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Sustained low-efficiency dialysis with regional citrate anticoagulation in critically ill patients with COVID-19 associated AKI: A pilot study

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ABSTRACT

Acute Kidney Injury (AKI) is a frequent complication in critically ill patients with Coronavirus disease 2019 (COVID-19), and it has been associated with worse clinical outcomes, especially when Kidney Replacement Therapy (KRT) is required. A condition of hypercoagulability has been frequently reported in COVID-19 patients, and this very fact may complicate KRT management. Sustained Low Efficiency Dialysis (SLED) is a hybrid dialysis modality increasingly used in critically ill patients since it allows to maintain acceptable hemodynamic stability and to overcome the increased clotting risk of the extracorporeal circuit, especially when Regional Citrate Anticoagulation (RCA) protocols are applied. Notably, given the mainly diffusive mechanism of solute transport, SLED is associated with lower stress on both hemofilter and blood cells as compared to convective KRT modalities. Finally, RCA, as compared with heparin-based protocols, does not further increase the already high hemorrhagic risk of patients with AKI. Based on these premises, we performed a pilot study on the clinical management of critically ill patients with COVID-19 associated AKI who underwent SLED with a simplified RCA protocol. Low circuit clotting rates were observed, as well as adequate KRT duration was achieved in most cases, without any relevant metabolic complication nor worsening of hemodynamic status.

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1. Introduction

In the course of the severe acute respiratory syndrome associated with Coronavirus disease 2019 (COVID-19) the percentage of patients with Acute Kidney Injury (AKI) requiring Kidney Replacement Therapy (KRT) varies significantly among different studies, ranging from 0% to 35% according to the number of critically ill patients included, geographic location, racial and ethnic groups considered, prevalence of comorbidities and local institutional procedures [1,2]. The pathophysiological mechanism of this specific form of AKI remains still unclear. Indeed, while in most cases the etiology seems to be directly related to sepsis and multiorgan dysfunction, specific alterations associated with the viral infection have not been completely excluded [1,3]. Remarkably, a hypercoagulable state attributed to systemic inflammation, platelet dysfunction and microvascular alterations is often reported, and it has been associated with a high incidence of thrombotic complications [4,5]. In this complex clinical scenario, continuous KRT (CKRT)

have been frequently adopted in the Intensive Care Unit (ICU) patients with hemodynamic instability [1]. However, a high rate of extracorporeal circuit clotting has been often described, leading to frequent treatment downtime, increased transfusion needs and waste of health resources [4–7]. Sustained Low Efficiency Dialysis (SLED) is a modality of Prolonged Intermittent KRT (PIKRT) with a typical 8–12 h treatment time, which is increasingly used in ICU patients, since it combines the most favorable characteristics of both CKRT and conventional Intermittent Hemodialysis (IHD) [8] (Fig. 1). PIKRT can be performed either with CKRT or IHD machines, providing adequate daily treatment dose in less time compared with CKRT, thus optimizing the often limited available resources in the overcrowded clinical context of SARS-CoV-2 in the ICUs [1]. Moreover, the diffusive solute transport characteristic of this KRT technique may help reduce the mechanical stress on the hemofilter, and consequently the risk of extracorporeal circuit clotting [9]. Given the prolonged duration of SLED, an anticoagulation strategy is commonly recommended. The most recent guidelines on AKI suggest the use of Regional Citrate Anticoagulation (RCA) in all patients without specific contraindications for citrate, irrespective of the bleeding risk [10,11]. Indeed, several clinical studies have extensively demonstrated the advantages of RCA over systemic heparin anticoagulation protocols

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Variable	
Dialysis machine	Any conventional hemodialysis or CKRT machine
Blood flow, ml/min	150-200
Main solute transport mechanism	Diffusion
Dialysate flow, ml/min	50-100 (CKRT machine), 100-300 (conventional hemodialysis machine)
Ultrafiltration target, ml/h	Variable, according to patient needs and hemodynamic status, typically 100-300
Urea clearance, ml/min	70-90
Duration, hours	8-12
Anticoagulation strategy	RCA mostly with concentrated citrate solutions (3%)
Theoretical advantages	
<ul style="list-style-type: none"> – SLED can be performed with any kind of KRT machine – SLED is a well-tolerated KRT modality also in critically ill patients with hemodynamic instability – SLED may provide an adequate daily treatment dose in less time compared with CKRT, thus allowing to optimize the available resources in the ICUs by using the same dialysis machine for more than one patient per day – The reduced daily treatment time compared to CKRT allows to perform any diagnostic or therapeutic procedures (included prone positioning) reducing any treatment downtime – The diffusive solute transport may help to blunt the mechanical stress on the hemofilter and blood cells, and consequently it may reduce the risk of extracorporeal circuit clotting, frequently observed among patients with COVID-19 – The adoption of specifically designed RCA protocols for SLED may be associated with prolonged filter life span and reduced incidence of both hemorrhagic complications and transfusion requirements – The reduced KRT duration compared to CKRT permits to reduce the healthcare workers exposure risk 	
Abbreviations: SLED, Sustained-Low Efficiency Dialysis; RCA, Regional Citrate Anticoagulation; AKI, Acute Kidney Injury; CKRT, Continuous Kidney Replacement Therapy; KRT, Kidney Replacement Therapy; ICUs, Intensive Care Units.	

Fig. 1. Typical setting and theoretical advantages of SLED with RCA in the specific clinical context of critically ill patients with COVID-19 associated AKI.

in terms of prolonged filter life span and reduced incidence of both hemorrhagic complications and transfusion requirements [12]. In particular, the percentage of premature treatment interruption secondary to circuit clotting is significantly higher in patients on CKRT with heparin-based protocols compared to those based on RCA protocols [13].

In this report we present preliminary data from a pilot study of critically ill patients with SARS CoV-2 related AKI who underwent 49 SLED sessions with a simplified RCA protocol. This approach allowed both to overcome the increased clotting risk observed in this peculiar clinical setting, and to deliver the prescribed dialysis dose.

2. Case series

One-hundred thirty-five consecutive patients with COVID-19 were admitted to the General ICU of the Parma University Hospital between February 23 and May 5, 2020. AKI, defined according to the most recent guidelines [14], was detected in 43 (31.9%) patients. Five (11.6%) of these patients were scheduled to be started on KRT; however, one patient died six hours before the effective start of KRT. The demographic and clinical characteristics at ICU admission of patients underwent KRT are reported in Table 1. All patients were mechanically ventilated and required prone positioning. The coagulation profile was within

the normal range in all patients (Table 1); all of them were given subcutaneous low molecular weight heparin as prophylaxis. In particular, given the evidence of reduced kidney function at ICU admission, 3 of 4 patients received a reduced dose of enoxaparin 4.000 UI once daily and the other a full dose of 6.000 UI. KRT was started after an average time from ICU admission of 5 days. The main indication for starting KRT was progressive fluid overload associated with stage 3 oliguric AKI. Each patient underwent repeated SLED sessions, for a total of 49 treatments. The extracorporeal treatment was performed either by using the Prisma System (Baxter) with polyacrylonitrile AN69 filters (ST 150, 1.5 m², Baxter) or, alternatively, the AK200S Ultra type 1 machine (Gambro, Medolla, Italy) with polysulfone filters (F8HPS, 1.8 m², Fresenius, Italy), on the basis of machine availability at the moment. Double lumen 12 Fr dialysis catheters were used. The prescribed SLED duration was 8–12 h with a prescribed net fluid removal per hour of 100–300 mL/h, according to patient's needs and hemodynamic status. The concentrated citrate solution (ACD-A; citrate anion 112.9 mmol/L or 3%, of which 0.8% from citric acid and 2.2% from trisodium citrate, Fresenius Italy) was infused in the extracorporeal circulation before the filter at in proportion to the blood flow rate (Q_b, 150–200 mL/min –Q_{ACD-A} approximately 250–300 mL/h), aiming at a target 2.5–3 mmol/L citrate concentration in the hemofilter. When the CKRT dialysis machine was used, a calcium and bicarbonate containing

Table 1
Demographic and clinical characteristics at ICU admission, and SLED parameters.

Variable	Pt. 1	Pt. 2	Pt. 3	Pt. 4
Age, yr	49	63	54	47
Male	Y	Y	Y	Y
Comorbidities,				
Arterial hypertension	N	Y	Y	N
Diabetes mellitus	Y	Y	Y	N
CKD	N	N	N	N
APACHE II score	36	31	22	30
SOFA score	16	14	12	16
Invasive mechanical ventilation	Y	Y	Y	Y
Serum creatinine, mg/dL	2	0.6	4.2	1.5
BUN, mg/dl	24	18	80	26
Platelet count, x 10 ³ /mL	118	284	248	448
INR	1.33	1.34	1.28	1.32
aPTT ratio	1.02	1.11	1.22	1.02
ICU stay, days	33	40	48	75
Duration of mechanical ventilation, days	30	38	48	70
Death in the ICU	N	N	N	N
Death during hospital stay	N	N	N	N
Prescribed SLED sessions, n/patient	23	16	2	8
SLED duration, hours (median, IQ range)	12 (9.5–12.5)	8 (8–12)	10 (9–11)	10 (8.7–12)
Causes of SLED interruption				
Programmed end of treatment (%)	18 (78.3)	14 (87.5)	2 (100)	6 (75)
Circuit clotting (%)	2 (8.7)	1 (6.2)	-	-
CVC malfunctioning (%)	2 (8.7)	1 (6.2)	-	1 (12.5)
Other clinical reasons (%)	1 (4.3)	-	-	1 (12.5)
Duration of KRT, days	29	27	4	8

ICU, Intensive Care Unit; SLED, Sustained Low-Efficiency Dialysis; Pt, Patient; CKD, Chronic Kidney Disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; BUN, Blood Urea Nitrogen; CVC, Central Venous Catheter; KRT, Kidney Replacement Therapy. Y, Yes; N, No.

solution (Baxter PrismaSol 4: Ca²⁺ 1.75 mmol/L, HCO₃⁻ 32 mmol/L, Na⁺ 140 mmol/L, Cl⁻ 113.5 mmol/L, K⁺ 4 mmol/L, Mg²⁺ 0.5 mmol/L; Lactate 3 mmol/L; Glucose 6.1 mmol/L) was selected as dialysis fluid and set at 100 mL/min. Alternatively, when the conventional hemodialysis machine was used, the on-line generated ultrapure dialysate with a Ca⁺⁺ concentration of 1.25 mmol/L was run at 300 mL/min in a counter-current direction. Calcium gluconate (10% solution, calcium 0.24 mmol/mL) was infused in a central venous line to maintain the systemic ionized calcium (s-Ca²⁺) concentration within the normal range (0.90–1.20 mmol/L). In particular, the infusion was started at 5 mL/h whenever s-Ca²⁺ fell below 0.9 mmol/L. The intradialytic variables related to RCA are reported in Table 2. Electrolytes and acid-base parameters were maintained within the normal range without any relevant episode of hypo-hypercalcemia and metabolic acidosis/alkalosis. Calcium supplementation at fixed rate 1.13 mmol/h was needed in 13/49

Table 2
Intradialytic clinical monitoring and intradialytic variables related to Regional Citrate Anticoagulation.

Variable	SLED Start	SLED 2 h	SLED 6 h	SLED 10 h	SLED 12 h	P
SBP, mmHg	130.1 (20.4)	129.0 (24.0)	119.9 (23.2)	117.2 (24.4)	118.4 (15.0)	0.0046
DBP, mmHg	62.2 (10.55)	62.2 (13.98)	61.6 (9.48)	60.7 (11.53)	61.1 (11.42)	NS
Heart rate, bpm	94.9 (12.4)	96.8 (13.5)	96.9 (14.8)	100.2 (13.5)	94.5 (15.2)	NS
Dopamine, mcg/Kg/min	0.73 (2.08)	0.67 (1.98)	0.89 (2.47)	0.78 (2.27)	0.71 (2.28)	NS
Norepinephrine, mcg/Kg/min	0.06 (0.11)	0.06 (0.11)	0.06 (0.14)	0.05 (0.15)	0.05 (0.15)	NS
Dobutamine, mcg/Kg/min	0.14 (0.37)	0.14 (0.37)	0.14 (0.37)	0.09 (0.31)	0.09 (0.31)	NS
SpO ₂ , %	97.5 (2.9)	98.0 (2.1)	97.2 (6.6)	98.6 (1.7)	99.3 (0.8)	NS
FiO ₂ , %	50.9 (20.0)	50.3 (18.1)	51.4 (18.6)	50.6 (17.5)	51.1 (15.0)	NS
ACT, sec	110.6 (10.53)	111.8 (10.54)	116.8 (10.87)	110.9 (6.33)	109.1 (14.25)	NS
Ionized calcium (s-Ca ²⁺), mmol/L	1.16 (0.08)	1.12 (0.07)	1.16 (0.07)	1.15 (0.08)	1.16 (0.08)	NS
Bicarbonate (HCO ₃ ⁻), mmol/L	24.4 (2.6)	24.7 (2.7)	24.6 (1.8)	25.9 (3.2)	26.5 (1.1)	

Data are presented as mean (SD). Values were measured on patients' arterial line if not otherwise indicated.

Abbreviations: SLED, Sustained Low Efficiency Dialysis; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SpO₂, Peripheral Oxygen Saturation, FiO₂, Fraction of Inspired Oxygen; ACT, Activated coagulation time; NS, not statistically significant.

treatments. Calcium ratio was steadily maintained below the threshold of 2.5. Clinical monitoring data during SLED treatments are reported in Table 2. The ultrafiltration target was achieved in most sessions, with only a mild decrease in Systolic Blood Pressure (SBP). Vasopressor amines were being infused before SLED start in 23 sessions, and infusion was initiated in the course of 2 sessions, in both cases at the second hour of treatment. We did not observe any statistically significant difference in the vasopressors dose in course of SLED sessions; no SLED session was interrupted for severe hemodynamic instability. No KRT-related bleeding complication was observed. Three out of 49 (6.1%) SLED sessions were prematurely interrupted for circuit clotting (Table 1); a complete restitution the extracorporeal circuit blood to the patient was achieved in 2 of the 3 cases. Relevant modifications of operative SLED parameters in the course of treatment were not required, and the extracorporeal circuit pressures remained within the safety limits. In all of the four patients SLED was discontinued following recovery of an adequate urine output.

3. Discussion

Our pilot study suggests that, in patients with COVID-19 associated AKI, SLED with RCA is a well-tolerated KRT modality which allows to deliver the prescribed dialysis dose and to maintain an adequate fluid balance even in patients with severe hemodynamic instability. According to our knowledge, the present study is the first to provide data on the use of RCA in the course of SLED in critically ill patients with COVID-19 associated AKI. Indeed, the adoption of a KRT technique mainly based on diffusion reduces the mechanical stress on both the hemofilter and blood cells, leading to a lower incidence of extracorporeal circuit clotting, particularly common in COVID-19 patients with AKI [4–7]. Moreover, given the dramatically elevated number of patients requiring an intensive clinical management in this clinical setting, the shortening of daily treatment time characteristic of SLED as compared to CKRT, might contribute to deliver the dialysis treatment to more patients by using the same dialysis machine (Fig. 1). Our report confirms the feasibility and safety of PIKRT, recently reported in a prospective observational study performed in 136 critically ill patients with COVID-19 associated AKI [15], where 108/130 PIKRT sessions (83%) were performed with a systemic heparin-based anticoagulation protocol. The ultrafiltration target was attained in most cases; however, in this report 17 sessions (13%) based on a heparin-based protocol were complicated by premature interruption for extracorporeal circuit clotting [15]. In this context, notably, circuit clotting rates are particularly high in patients undergoing convective CKRT (i.e. Continuous Venovenous Hemofiltration, CVVH), despite the higher delivered dose or the use of pre-dilution modality [3,8]. Frequent premature circuit clotting was also reported in a recent study on 37 critically ill patients with SARS-CoV-2 who underwent Continuous Venovenous Hemodiafiltration

(CVVHDF) with a heparin-coated hemodiafilter aimed at enhancing cytokine adsorption [16]. In our study, the application of a simplified RCA protocol specifically designed for the SLED modality significantly contributed to achieve the prescribed dialysis duration, without any relevant metabolic complications, even in presence of impaired liver function [12]. As a matter of fact, it is well known that RCA protocols optimized the hemofilter efficiency and circuit life span, without interfering with systemic coagulation, even in patients with very high bleeding risk [11–13].

In conclusion, notwithstanding the limited number of observations which require further confirmation in a study with a more numerous patient population, our pilot study suggests that SLED with RCA is a safe and feasible KRT modality in critically ill patients with COVID-19 associated AKI requiring KRT. Moreover, given the peculiar operative setting, this form of KRT may allow to reduce the otherwise increased rate of extracorporeal circuit clotting, particularly when RCA protocols are applied. Finally, by shortening treatment time, SLED could represent a rationale therapeutic alternative to CKRT, since it allows health resources optimization in the ICU.

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CRedit authorship contribution statement

Di Mario Francesca: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. **Regolisti Giuseppe:** Methodology, Investigation, Formal analysis, Writing - review & editing. **Di Maria Alessio:** Investigation, Data curation. **Parmigiani Alice:** Investigation, Data curation. **Benigno Giuseppe Daniele:** Investigation, Data curation. **Picetti Edoardo:** Resources, Data curation. **Barbagallo Maria:** Resources, Data curation. **Greco Paolo:** Resources, Data curation. **Maccari Caterina:** Resources, Data curation. **Fiaccadori Enrico:** Supervision, Methodology, Writing - review & editing, Project administration.

Declaration of Competing Interest

Disclosure of potential conflicts of interest: the authors declare that they have no conflict of interest.

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