels from standard dialysate, a direct effect of citrate, and the absence of acetate in the dialysate. Acetate can induce the production of nitric oxide, a vasodilator [22] that can cause intradialytic cardiovascular instability [23, 24], and therefore

elevated acetate load might lead to hemodynamic instability. Following treatment with acetate-free dialysate, we found a significant increase in pH and HCO_3^- concentration, and these levels were significantly higher after treatment in the SHDF arm than in the CVVHDF arm. There was no significant difference in the requirement for vasopressors during RRT between the two groups.

Therefore, in contrast to CVVHDF, SHDF may be suitable for both hemodynamically stable and unstable subjects. It

TABLE 5: Outcome by treatment group.

Characteristic	CVVHDF	SHDF	P value
Total ICU days	18.8 ± 11.1	14.1 ± 7.2	NS
Total hospital days	42.3 ± 18.8	33.7 ± 18.8	<.05
Survival until discharge from ICU or for 30 d (%)	76	88	NS
ICU survival (%)	72	84	NS
Hospital survival (%)	64	80	NS
ICU renal recovery (%)			
All patients	20	44	<.05
Survivors	27.8	52.3	<.05
Hospital renal recovery (%)			
All patients	40	68	<.05
Survivors	62.5	85	<.05

CVVHDF: continuous venovenous hemodiafiltration; ICU: intensive care unit; SHDF: sustained hemodiafiltration.

is difficult to ascertain whether this finding can be attributed to the use of dialysate “without” acetate, which might cause vasodilation and hypotension, since we could not measure blood acetate concentrations in the present study to compare the two dialysates. Further studies would be needed to clarify the efficacy of completely acetate-free dialysate. Acetate-free dialysate has several advantages. Rapid correction of acidosis is possible because of the greater bicarbonate concentration. Also, acetate-free dialysate contains 12.8 mg/dL (667 μ mol/L) of citrate instead of acetate to adjust the pH. Citrate has a long history of use in medicine as an anticoagulant and has the ability to chelate calcium ions. The half-life of citrate is very short, allowing it to be rapidly metabolized by the liver. Indeed, the successful use of citrate dialysate in liver transplant patients and in high bleeding risk patients has been reported [15]. These advantages suggest that acetate-free dialysate may be suitable for critically ill patients with AKI, without precipitating metabolic acidosis. Although CVVHDF was continued for 15.2 h, the pH level and HCO_3^- concentration following CVVHDF treatment were similar to pre treatment in the SHDF arm. In the SHDF arm, diffusive transport was engendered by a dialysate flow rate of 471 mL/min, with an extended session duration (6.0 h). SHDF convective transport was characterized by post-filter infusion of replacement fluid and a total effluent volume of 12.0 L/session, which was not significantly different from the CVVHDF arm. Therefore, SHDF showed superior efficacy of diffusive transport and equivalent efficacy of convective transport to those reported in previous studies that used “more intensive CRRT.”

The present study has several limitations. Firstly, our study was performed on a small number of patients and was a single-center study. A randomized, prospective trial comparing SHDF with conventional CRRT in a large cohort of patients is necessary to determine the relative impact of SHDF on mortality. Secondly, severity as assessed by APACHE II and SOFA scores in our patients was mild compared to other trials because subjects with nephrogenic AKI, including acute tubular necrosis (ATN), were included,

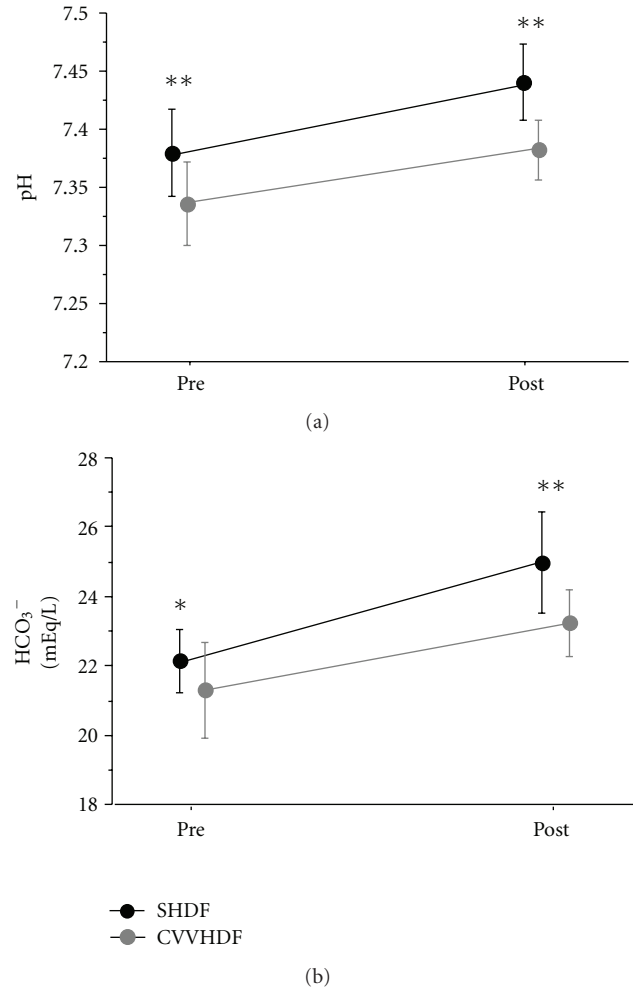


FIGURE 1: Changes in arterial blood pH and HCO_3^- concentration before and after treatment in the two treatment arms. * $P < .01$, ** $P < .001$ versus CVVHDF.

and so the survival rate was very high even in the CVVHDF arm. Thirdly, 16% of patients in the CVVHDF arm and 8% of those in the SHDF arm were transitioned to IHD while in the ICU (no significant difference). Therefore, in those subjects, there was the possibility that the efficacy of treatment could not be accurately assessed. Lastly, since the sterile bicarbonate solution (Sublood-BS®) used as replacement fluid in our SHDF contained a small amount of acetate, this method was not completely acetate-free. Therefore, in order to further validate the effectiveness of acetate-free SHDF for the treatment of critically ill patients with AKI, further studies are needed; these should involve a comparison of completely acetate-free dialysate and replacement fluid, with conventional dialysate and replacement fluid both containing a small amount of acetate.

5. Conclusion

Our results suggest that compared with conventional CRRT, a strategy of more intensive renal support involving daily

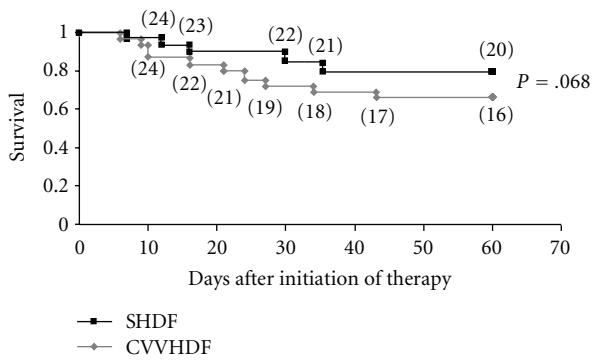


FIGURE 2: Kaplan-Meier analysis of hospital survival rates after CVVHDF versus SHDF. (): number of subjects alive.

postdilution SHDF with acetate-free dialysate may accelerate the recovery of kidney function in critically ill patients with AKI. The interruption of RRT by hemofilter thrombosis and catheter dysfunction was more frequent during CVVHDF than during SHDF. These advantages suggest that acetate-free dialysate may be preferable for patients with AKI. As this study was performed on a small number of patients in a single center, a randomized, prospective trial comparing the efficacies of acetate-free dialysate with conventional dialysate in a large cohort of patients is warranted in order to determine the relative impact of acetate-free dialysate and SHDF on mortality.

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