Original Article

Enhancing Cytokine Clearances with Sustained Low-Efficiency Diafiltration (SLED-f) Using High Cut-off Dialyzer in Septic AKI Patients: A Randomized Trial

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Background: Hypercytokinemia contributes a major role in the pathogenesis and is associated with the high mortality in sepsis-related acute kidney injury (AKI). Reductions of these cytokines have been reported to improve clinical outcomes. Online sustained low-efficiency diafiltration (SLED-f) using traditional high-flux (HF) dialyzer could remove some cytokines. Interestingly, the potential of enhancing cytokine removal by using newly designed high cut-off (HCO) dialyzer that could theoretically remove larger molecular weight solutes has never been studied in SLED-f before.

Materials and Methods: The present randomized controlled trial was conducted in sepsis-related AKI patients to compare the efficacy of cytokine removal including interleukin (IL)-6, IL-8, IL-10, and tumor necrotic factor (TNF)-α by six-hour SLED-f between using HCO dialyzer (HCO-SLED-f, n = 8) and HF dialyzer (HF-SLED-f, n = 8).

Results: HCO-SLED-f provided significantly higher clearances of TNF-α, IL-6, and IL-10 than HF-SLED-f. HCO-SLED-f demonstrated significant IL-8 and TNF-α reductions, (p=0.012 for both) after treatment whereas HF-SLED-f could only yield significant TNF-α reduction (p=0.018). The degree of all cytokine reductions did not show significant differences between both treatment groups. There were significantly higher total albumin losses in effluent fluid in HCO-SLED-f group than HF-SLED-f group, (p<0.001). The percentage of plasma albumin reduction was not different between both treatment groups. There were no significant differences in intra-dialytic blood pressure parameters during both treatments.

Conclusion: In sepsis-related AKI, HCO-SLED-f could be safely applied and could enhance cytokine clearances as well as reduce more types of cytokines when compared with HF-SLED-f, although the degree of reduction did not show significant difference. The higher degree of albumin loss should be considered when using HCO-SLED-f.

Trial registration: ClinicalTrials.gov, NCT03014232

Keywords: Sustained low-efficiency diafiltration (SLED-f), High cut-off dialyzer, Cytokines

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Sepsis has been clearly established to be the major cause of acute kidney injury (AKI)[1] and is importantly related to the higher mortality rate compared with AKI from other causes despite the advancement in extracorporeal renal replacement therapy (RRT)[2]. Excess hypercytokinemia from either proinflammatory cytokines such as tumor necrosis factor-α (TNF-α, 17kDa), interleukin (IL)-6 (26 kDa), and IL-8 (8 kDa), or anti-inflammatory cytokines such as IL-10 (36 kDa) are thought to play a principal role in the catastrophic consequences of sepsis and sepsis-related AKI[3]. The earliest cytokines including IL-6 and TNF-α are illustrated to be significantly higher in sepsis-related than non-sepsis related AKI patients[4,5].

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A recent study demonstrated that lower plasma cytokine levels produce a better renal recovery rate and superior overall clinical outcomes[5].

Due to hemodynamic instability of patients with sepsis-related AKI, continuous RRT (CRRT) appears to be more popular than intermittent hemodialysis (HD). Sustained low-efficiency dialysis (SLED), one of the current standard prolonged intermittent RRT, has emerged as an alternative to CRRT in the treatment of critically ill sepsis-related AKI with comparable ultrafiltration and solute removal while providing additional advantages over CRRT in term of lower cost of treatment and less nursing workload[6-8]. However, SLED operates mainly via diffusion process and thus provides limitation in removing large molecules including cytokines. Online sustained low-efficiency diafiltration (online SLED-f), which combines convection and diffusion solute clearances by using online hemodiafiltration (HDF) machine with high-flux (HF) dialyzer was recently innovated to enhance these large solute clearances[9-11] and could demonstrate the potential benefits of renal recovery and patient survival in sepsis-related AKI when compared with SLED[10]. Although, there were no data regarding cytokine removal, the enhancement of larger cytokine clearances was postulated to yield these benefits. However, the pore size cut-off of HF dialyzer was still a limiting factor regarding clearances of other large cytokines.

To enhance the clearances of larger cytokines, high cut-off (HCO) dialyzers, a novel type of dialyzers with molecular weight cut-off closer to that of the native kidney (65 kDa) were recently utilized and could reduce plasma cytokines more effective than HF dialyzers in diffusive clearance in previous animal and ex vivo sepsis-model studies[12]. In sepsis-related AKI, HCO dialyzers were utilized only in intermittent HD[13] and CRRT modes[14-16] with better removal of cytokines but greater albumin loss when compared with the HF membrane[13,14,17]. An integration of HCO dialyzer in SLED-f mode in sepsis-related AKI has never been examined before.

The present randomized controlled trial was conducted to compare the efficacy between SLED-f with HCO and SLED-f with HF dialyzer as the control in removal of circulating mediators, including pro- (IL-6, IL-8, and TNF-α) and anti-inflammatory mediators (IL-10) in patients with sepsis-related AKI. The undesired effects regarding albumin lost were compared. Other clinical and laboratory parameters including hemodynamic parameters during treatment were also determined.

Materials and Methods

Patients

The present randomized controlled study was conducted in sixteen sepsis-related AKI patients who fulfilled the indications for prolonged intermittent RRT at King Chulalongkorn Memorial Hospital in 2012. The study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No.271/54). Written informed consent was obtained in all cases. Sepsis and AKI were defined by the current consensus criteria for sepsis[18] and Acute Kidney Injury Network (AKIN) or modified RIFILE criteria[19], respectively. Exclusion criteria comprised of patients with profound hemodynamic instability with more than one inotropic drug, pregnancy, breast-feeding, or delayed receiving antibiotic for up to six hours after beginning of septic shock. All included patients were randomized using computer-generated number in opaque sealed envelopes (block of four) to undergo online SLED-f using HF or HCO dialyzer by principle investigator.

The demographic variables including age, sex, and pre-existing underlying diseases were recorded. The severity of illness in each patient was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score on the first day when the RRT was started. The usages of ventilator or vasoactive support were recorded.

Online SLED-f with HF and HCO dialyzer prescription

Online SLED-f with HF and HCO dialyzers were performed using the Fresenius 5008S HDF machines (Fresenius Medical Care, Bad Homburg, Germany). New HF ELISIO 150H (Nipro Corporation, Osaka, Japan; polynephron material, pore size 50 to 60 A°, Kuf 67 mL/hour/mmHg, surface area 1.5 m^2) and super-flux, Sureflux 150FH (Nipro Corporation, Osaka, Japan; cellulose triacetate material, pore size 78 A°, Kuf 66.9 mL/hour/mmHg, surface area 1.5 m^2) were used for online SLED-f with HF and HCO dialyzers, respectively. Dialysis time and blood flow rate were six hours and 200 mL/minute, respectively. The predilution reinfusion fluid rate and dialysate flow rate were 80 and 220 mL/minute, respectively, (the total dialysis fluid flow rate was 300 mL/minute). The dialysate/infusate compositions were sodium 140 mEq/L, potassium 3 mEq/L, calcium 3.5 mEq/L, bicarbonate 30 to 35 mEq/L, and magnesium 1.2 mg/dL. Net ultrafiltration loss rates were prescribed according to individual needs and were kept constant throughout the study period as long as hemodynamics

were stable. To prevent filter clotting, unfractionated heparin was administered for cases that had no contraindication. These online SLED-f treatments were continuously prescribed at least thrice-a-week to the patients until renal recovery or death.

The dialysis fluid purity utilized in the present study was met by the ISO criteria for ultrapure dialysis fluid indicated by total viable microbial counts of less than 0.1 CFU/mL and endotoxin concentrations of less than 0.03 EU/mL[20]. The water and dialysate samples were monthly tested for biological contamination.

Sample collection and measurement

Blood samples were taken from patients before and at the end of 6-hour in the first online SLED-f session. The percentage of reduction ratio were calculated from the before and ending samples. Simultaneous pre-and post-dialyzer blood samples from arterial and venous sampling ports were collected at 30 minutes after the treatment was started for determination of dialyzer clearances. Continuous sampling of spent effluent dialysate and ultrafiltrate were carried out with a collection pump inserted into the effluent outlet line via a special connector for total albumin loss determination.

The cytokines (IL-6, IL-8, IL-10, and TNF-α) were determined in the plasma separated from EDTA blood. After collection, plasma separation was achieved by centrifugation for 10 minutes at 1,500 g. Immediately after separation, the samples were stored at –70°C until further analysis. All determinations were carried out in duplicate. The panels of cytokines (IL-6, IL-8, IL-10, and TNF-α) were measured using Luminex xMap-based multiplex technology. Assays were performed using the MILLIPLEX MAP (multi-analyte panels) Cytokine Kit (Millipore, Billerica, MA) on the Luminex® instrument according to the manufacturer's procedure.

Instantaneous plasma cytokine clearances were calculated according to the formula:

$$\text{Clearance (mL/minute)} = \frac{Q_B (C_a - C_v)}{C_a}$$

Where C_a is pre-dialyzer cytokine concentration at arterial port (pg/mL); C_v is post-dialyzer cytokine concentration at venous port (pg/mL); Q_B is blood flow rate at arterial line (cc/minute)

The percentage of reduction ratio was calculated as follows:

$$\text{Reduction of cytokine (\%)} = \frac{(C_{pre} - C_{post}) \times 100}{C_{pre}}$$

Where C_{pre} is pre-treatment (baseline) concentration (pg/mL); C_{post} is post-treatment (end of the session) concentration (pg/mL)

The albumin losses into the effluent were calculated according to the equation:

$$\text{Albumin losses (g)} = C_{Alb} (Q_D + Q_{UF}) \times t$$

Where C_{Alb} is albumin concentration in a representative sample of spent effluent (g/dL); (Q_D + Q_{UF}) is the sum of effluent flow, infusion flow, and ultrafiltration flow (mL/minute); t is time of online SLED-f treatment (minute)

The intradialytic blood pressure parameters were monitored periodically. In patients previously required inotropic drug, it was adjusted to maintain the mean arterial pressure greater than 65 mmHg. The percent of intradialytic hypotension with or without inotropic adjustment, clinical outcomes as well as the percentage reduction of blood urea nitrogen (BUN), phosphate, albumin, and β2-microglobulin were also determined.

Statistical analysis

Sample size was calculated based on the difference in clearance of cytokine (IL-6) at 43%[21,22] with type I error of 0.05 and power of 80%. The number of patients needed in each group was eight. All analyses were performed with the SPSS 11.5 software system (SPSS, Chicago, IL, USA). The continuous data of baseline characteristic were reported as median (25^{th} to 75^{th} percentiles). The nominal data were presented as percentages. The Mann-Whitney U test was used to analyze differences between the two dialyzer groups whereas Wilcoxon signed-rank test were applied to determine the differences between the two time points within each group. The differences were considered significant at p-value lower than 0.05. The patient survival times were obtained using the Kaplan-Meier method with log-rank testing.

Results

Patient demographics and baseline data

Sixteen sepsis-related AKI patients were recruited and randomized into HCO-SLED-f (n = 8) and HF-SLED-f (n = 8) groups. The demographic data and clinical characteristics of the studied patients before SLED-f treatment are listed in Table 1. The median age of patients in HCO-SLED-f group was 70 (46.5 to 75.3) years while in HF-SLED-f group was 76 (56.0 to 79.0) years (p=0.18). The co-morbid diseases in both groups were comparable. The baseline laboratory values, respiratory setting, hemodynamic parameters, and total amount of urine output volume in 24 hours were mostly comparable between the two groups,

Table 1. Clinical characteristics of the studied patients before SLED-f treatment

	HF (n = 8)n (%)	HCO (n = 8)n (%)	p-value
Age (years), Median (25^{th} to 75^{th} percentile)	76 (56.0 to 79.0)	70 (46.5 to 75.3)	0.18
Sex			
Male	6 (75.0)	3 (37.5)	0.13
Female	2 (25.0)	5 (62.5)	0.13
Co-morbid diseases	7 (87.5)	6 (75.0)	0.52
Diabetes mellitus	3 (37.5)	4 (50.0)	0.61
CKD stage ≥ III	3 (37.5)	3 (37.5)	1.00
Coronary artery disease	1 (12.5)	1 (12.5)	1.00
Liver disease	1 (12.5)	0 (0.0)	0.30
Hypertension	7 (87.5)	4 (50.0)	0.11
Source of infection			
Catheter	1 (12.5)	1 (12.5)	1.00
Gastrointestinal tract	2 (25.0)	4 (50.0)	0.30
Respiratory tract	5 (62.5)	2 (25.0)	0.13
Unknown source	0 (0.0)	1 (12.5)	0.30
Positive hemoculture	4 (50.0)	5 (62.5)	0.83
APACHE II score, Median (25^{th} to 75^{th} percentile)	25.5 (21 to 28.5)	22.3 (20.1 to 29.4)	0.42
SOFA score, Median (25^{th} to 75^{th} percentile)	12 (10 to 15)	9 (6 to 13.8)	0.10
aBP (mmHg), Median (25^{th} to 75^{th} percentile)			
Mean aBP	96 (69.0 to 101.0)	91 (77.0 to 102.3)	0.86
Systolic aBP	135 (127.0 to 151.0)	140 (118.8 to 161.3)	0.95
Diastolic aBP	67 (47.0 to 85.0)	70 (60 to 81.5)	0.60
On norepinepine	2 (25.0)	2 (25.0)	0.58
Urine output (mL/day), Median (25^{th} to 75^{th} percentile)	600 (110 to 1,000)	450 (8 to 1,837)	0.91
Indication for RRT			
Azotemia	3 (37.5)	4 (50.0)	0.61
Volume overload	4 (50.0)	3 (37.5)	0.45
Hyperkalemia	1 (12.5)	2 (25.0)	0.52
Metabolic acidosis	1 (12.5)	2 (25.0)	0.52
Laboratory parameters, Median (25^{th} to 75^{th} percentile)			
BUN (mg/dL)	76.0 (67.0 to 79.0)	71.0 (56.3 to 96.3)	0.86
Creatinine (mg/dL)	3.9 (3.3 to 4.6)	6.8 (4.5 to 9.2)	0.015
Albumin (g/dL)	2.9 (2.8 to 3.2)	2.8 (2.4 to 3.0)	0.22
Phosphate (mg/dL)	5.2 (2.8 to 6.2)	4.3 (3.6 to 4.6)	0.42
β_2-microglobulin (mg/dL)	23.9 (20.4 to 74.4)	19.8 (17.9 to 23.5)	0.11
Total bilirubin (mg/dL)	3.1 (2.6 to 5.8)	0.5 (0.4 to 9.6)	0.08
Arterial pH	7.45 (7.36 to 7.47)	7.43 (7.30 to 7.46)	0.73

SLED-f=sustained low-efficiency diafiltration; HF=high-flux dialyzer; HCO=high cut-off dialyzer; CKD=chronic kidney disease; APACHE II=Acute Physiology and Chronic Health Evaluation version II; SOFA, Sequential Organ Failure Assessment; aBP=arterial blood pressure; RRT=renal replacement therapy; BUN=blood urea nitrogen

Table 2. Plasma cytokines at baseline before SLED-f treatment and percentage reduction after SLED-f treatment

Cytokines	Plasma levels at baseline (pg/mL)			Percentage reduction (%)		
	HF-SLED-f	HCO-SLED-f	p-value	HF-SLED-f	HCO-SLED-f	p-value
TNF-α	39.5 (23.1 to 55.9)	46.4 (31.9 to 58.2)	0.487	38.6 (16.0 to 44.2)	43.3 (19.8 to 49.5)	0.418
IL-6	64.8 (25.9 to 503.0)	19.7 (12.1 to 71.3)	0.049	–38.5 (–129.6 to 25.6)	–3.2 (–40.6 to 38.0)	0.355
IL-8	185.0 (109 to 261.0)	219.5 (102.4 to 412.3)	0.487	29.8 (12.8 to 65.2)	38.3 (28.3 to 77.8)	0.355
IL-10	59.2 (17.3 to 88.2)	66.9 (26.7 to 119.1)	0.643	–5.2 (–42.8 to 9.9)	10.1 (–15.1 to 24.2)	0.418

SLED-f=sustained low-efficiency diafiltration; HF=high-flux dialyzer; HCO=high cut-off dialyzer; TNF-α=tumor necrosis factor-α; IL=interleukin

except creatinine levels. The severity of sepsis was assessed by APACHE II score and SOFA score in HCO- and HF-SLED-f groups were not significantly different.

Small and middle-molecule solutes

The percentage of urea reduction in HCO-SLED-f group was significantly greater than HF-SLED-f group [79.8 (73.3 to 92.3) versus 65.2 (64.2 to 76.8), p=0.021] (Figure 1A), while the percentages of phosphate were comparable. The percentages of reductions of β_2-microglobulin, representing middle-molecule solute after SLED-f treatment were similar between both groups (Figure 1B).

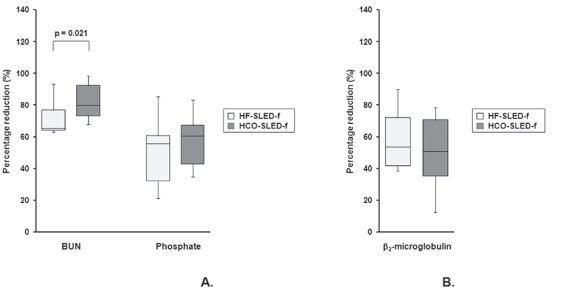

Figure 1. The percentage reduction of (A) small molecules (BUN and phosphate) and (B) middle molecule (β2-microglobulin) after SLED-f treatment.

Removal of cytokines

At baseline, most of the cytokine levels including TNF-α, IL-8, and IL-10 were comparable between both groups except for IL-6, of which the levels in HF-SLED-f were slightly and significantly higher than HCO-SLED-f groups (p=0.049) (Table 2).

Instantaneous cytokine clearances that were determined from the simultaneous pre- and post-dialyzer blood samples at half an hour after starting SLED-f treatment are shown in Figure 3. HCO-SLED-f provided significantly higher plasma clearances of TNF-α, (p=0.037), IL-6, (p=0.037), and IL-10 (p=0.002) than HF-SLED-f, whereas IL-8 clearances were comparable (Figure 2).

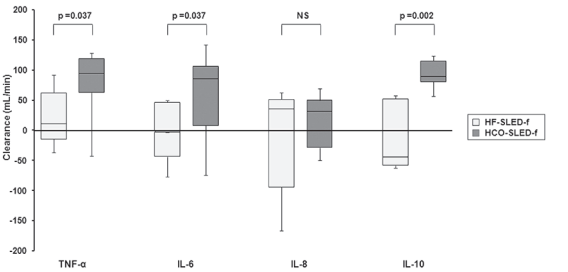

Figure 2. Instantaneous cytokine clearances.

At the end of the treatment, HCO-SLED-f provided significant reduction of IL-8 and TNF-α levels after treatment [219.5 (102.4 to 412.3) versus 71.0 (42.2 to 193.3) pg/mL, p=0.012 and 46.4 (31.9 to 58.2) versus 29.4 (15.0 to 38.2) pg/mL, p=0.012 for pre- and post-HCO-SLED-f treatment of IL-8 and TNF-α, respectively]; whereas HF-SLED-f could only demonstrate significant reduction of TNF-α [39.5 (23.4 to 55.9) versus 21.3 (14.6 to 37.2) pg/mL, p=0.018 for pre- and post-HF-SLED-f treatment, respectively] (Figure 3). However, the degree of all cytokine percentage reductions between HF-SLED-f and HCO-SLED-f for TNF-α, IL-6, IL-8, and IL-10 did not show significant differences (Table 2).

Albumin losses

The albumin levels at the start and end of SLED-f treatment are shown in Figure 4A. The total albumin losses in spent dialysate/ultrafiltrate were significantly higher in HCO-SLED-f compared with HF-SLED-f [4.7 (3.5 to 5.8) versus 0 (0 to 0.11) grams, respectively, p<0.001) (Figure 4B). However, the percentage reduction of serum albumin was not different between both treatment (p=0.908).

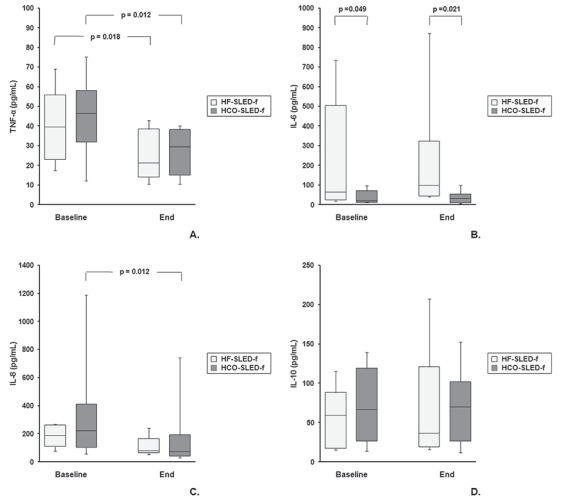

Figure 3. Plasma cytokine levels at the baseline and the end of SLED-f treatment.

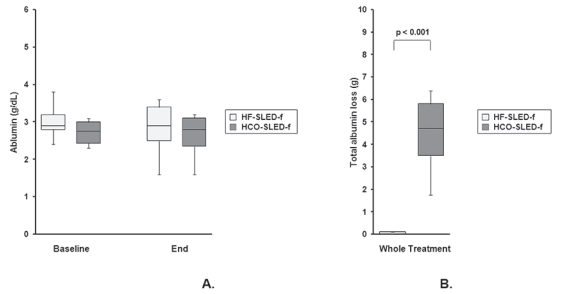

Figure 4. (A) Serum albumin at the baseline and the end of SLED-f treatment. (B) Total albumin loss in spent dialysate/ultrafiltrate.

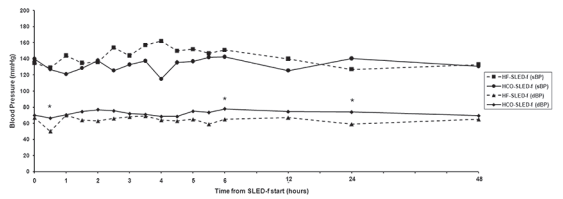

Figure 5. The median systolic blood pressure (sBP) and diastolic blood pressure (dBP) values from start until 48 hours after SLED-f.

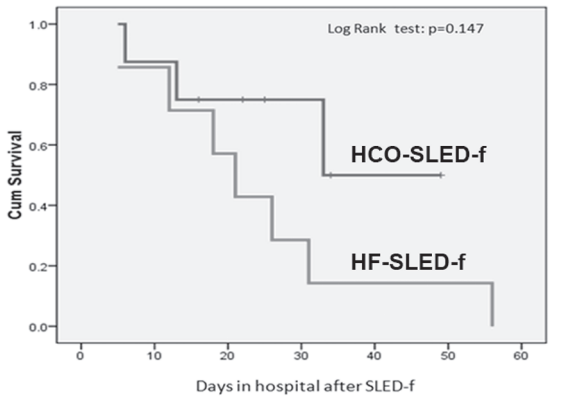

Figure 6. The cumulative hospital survival rate of sepsis-related AKI patients after randomization into the study, stratified according to treatment groups.

Hemodynamic parameters and complications

The hemodynamic profiles were recorded during the start until 48 hours after SLED-f (Figure 5). The arterial blood pressure (aBP) parameters before starting of treatment in HCO-SLED-f group were comparable to HF-SLED-f group including systolic aBP [140 (118.8 to 161.3) versus 135 (127 to 151) mmHg], diastolic aBP [70 (59.5 to 81.5) versus 67 (47 to 85) mmHg], and mean aBP [91 (77 to 102.3) versus 96 (69 to 101) mmHg]. Blood pressure parameters during treatment until 48 hours after treatment were mostly comparable between both groups. However, HCO-SLED-f group provided significantly higher dBP than HF-SLED-f at half an hour and six hours [78 (73 to 92.3) versus 65 (63 to 75) mmHg, p=0.032] during treatment period as well as at twenty-four hour after treatment [74 (68.5 to 83.5) versus 59 (53 to 69) mmHg, p=0.036].

There were no significant differences in the total doses of intradialytic inotropic drug adjustment. HCO-SLED-f group had slightly higher total ultrafiltration fliud than HF-SLED-f group [2,400 (1,900 to 3,400) versus 200 (0 to 2,025) mL, p=0.048].

The incidence of intradialytic hypotension was 50% in HCO-SLED-f group, which was comparable with 42.3% in HF-SLED-f. Other observed adverse clinical parameters including bleeding complications, thrombocytopenia, and electrolyte abnormality parameters were not significantly different between the two groups.

Patient survival

The 28-day survival in HCO-SLED-f group was higher than HF-SLED-f, although the statistical significance was not attained (75.0% versus 28.6%, p=0.147) (Figure 6). The overall mortality in HF-SLED-f group was 100% whereas in HCO-SLED-f group was 37.5%. The renal outcomes among these survivors in HCO-SLED-f group were partial recovery (80%) and no recovery that required long-term dialysis (20%).

Discussion

Hypercytokinemia and subsequent endothelial activation play important roles in the pathogenesis of severe sepsis[3,14], initiation and extension phases of AKI as well as causing adverse distant-organ injury after AKI[23]. The modalities that could cut the peak of inflammatory mediators might attenuate the adverse consequences of sepsis-related AKI. In sepsis-related AKI, online SLED-f using standard HF membrane demonstrated the clinical safety and efficacy[9-11]. However, the roles of using HCO membrane in online SLED-f in sepsis-related AKI patients have never been explored before. In the present study, online SLED-f technique, which combined diffusive and convective clearance, and HCO dialyzer, which had larger pore size than HF dialyzer, were simultaneously utilized with the aim to enhance the removal of larger inflammatory cytokines.

The results showed that HCO-SLED-f provided significantly higher TNF-α (17kDa), IL-6 (26 kDa), and IL-10 (36 kDa) clearances than HF-SLED-f but comparable clearance of IL-8 (8 kDa) (Figure 2). This observation might be explained by the lowest molecular weight of IL-8 compared with other studied cytokines. The benefit of HCO membrane was obvious in removing larger cytokines, at least 17 kDa of TNF-α. Interestingly, the adsorptive capacity of HCO membrane might also contribute to these total clearances. The cytokine clearances by HCO-SLED-f resulted in significant TNF-α and IL-8 reductions, ($p=0.012$ for both) after treatment, whereas HF-SLED-f could provide only significant reduction of TNF-α ($p=0.018$). The possibility of HCO-SLED-f in decreasing IL-8 (pro-inflammatory cytokine) and enhance IL-10 (anti-inflammatory cytokine) productions might explain these changes in plasma levels. Indeed, application of HCO membrane for sepsis-related AKI patients were limitedly reported in intermittent HD[13] and CRRT[14-17] modes, of which the results also showed the potentially significant removal of cytokines compared with the standard HF membrane. Interestingly, IL-6 clearance, which was the common surrogate cytokine removal measured in most sepsis-related studies, showed the highest value in HCO-SLED-f in the present study (85.3 mL/minute) (Figure 2) when compared with intermittent HD (14.1 mL/minute)[13] and CVVH (10 to 40 mL/minute)[15-17].

Of interest, this enhanced removal by HCO-SLED-f in the present study involved not only pro-inflammatory cytokines but also anti-inflammatory cytokines (Figure 2). The concept of "peak concentration hypothesis", which described that early cutting the peak of both pro- and anti-inflammatory cytokines, might result in effective immunomodulation and could alleviate monocyte inactivation and eventually immunoparalysis[24]. Therefore, early starting of HCO-SLED-f in sepsis-related AKI patients to remove cytokines should be considered in order to offer this crucial benefit besides providing RRT purpose.

Because of the limitation in the number of studied population and in the treatment time of SLED-f in the present study, the percentage reduction in all studied cytokines, which were continuously generated even during SLED-f treatment, were not obviously high and did not reach statistically significant differences (Table 2, Figure 3). Thus, extended time of SLED-f treatment up to 18 to 24 hours in the larger study population might intensify the cytokine reduction and make the differences between HF and HCO groups more obviously observed.

Regarding small and middle molecule solute removal, HCO-SLED-f could provide significantly higher percentage reduction of urea than HF-SLED-f (Figure 1A) but did not yield significant difference in percentage reduction of β2-microglobulin (11.8 kDa) (Figure 1B). The molecular weight of β2-microglobulin was less than TNF-α, which was demonstrated comparable clearance between both dialyzers (Figure 2). These would confirm the finding that HCO dialyzer did not provide superior convective removal of molecule up to 17 kDa. Indeed, the urea clearance depends mainly on diffusion. The pore sizes of both dialyzers are too large to make any superiority of each other. Therefore, the differences in other properties of the dialyzer membrane which influence the diffusive process such as material, thickness, and porosity structure would be the explanation of the higher percentage urea reduction in HCO-SLED-f groups.

The benefits of enhancement of larger molecule removal should be considered with the risk of albumin loss and slightly higher cost of treatment. The present study also demonstrated significantly higher total albumin losses in effluent fluid in SLED-f mode using HCO dialyzer (Figure 4B). However, the percentage of plasma albumin reduction was not different between both groups (Figure 4A). Indeed, the data of total albumin losses of HCO dialyzer in sepsis-related AKI were available only in other modalities which were up to 7.6 g/12 hours[17] during CVVH and 7.7 g during 4-hour intermittent HD[13]. Comparing the magnitude of total albumin loss of HCO dialyzer among different modalities, the total albumin loss of median 4.7

g in HCO-SLED-f in the present study was lower than both CVVH and intermittent HD in previous studies[13,17]. The differences in modalities might be one explanation. HCO-SLED-f in the present study is the combination of convective and diffusive clearances whereas CVVH using HCO dialyzer depends on only convective clearance, which causes high albumin loss. The lower dialysis fluid flow rate in HCO-SLED-f when compared with intermittent HD using HCO dialyzer might be another possible explanation of slightly lower albumin loss of SLED-f when compared with intermittent HD. In term of albumin loss, thus, SLED-f mode might be safer than CVVH or intermittent HD when using HCO membrane. However, this degree of albumin loss was still higher than HF-SLED-f. The repeated loss of albumin might cause hypoalbuminemia and adversely affect clinical outcome. Thus, albumin supplement might be required in patients who had obviously reduced albumin levels.

The cost-effective issue of the treatment might be another consideration. The cost of SLED-f treatment was obviously lower than CVVH and should be preferred for the eligible patients. For SLED-f treatment, the cost of dialyzer contributed only one-third. The price of HCO dialyzer in the present study was only 14% higher than HF dialyzer. Therefore, HCO-SLED-f treatment provided only 4% higher cost than HF-SLED-f treatment.

A previous study in CVVH using HCO membrane demonstrated the clinical benefit in term of lower dosage of inotropic drugs during HCO usage when compared with HF[15]. Although the present study did not show the difference in inotropic drug dosage, better aBP in several time points in HCO group were observed (Figure 5). These would be in agreement in term of hemodynamic benefit of HCO membrane enhancing cytokine removal. Further larger studies are required to delineate this clinical hemodynamics as well as survival benefits.

Regarding RRT in sepsis-related AKI, several recent large RCTs had failed to demonstrate the clinical improvement following treatment with intensive HF RRT by daily HD/SLED when compared with standard alternate-day HD/SLED or between high volume and standard volume CRRT[25,26]. Although the dosage comparisons have not been studied in HF-SLED-f mode, the results might be in the similar direction. These negative findings might be partly explained by the limitation of large molecular weight cytokine clearance of the HF dialyzer used in all of these studies. This explanation, however, might not be applied to RRT utilizing HCO dialyzer including HCO-SLED-f mode. It would be interesting to examine whether alternate-day or daily HCO-SLED-f could improve patient survival when compared with the standard HF-SLED or HF-SLED-f in sepsis-related AKI.

In conclusion, HCO-SLED-f could be safely applied and could enhance cytokine clearances as well as reduce more types of cytokines in sepsis-related AKI when compared with HF-SLED-f although the degree of reduction did not show significant difference. The higher degree of albumin loss should be considered when using HCO-SLED-f.

What is already known on this topic?

Excess hypercytokinemia such as tumor necrosis factor-α (TNF-α, 17kDa) and interleukin (IL)-6 (26 kDa) play a principal role in the catastrophic consequences of sepsis-related AKI. Online SLED-f, which combines convection and diffusion solute clearances by using online HDF machine with high-flux dialyzer (HF-SLED-f) was recently innovated to enhance these large solute clearances and could demonstrate the potential benefits of renal recovery and patient survival in sepsis-related AKI when compared with sustained low-efficiency dialysis (SLED).

What this study adds?

The potential of enhancing cytokine clearances by integrating the newly design high cut-off (HCO) dialyzers, the novel type of dialyzers with molecular weight cut-off closer to that of the native kidney (65 kDa), in SLED-f mode was explored in the present study. The results demonstrated this new modality (HCO-SLED-f) could be safely applied and could enhance cytokine clearances as well as reduce more types of cytokines in sepsis-related AKI when compared with HF-SLED-f. The higher degree of albumin loss should be considered when using HCO-SLED-f.

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Conflicts of interest

The authors declare no conflict of interest.

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