

Continuous Venovenous Hemodiafiltration versus Sustained Low-Efficiency Hemodialysis for Critically-Ill Patients with Acute Kidney Injury

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Objective: Renal replacement therapy [RRT] is a complex procedure in critically-ill patients. None of the available techniques has been shown to be superior in terms of a reduction of mortality rate. We assessed clinical outcomes including all-cause mortality within 30 days of continuous venovenous hemodiafiltration [CVVHDF] and sustained low-efficiency dialysis [SLED].

Materials and Methods: Medical history, findings from physical examination and laboratory investigations, and clinical outcomes of critically-ill patients who had continuous venovenous hemodiafiltration [CVVHDF] or sustained low-efficiency dialysis [SLED] were compared.

Results: Of 27 patients with acute kidney injury [AKI], 12 were treated with CVVHDF and 15 with SLED. There was no significant difference in 30-day all-cause mortality (75.0% in the CVVHDF group compared with 73.3% in the SLED group, $p = 0.922$). There were also no significant differences in duration of ICU or hospital stay, renal recovery or the incidence of RRT-related complications between the 2 groups.

Conclusion: In critically-ill patients with AKI, CVVHDF and SLED were comparable in terms of mortality and recovery of renal function.

Keywords: Acute kidney injury, Adequacy of dialysis, Continuous venovenous hemodiafiltration, Sustained low-efficiency dialysis, Intermittent hemodialysis

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There are several different techniques for the delivery of renal replacement therapy [RRT]. However, there is no consensus regarding the best RRT procedure in critically-ill patients with acute kidney injury [AKI]⁽¹⁾. Continuous RRT [CRRT] has been advocated in hemodynamically unstable patients as it permits gradual fluid and solute removal and provides greater hemodynamic stability than intermittent hemodialysis [IHD]⁽²⁾. Nevertheless, CRRT had some disadvantages of a high cost⁽³⁾ and a need for anticoagulation^(4,5) which preclude its common use. Prolonged intermittent renal replacement therapy, known as sustained low-

efficiency dialysis [SLED], is emerging as a promising alternative means of providing RRT in critically-ill patients with AKI⁽⁶⁾. SLED provides gradual, safe and well-tolerated metabolic control with ultrafiltration and solute removal comparable with CRRT in this group of patients^(7,8). Previous studies reported comparable outcomes of CRRT and SLED^(9,10).

We undertook a study to compare SLED with CRRT in critically-ill patients with AKI. The primary outcome was 30-day all-cause mortality; secondary outcomes were recovery of renal function, RRT-related complications, length of ICU stay and duration of hospitalization.

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Materials and Methods

Patients

This was a retrospective cohort study of 27 critically-ill patients admitted to the intensive care unit

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[ICU] of Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand, between February 2009 and March 2010. The study was approved by the local ethics committee. Clinical assessments, including medical history, physical examination and laboratory investigations were performed on admission to ICU.

Inclusion criteria

We included patients with AKI requiring RRT, had hemodynamic instability, and required vasopressor support. The baseline value was measured at hospital admission or the minimum value during hospitalization. A serum creatinine concentration [sCr] more than 1.2 mg/dl at baseline was considered as pre-existing renal dysfunction. A diagnosis of AKI followed the criteria of the Acute Kidney Injury Network [AKIN]⁽¹¹⁾. Hemodynamic instability was defined when a systolic blood pressure was less than 90 mmHg or lower and/or a diastolic blood pressure was less than 60 mmHg or lower.

Exclusion criteria

We excluded patients with pre-existing chronic kidney disease [CKD] defined as an estimated glomerular filtration rate less than 30 ml/min/1.73 m².

Data collection

The following data were collected: age, sex, weight, height, duration of ICU stay, date of AKI diagnosis, etiology of AKI, serial sCr measurements, eGFR at hospital discharge according to the CKD Epidemiology Collaboration, the Sequential Organ Failure Assessment [SOFA] severity of illness score for hospital mortality⁽¹²⁾, and the Acute Physiology and Chronic Health Evaluation [APACHE] II score⁽¹³⁾ at the time of admission to ICU. Other laboratory investigations data collected were: biochemical study, metabolic and hematologic investigations, urine output, net ultrafiltration volume per session, dose of anticoagulants, length of RRT session and overall duration of RRT, and the occurrence of complications such as hypotension, catheter-related infection or bleeding.

Renal replacement therapy

Patients were divided into 2 groups according to the different types of treatment: CRRT or SLED. As a routine practice in our institution, the following procedures were carried out. Unfractionated heparin was administered as an anticoagulant to prevent

clotting of the extracorporeal circuit; the target partial thromboplastin time was maintained at ≤ 2 times the control level. For CRRT, we undertook continuous venovenous hemodiafiltration [CVVHDF] using an Aquamax HF 12 dialyzer (Edwards Lifesciences, Irvine, CA, USA). Blood flow rate was maintained in the range 100 to 200 ml/h and the target effluent rate was 20 ml/h. The substitution fluid was infused at a rate of 1,000 ml/h with an ultrafiltration rate of 100 to 300 ml/h. We undertook SLED using a Fresenius 4008B dialysis machine (Fresenius, Bad Homburg, Germany with an FDX 120 GW dialyzer [Nikkiso, Fukuoka, Japan]). Each session of renal replacement therapy took approximately 6 to 8 hours. The sessions were performed four times per week and could be increased in the patients with severe volume overload. Blood flow was maintained between 150 to 200 ml/h and dialysate flow at 300 ml/h. The SLED dose was assessed through a single-pool Kt/V. The Kt/V_{urea} was maintained at 1.2 to 1.4 for each session.

Renal replacement therapy was continued if the eGFR was <12 ml/min/1.73 m² and was discontinued if it exceeded 20 ml/min/1.73 m². Decisions to withdraw RRT for reasons other than the maintenance of renal function were made at the discretion of the nephrologist.

Outcomes

The primary outcome was all-cause mortality within 30 days of initiation of RRT. The secondary outcomes included: time to recovery of renal function (defined as lack of requirement for further RRT with an eGFR more than 20 ml/min/1.73 m²); duration of ICU and hospital stay; and the occurrence of RRT-related complications, such as catheter-related complications, intradialytic hypotension and electrolyte disturbance.

Statistical analysis

Continuous variables are expressed as mean (standard deviation) or median (range), and categorical variables as number (proportion, %). Comparative analysis of categorical variables was undertaken using the Chi-squared test and continuous variables using the independent t-test. All *p*-values presented are two-tailed; a *p*-value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS software (version 22, SPSS Inc., Chicago, IL).

Results

Baseline characteristics

The baseline demographic and clinical characteristics of the 27 patients were comparable

between the groups (Table 1). The mean age of the whole cohort was 63.8 ± 7.2 years and 55.6% were men. The mean sCr before onset of AKI was 1.38 ± 0.3 mg/dl and mean eGFR was 44.5 ± 15.2 ml/min/1.73 m². Ischemia was judged to be the cause of AKI in most cases ($n = 22$, 81.5%). The mean APACHE II score was 33.1 ± 2.6 , and the mean SOFA score was 14.0 ± 1.5 . There was no significant difference in baseline renal function or severity of illness scores between the groups. All patients had AKIN Stage 3 renal impairment requiring RRT.

The indications for acute dialysis included: azotemia (blood urea nitrogen >80 mg/dl or sCr >2 mg/dl with symptoms of uremia, fluid overload, hyperkalemia despite medical treatment (serum K⁺ concentration >5.5 mmol/l), and oliguria (urine output <100 ml in 8 h) without the use of diuretics⁽¹²⁻¹⁴⁾.

Sustained low-efficiency dialysis protocol

The mean number of SLED treatments per patient was 4.1 ± 2.7 with a mean interval between treatments of 2.0 days. The mean SLED treatment duration was 7.4 ± 0.6 h per session. All treatments were performed with a dialysate flow of 300 ml/min; the mean prescribed blood flow rate was 205 ± 25 ml/min. The mean heparin dose per session was $4,000 \pm 653$ IU. The overall mean delivered Kt/V_{urea} per session after the first

hemodialysis session was 1.33 ± 0.18 .

Continuous venovenous hemodiafiltration

The mean duration of CVVHDF therapy was 4.3 ± 1.9 days, and the mean daily duration of treatment was 20.8 ± 0.6 h. The mean prescribed CVVHDF volume was 19.5 ± 7.3 ml/kg/h and treatment was undertaken in pre-dilution mode in all patients. The prescribed blood flow rate was 134.2 ± 17.8 ml/min and mean net ultrafiltration was 125.0 ± 17.3 ml/min. The mean daily dose of heparin was $20,000 \pm 1,253$ IU. The overall mean delivered Kt/V_{urea} per week was 7.3 ± 3.2 .

Primary outcome

Nine of the 12 patients (75.0%) in the CVVHDF therapy group died within 30 days compared with 11 of the 15 patients (73.3%) in SLED therapy group ($p = 0.922$, Table 2). In the SLED group, the cause of death was sepsis in five patients and myocardial infarction [MI] in seven; in the CVVHDF group the cause of death was sepsis in four patients and MI in five.

Secondary outcomes

There were no significant differences in duration of ICU or hospital stay between the groups (Table 2). Renal function recovered in three out of 12

Table 1. Baseline characteristics of the patient cohort

Baseline characteristics	SLED	CVVHDF	<i>p</i> -value
Number of patients	15	12	0.097
Age	68.1 ± 7.3	59.5 ± 72.3	0.090
Sex			
Male, n (%)	9 (60.0%)	7 (58.3%)	0.619
Female, n (%)	6 (40.0%)	5 (41.7%)	
Renal function before AKI			
Serum creatinine concentration (mg/dl)	1.46 ± 0.24	1.23 ± 0.31	0.502
eGFR (ml/min/1.73 m ²)	41.97 ± 11.07	47.99 ± 17.19	0.484
Cause (ATN)			
Ischemic, n (%)	12 (80.0%)	10 (83.3%)	0.825
Toxic, n (%)	3 (20.0%)	2 (16.7%)	0.790
Weight (kg)	59.3 ± 12.3	54.9 ± 7.5	0.285
APACHE II score	31.2 ± 2.1	34.9 ± 2.8	0.570
SOFA score	13.7 ± 1.3	14.1 ± 1.5	0.528
BUN at initiation of RRT (mg/dl)	101.4 ± 15.2	111.4 ± 10.6	0.064

Data are presented as the mean \pm standard deviation or number (proportion, %).

SLED = sustained low-efficiency dialysis; CVVHDF = continuous venovenous hemodiafiltration; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; ATN = acute tubular necrosis; APACHE = acute physiology and chronic health evaluation; SOFA = sequential organ failure assessment; BUN = blood urea nitrogen; RRT = renal replacement therapy

patients (25.0%) in the CVVHDF therapy group compared with four out of 11 patients (26.7%) in the SLED group ($p = 0.381$). There were no significant differences in the incidence of catheter-related complications, intradialytic hypotension, hypokalemia or hypophosphatemia between the groups (Table 3).

Discussion

The optimum method of providing RRT to critically-ill patients has not yet been established. Intermittent hemodialysis is often complicated by hypotension, inadequate fluid, and solute removal leading to further renal injury and prolongation of AKI⁽¹⁵⁾. Many retrospective studies suggested that CRRT was superior to IHD in terms of hemodynamic stability⁽¹⁶⁻¹⁸⁾. However, there had been no controlled studies which could demonstrate definitive advantage of CRRT over IHD in terms of survival^(19,20). Furthermore, CRRT has several disadvantages including limited urea clearance by exchange volume, the need for continuous anticoagulation, intensive nursing requirements and higher costs⁽²¹⁾. Hence, finding alternatives to CRRT is

crucial in critically-ill patients with AKI^(22,23).

Sustained low-efficiency dialysis is a hybrid technique that was adopted as an alternative to CRRT in 1988, and has been practiced worldwide since then⁽⁸⁾. The technique causes less hemodynamic instability and ultrafiltration goals can be achieved in most cases. Other advantages of SLED include a reduced requirement for systemic anticoagulation and staff training, and lower total costs. Schwenger et al were the first to compare and reported that SLED was superior to CVVH in terms of shorter ICU stay and duration of mechanical ventilation in critically-ill patients⁽²⁴⁾. However, survival benefit at 90 days could not be demonstrated in their study.

Several small randomized controlled trials [RCTs] compared SLED with CCRT in the treatment of AKI in critically-ill patients^(12,24-26). Most showed no difference in outcomes between the 2 methods. Chen and colleagues prospectively randomized 56 critically-ill patients to receive either CRRT or SLED, and found that SLED was comparable with CRRT in terms of hemodynamic and biochemical parameters, and short-

Table 2. Primary and secondary outcomes

	SLED	CVVHDF	<i>p</i> -value
Primary outcome			
Survival, n (%)	4 (26.7)	3 (25.0)	0.922
Death, n (%)	11 (73.3)	9 (75.0)	0.682
Secondary outcomes			
ICU stay (days)	8.8±6.3	7.8±4.2	0.629
Hospital stay (days)	11.8±9.6	8.4±7.7	0.496
Recovery of kidney function			
No, n (%)	11 (73.3)	9 (75.0)	0.850
Yes, n (%)	4 (26.7)	3 (25.0)	0.381

Data are presented as the mean ± standard deviation or number (proportion, %)

SLED = sustained low-efficiency dialysis; CVVHDF = continuous venovenous hemodiafiltration; ICU = intensive care unit

Table 3. Summary of complications associated with renal replacement therapy

	SLED	CVVHDF	<i>p</i> -value
Catheter-related complications, n (%)	2 (13.3)	3 (25.0)	0.381
Intradialytic hypotension, n (%)	11 (42.6)	9 (6.5)	0.630
Hypokalemia, n (%)	2 (13.3)	2 (16.7)	0.309
Hypophosphatemia, n (%)	4 (26.7)	3 (25.0)	0.422

Data are presented as the number (proportion, %)

SLED = sustained low-efficiency dialysis; CVVHDF = continuous venovenous hemodiafiltration

term mortality rates⁽²⁷⁾. Berbece et al compared 23 patients who underwent 8 h of SLED six days a week with 11 patients who underwent CRRT, and reported that SLED provided equivalent solute removal to CRRT but at a significantly lower cost⁽²⁸⁾. Kitchu and colleagues compared SLED with CRRT in a cohort of 158 critically-ill patients with AKI, and found that outcomes, including 30-day mortality, were broadly comparable⁽²⁹⁾. A recent meta-analysis of 17 studies conducted between 2000 and 2014, which included seven RCTs and 10 observational studies that recruited 533 and 675 patients respectively, identified no difference in mortality rates between SLED and CRRT⁽³⁰⁾.

We compared the efficacy of different RRT modalities in critically-ill patients with AKI in an observational, non-randomized cohort study. Our findings corroborated those of previous reports that the therapeutic benefits of SLED and CRRT are broadly comparable⁽²⁵⁻³⁰⁾. We found CVVHDF had no additional benefit over the conventional SLED technique in terms of mortality, duration of ICU or hospital, renal function at hospital discharge, or the incidence of RRT-related complications.

In our study, the mean Kt/V per treatment in the SLED group was 1.33 ± 0.18 . The projected weekly Kt/V for a protocol of six treatments per week was 7.98 ± 4.80 , but we only undertook four sessions per week. Our CRRT group had a mean urea clearance of 42.3 ± 12.0 l/day. The corresponding Kt/V for CRRT was therefore 1.10 ± 0.20 , equivalent to a weekly Kt/V of 7.33 ± 3.20 , which is not significantly different from that achieved by SLED. The incidences of electrolyte disturbances such as hypokalemia and hypophosphatemia were similar between the groups. We also observed comparable volume control in SLED and CRRT recipients in the week after initiating RRT. These were consistent with the findings of previous reports^(8,9). Although our follow-up period was relatively short, we found no significant difference in renal recovery rate between the 2 groups.

The complications of CRRT were typical as seen in previous reports^(31,32). The rates of intradialytic hypotension and catheter-related symptoms including infection or clotting in the SLED and CRRT groups were 42.6% vs. 36.5% ($p = 0.631$) and 13.3% vs. 25.0%, respectively ($p = 0.381$). Nonetheless, SLED had a few safety advantages that it required less manipulation and training experience as reported in previous study among ICU nurses that SLED was preferred than CVVHDF due to simpler management⁽³³⁾.

Systemic anticoagulation with heparin is generally recommended to prevent filter clotting in CVVHDF and SLED; however, heparin is frequently contraindicated in the ICU. We did not administer heparin in approximately 60% of the patients in the SLED group. Although filter clotting was found in 15% of them, no significant adverse events were encountered. One study by Kumar et al who administered heparin to the majority of their patients (68%) found higher rate of clots (27%) among those who did not have heparin⁽⁸⁾. However, 17% of filter clotting was still experienced in those treated with heparin. Our findings suggest that patients undergoing SLED can be performed without systemic anticoagulation if necessary.

Our study had some limitations. Our study had small number of patients and being retrospective that some parameters such as vasopressor doses or mean arterial pressure were lacking. Also without a randomization, more severe hemodynamic instability patients were preferably treated with CRRT than SLED. Furthermore, a 30-day mortality was a short-term outcome and we could not comment on the overall mortality or longer-term dialysis dependence. Future studies in a larger group of patients, in a randomization manner, and with a long-term follow-up are warranted. In summary, in critically ill patients with AKI, SLED and CRRT achieved comparable renal recovery and survival at 30 days, with comparable incidences of complications. We judge that SLED is an acceptable alternative to CRRT for hemodynamically unstable patients with AKI and can be delivered in only four sessions per week.

What is already known on this topic?

Renal replacement therapy [RRT] is a complex procedure in critically-ill patients. Continuous venovenous hemodiafiltration [CVVHDF] and sustained low-efficiency dialysis [SLED] has been advocated in hemodynamically unstable patients with acute kidney injury.

What this study adds?

In critically-ill patients with AKI, CVVHDF and SLED are comparable in terms of reduction of all-cause mortality within 30 days.

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Potential conflicts of interest

The authors declare no conflict of interest.

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