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CLINICAL RESEARCH

Use of the Selective Cytopheretic Device in Critically Ill Children

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Introduction: Critically ill children with acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT) are at increased risk of death. The selective cytopheretic device (SCD) promotes an immunomodulatory effect when circuit ionized calcium (iCa^{2+}) is maintained at <0.40 mmol/l with regional citrate anticoagulation (RCA). In a randomized trial of adult patients on CRRT, those treated with the SCD maintaining an iCa^{2+} <0.40 mmol/l had improved survival/dialysis independence. We conducted a US Food and Drug Administration (FDA)–sponsored study to evaluate safety and feasibility of the SCD in 16 critically ill children.

Methods: Four pediatric intensive care units (ICUs) enrolled children with AKI and multiorgan dysfunction receiving CKRT to receive the SCD integrated post-CKRT membrane. RCA was used to achieve a circuit iCa^{2+} level <0.40 mmol/l. Subjects received SCD treatment for 7 days or CKRT discontinuation, whichever came first.

Results: The FDA target enrollment of 16 subjects completed the study from December 2016 to February 2020. Mean age was 12.3 ± 5.1 years, weight was 53.8 ± 28.9 kg, and median Pediatric Risk of Mortality II was 7 (range 2–19). Circuit iCa^{2+} levels were maintained at <0.40 mmol/l for 90.2% of the SCD therapy time. Median SCD duration was 6 days. Fifteen subjects survived SCD therapy; 12 survived to ICU discharge. All ICU survivors were dialysis independent at 60 days. No SCD-related adverse events (AEs) were reported.

Conclusion: Our data demonstrate that SCD therapy is feasible and safe in children who require CKRT. Although we cannot make efficacy claims, the 75% survival rate and 100% renal recovery rate observed suggest a possible favorable benefit-to-risk ratio.

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Acute kidney injury (AKI) is a significant complication in critically ill children, as it results in increased morbidity and mortality.[1–4] AKI develops predominantly because of the injury and necrosis of renal proximal tubule cells, often concurrently with sepsis (sepsis-associated AKI, SA-AKI). Part of the disease process in patients with AKI is often the development of a systemic inflammatory response syndrome (SIRS), resulting in cardiovascular collapse, ischemic damage to vital organs, and multiorgan dysfunction (MOD).[5,6]

The development of AKI in children with sepsis is associated with higher mortality.[7,8] The major clinical manifestations of sepsis and SIRS are due to the excessive dysregulation of the host response to infection or injury rather than direct consequences of the invading pathogen or tissue damage.[9,10] Central to this initial immunologic response is activation of leukocytes, predominately neutrophils, and damaged microvascular endothelium resulting in cardiovascular instability, lung injury, and kidney dysfunction.[11] Although leukocytes play an essential role in combating septic shock as demonstrated by the recurrence of life-threatening infections in patients with neutropenia or leukocyte defects,[12,13] if the leukocyte response is uncontrolled, collateral tissue damage may occur, resulting in solid organ dysfunction.

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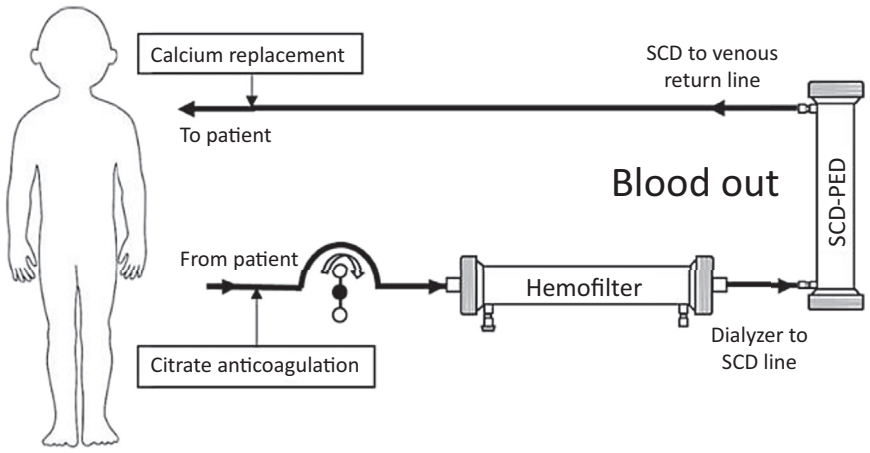


Figure 1. Schematic diagram of integration of the SCD into the CKRT circuit with the direction of blood flow in the extracorporeal CKRT-SCD circuit. CKRT, continuous kidney replacement therapy; PED, pediatric; SCD, selective cytopheretic device.

Despite advancements in kidney replacement therapy and blood purification technologies, little improvement in the morbidity and mortality rates of AKI or SA-AKI have occurred over the last several decades. The mortality rates in children with AKI and MOD requiring CKRT continues to approach 50%.[14–16] Children who survive an AKI episode are at increased risk of long-term sequelae, including chronic kidney disease (CKD).[17–19] Thus, for effective therapies for AKI/SA-AKI, both of these short- and long-term outcomes are needed. Because activated leukocytes are central to the pathogenesis/progression of septic shock and other clinical inflammatory disorders, a variety of new therapeutic approaches are being considered to limit the deleterious clinical effects of activated leukocytes that result from a dysregulated immune response to sepsis.[20]

The SCD (SeaStar Medical, Inc., Denver, CO) immunomodulates activated circulating leukocytes and provides a new therapeutic approach to SIRS and AKI. The discovery of this approach was based on an unexpected observation during a phase II clinical trial of a tissue-engineered bioartificial kidney in adult ICU patients with AKI progressing to MOD, whereby the control arm (without regenerated human acute tubular epithelial cells) had much better outcomes with RCA than heparin CKRT anticoagulation controls.[21–23] The SCD is used within an extracorporeal blood circuit (Figure 1) to sequester activated leukocytes. The leukocytes are deactivated within a low ionized calcium (iCa^{2+}) environment promoted with clinically accepted CKRT RCA protocols. The SCD combines a sequestering membrane and a biologic moiety (citrate) that together reset and immunomodulate the dysregulated leukocyte activation kinetics of SIRS associated with sepsis and AKI. This approach has been confirmed in a preclinical large animal model of septic shock,[24] and in human clinical trials.[23,25,26] Importantly, a phase III Investigational Device Exemption randomized controlled, multicenter trial demonstrated the effectiveness of SCD therapy to reduce a composite endpoint consisting of 60-day mortality or dialysis dependency in adult ICU patients with AKI and MOD requiring CKRT.[27] This study also demonstrated an excellent safety profile for the SCD.

With these promising preclinical and clinical results with SCD therapy, we conducted a prospective FDA-funded, multicenter safety and feasibility study of the SCD in 16 critically ill children with the goal of application for a Humanitarian Device Exemption (HDE) for the SCD in this population. We previously reported data from the first patient enrolled in this study to demonstrate feasibility.[28] We now report the results of this completed study.

Methods

We conducted this prospective study at 4 US centers (Cincinnati Children's Hospital Medical Center, University of Michigan / CS Mott Children's Hospital, University of Alabama at Birmingham / Children's of Alabama, and Emory University / Children's Healthcare of Atlanta at Egleston). Children of 15 kg or more in weight, up to 22 years of age, who were admitted to an ICU were screened for eligibility. Subjects who had AKI, as defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria,[29] and MOD and were receiving CKRT as part of the standard of clinical care were eligible to be enrolled in the study. MOD was defined as respiratory disease requiring invasive mechanical ventilation and/or cardiovascular compromise requiring the provision of a continuous infusion of an inotropic/vasoactive medication. These criteria have been repeatedly shown to be associated with AKI

development and mortality in critically ill children.[30–32] Subject severity of illness was assessed by the Pediatric Risk of Mortality II score (PRISM II) in the 12 hours before SCD initiation.[33] The adult phase III study exclusion criteria were modified over the course of this pediatric study to be more relevant to children (Supplemental Table S1). For example, the use of extracorporeal membrane oxygenation (ECMO) was a contraindication, but ECMO is used commonly in pediatric sepsis, and after several screen failures based on ECMO, the FDA agreed to lift this exclusion. The institutional review board at each center approved the study prior to patient enrollment. Written informed consent was obtained from the subject's parents for those younger than 18 years of age, and/or a person with medical decision-making power for subjects 18 years of age or older prior to subject enrollment. Study personnel adhered to the Declaration of Helsinki. The study received an Investigational Device Exemption (G120174) from the US FDA and was registered at www.clinicaltrials.gov (NCT02820350) prior to study commencement. The study was funded mostly by an Office of Orphan Products Development grant (R01FD005092) from the US FDA with a small subsequent grant from SeaStar Medical Inc. to complete the final 2 subjects' enrollment. As this was primarily a safety study (AEs and serious AEs [SAEs]), results and progress were reviewed by an external data safety monitoring board at least annually or at completion of 5, 10, and 16 subjects, whichever came first, to determine if any AEs occurred that would require study termination or modification.

CKRT-SCD Protocol

All centers provided CKRT with RCA as part of local standard of care with the following study-required constraints: (i) prescribed small solute clearance was required to be an effluent volume of at least 2000 ml/h per 1.73 m^2 of patient body surface area (not inclusive of the volumes of citrate and calcium infused and removed for RCA), (ii) RCA was provided with a well-described protocol[34–36] using anticoagulant dextrose A (ACD-A; Baxter Healthcare, Deerfield, IL) to maintain the CKRT circuit iCa^{2+} <0.40 mmol/l for at least 90% of the time a subject was receiving CKRT-SCD, (iii) CKRT circuit and subject systemic iCa^{2+} were measured at least every 6 hours, and (iv) only polysulfone-based CKRT membranes could be used (i.e., no AN-69 membranes).

CKRT was initiated prior to insertion of the SCD in line with the CKRT circuit (Figure 1). No other modification of the CKRT was needed. Subjects had to have a minimum blood pressure of 80/40 mmHg prior to SCD insertion into the CKRT circuit. The SCD was inserted 4 hours after CKRT initiation, which did not require a new CKRT circuit for SCD insertion. In addition, 2 consecutive CKRT circuit iCa^{2+} levels measuring <0.40 mmol/l at least 30 minutes apart were required before inserting the SCD into the CKRT circuit to optimize the circuit iCa^{2+} prior to SCD initiation. If 2 consecutive CKRT circuit iCa^{2+} levels <0.40 mmol/l were unable to achieve within 12 hours of CKRT initiation, the subject's participation in the study was terminated. The study targeted an iCa^{2+} target of <0.40 mmol/l for at least 90% of measurements. The subject's systemic iCa^{2+} was targeted to at least 1.0 mmol/l, but the target for an individual subject was determined by the clinical situation and local standard of clinical care. The CKRT and/or SCD circuits were primed with blood if the extracorporeal circuit volume (ECV) comprised more than 10% of the subject's estimated blood volume. All but 1 center used the Prismaflex CKRT platform (Baxter Healthcare) with the HF1000 filter; the remaining centers used the Diapact platform (B Braun Medical, Bethlehem, PA). The ECV of the HF1000 is 165 ml and SCD is 120 ml (HF1000 + SCD volume = 285 ml). Table 1 depicts the blood priming parameters for the study. The SCD was changed daily. SCD therapy was provided for up to 7 days of CKRT or until CKRT termination, whichever came first.

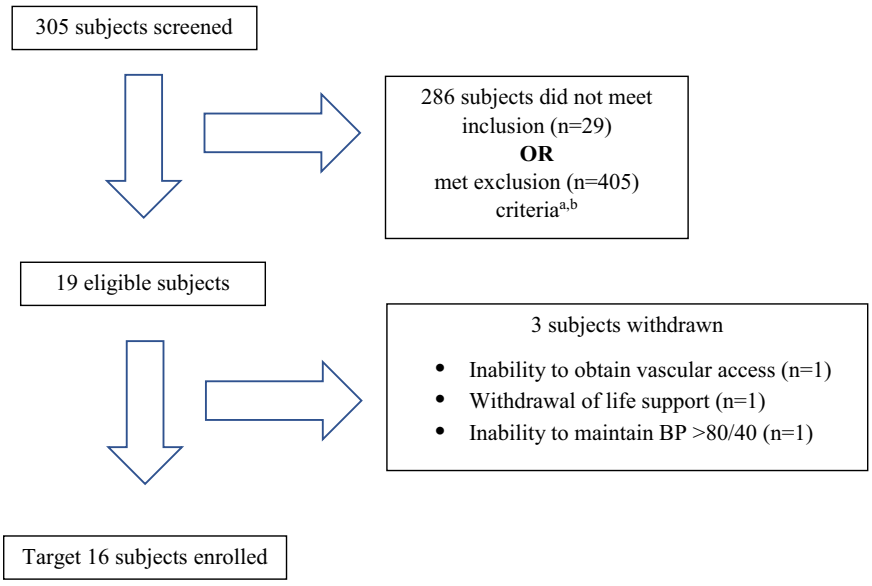
Table 1. Blood-priming parameters for the CKRT-SCD circuit

Patient Weight (kg)	Total Estimated Blood Volume (ml)	Blood Prime Need
>40	>2800	None
24–40	1680–2800	HF1000 alone
15–24	1050–1680	HF1000+SCD

CKRT, continuous kidney replacement therapy; ECV, extracorporeal circuit volume; SCD, selective cytopheretic device
The blood volume for the HF1000 is 165 ml and for the SCD is 120 ml, leading to a total ECV of 285 ml. Blood priming will occur if the ECV total is greater than 10% of the patient's blood volume, based on an estimate of blood volume = 70 ml/kg × patient body weight (kg).[24] As such, there are 3 patient weight ranges that will dictate the need, or lack thereof, for blood priming.

Analyses

As noted above, this US FDA funded and approved study was conducted to evaluate the safety of the SCD in children weighing more than 15 kg to support application for a Humanitarian Device Exemption. Given the small agreed upon sample size, no claims of efficacy could be made owing to a lack of power. Subject demographic data and CKRT/SCD data are aggregated and reported as mean (±SD) or median and interquartile range where appropriate. AEs and SAEs were reported by the site investigators based on predetermined criteria. The site investigator determined if any AE was related to the study treatment or not. An AE, whether considered study treatment related or not, which fit any of the criteria below, was considered an SAE:



[a] –Subjects may have met more than 1 inclusion and/or exclusion criteria.

[b] –The complete list of inclusion criteria not met and exclusion criteria met is listed in Supplemental Table

Figure 2. Study subject screening and enrollment flow, with numbers of subjects who did not meet inclusion criteria and/or met exclusion criteria. A complete list of reasons for study exclusion is detailed in Supplemental Table 2. BP, blood pressure.

- Resulted in death
- Was life-threatening (meaning that the patient was at risk of death at the time of the event; this does not refer to an event that might have caused death if it had occurred in a more severe form)
- Required inpatient hospitalization or prolongs the existing hospitalization
- Was a persistent disability/incapacity
- Was considered an important medical event by the investigator (e.g., surgery, return to ICU, emergency procedures)

AEs associated with CKRT or underlying critical illness are also considered to be anticipated. Such events include, but are not limited to, thrombocytopenia, hyponatremia, hypokalemia, hypo- or hypercalcemia, hypo- or hyperglycemia, air embolism, hypotension, hemolysis, increased oxygenation requirements, leukopenia, arrhythmias, hypothermia, lactic acidosis, temporary decrease in cardiac output or cardiac index, disruption of skin integrity, bleeding, shock, bacteremia, hypotension, seizure, and death. Although these events were considered anticipated, it did not necessarily mean they could not be related to the SCD. Patient white blood cell (WBC) and platelet counts were monitored immediately before and then every 12 hours while the subject received treatment with the SCD. The effect of the SCD on WBC and platelet counts was assessed by 1-way analysis of variance (Stata, version 16; StataCorp, College Station, TX). A P value of <0.05 was considered to be significant.

Results

The study flow diagram is depicted in Figure 2. Three hundred five patients were screened over the course of the study as they were receiving CKRT as part of the standard of clinical care. The most common reasons for exclusions were weight <15 kg (n=124) and presence of CKD stage 4 or 5 or ESRD (n=38) (the full list of inclusion criteria not met and exclusion criteria met is depicted in Supplementary Table S2). Nineteen patients met all inclusion and no exclusion criteria, but 3 of these patients were withdrawn prior to SCD therapy. This left the 16 patients (8 female/8 male) who were enrolled and completed the study from December 2016 through February 2020.

Mean subject age was 12.3 ± 5.1 years (range 4–21 years), weight was 53.8 ± 28.9 kg (range 19.1–111 kg), and median PRISM II score at CKRT initiation was 7 (range 2–19). Three patients weighed less than 24 kg and therefore required blood priming of both the CKRT circuit and SCD filter. Three additional patients weighed from 27.0 to 33.4 kg and required blood priming of the CKRT circuit alone. Two subjects received ECMO. The most common diagnosis leading to ICU admission was septic shock (n=6), followed by pneumonia (n=2) and then n=1 each for rhabdomyolysis, pulmonary hypertension, hemolytic uremic syndrome, encephalomyelitis, disseminated adenoviral infection, cardiac arrest, acute respiratory failure, and acute liver failure. The indications for initiating CKRT was fluid overload and stage 2 or 3 AKI.

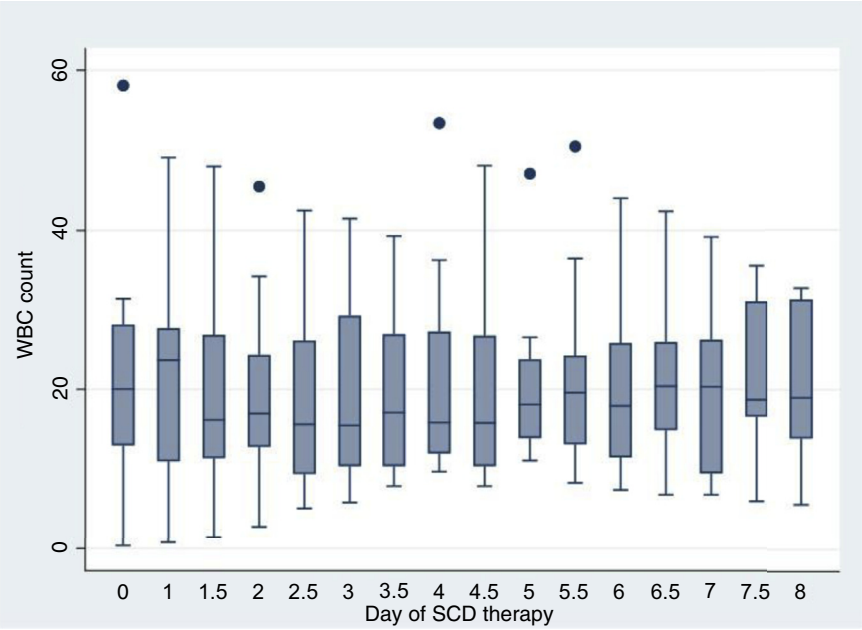


Figure 3. Cohort WBC counts ($\times 10^3$/mcl) during the time of SCD treatment. WBC counts were obtained immediately prior to and every 12 hours after initiation of SCD treatment. The horizontal lines represent the median count, boxes the IQR, vertical line limits the upper and lower adjacent values, and dots the outlier values. IQR, interquartile range; SCD, selective cytopheretic device; WBC, white blood cell.

Most subjects (n = 14) were enrolled between December 2016 through December 2018. The study was placed on hold from December 2018 through November 2019 at the request of the industry sponsor (SeaStar Medical, Inc.) because of concerns about a future potential change in SCD manufacturing. These concerns were not realized, so the study was resumed and completed.

The median SCD treatment course duration was 6 days (range 1–7 days). Four subjects received CKRT for 3 days or less, and 7 subjects received CKRT for 5 days or less. The circuit iCa^{2+} concentrations achieved the threshold of <0.40 mmol/l for 90.2% of the time subjects received CKRT-SCD therapy. No circuit was lost because of SCD filter clotting. The subject systemic iCa^{2+} concentrations were maintained at >1.0 mmol/l in 97.5% of measurements, with a lowest value of 0.89 mmol/l. Only 1 patient required a calcium bolus after initiating CKRT-SCD.

The median pre-SCD WBC count was 20.0 $\times$ 10^3/mcl (interquartile range 13.0–28.1, range 0.37–58.1 $\times$ 10^3/mcl) and the median platelet count was 113.5 $\times$ 10^3/mcl (interquartile range 94–266, range 42–417 $\times$ 10^3/mcl). Neither aggregate cohort median WBC counts (Figure 3) nor platelet counts (Figure 4) changed during SCD treatment ($P > 0.99$ and $P = 0.94$, respectively). The lowest WBC and platelet counts were 0.37 $\times$ 10^3/mcl and 27 $\times$ 10^3/mcl, respectively,

Fifteen of the 16 subjects survived to the end of SCD therapy. The 1 subject who did not survive SCD therapy died at 7 hours of therapy after developing irreversible ventricular tachycardia. Autopsy revealed severe myocardial inflammation. This SAE was considered to not be device related and was reviewed by both the FDA and the data safety monitoring board, both of which concurred. Twelve of the 16 patients survived to hospital discharge; 2 of the subjects who died were on ECMO, and the 1 other hospital death occurred on study day 16 because of cardiopulmonary failure requiring ECMO support. Of the 12 survivors, 10 were dialysis independent at 28 days but all 12 were dialysis independent and had a normal serum creatinine at 60 days.

The 12 study SAEs that occurred in 8 patients are listed in Table 2; 10 were listed as severe and 2 were listed as moderate. None of the SAEs were device related and none were related to the study. The 40 study AEs that occurred in 14 subjects are listed in Table 3.

DISCUSSION

We report the first multicenter experience of the SCD to support critically ill children with AKI and MOD. Our data suggest that the SCD therapy was safe and feasible in this cohort, as no device-related SAEs were observed. Furthermore, the 40 AEs observed were all related to subjects' underlying illness or the provision of CKRT itself, and not the SCD therapy.

Integration of the SCD filter was accomplished easily by all 4 centers that participated in this prospective study. In addition, the centers were able to maintain

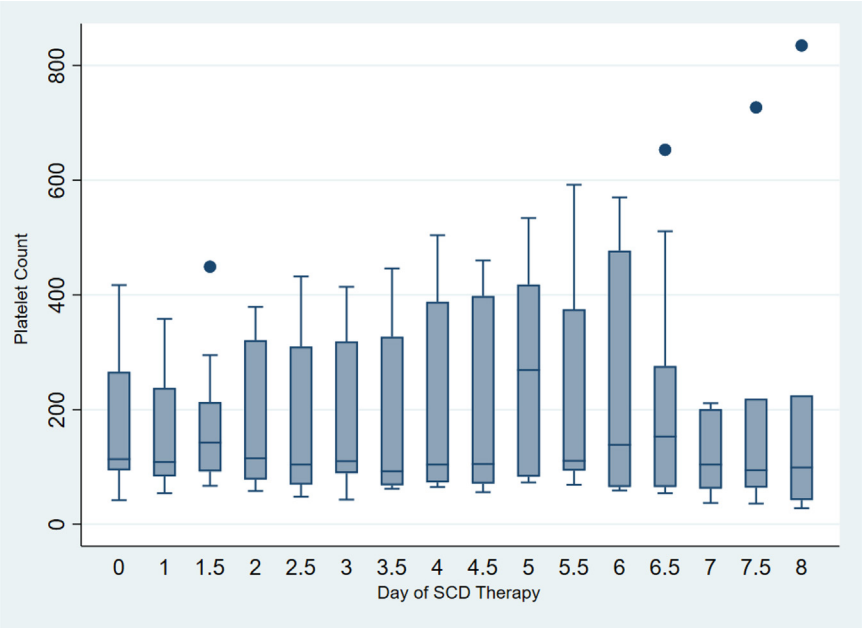


Figure 4. Cohort platelet counts ($\times 10^3$/mcl) during the time of SCD treatment. WBC counts were obtained immediately prior to and every 12 hours after initiation of SCD treatment. The horizontal lines represent the median count, boxes the IQR, vertical line limits the upper and lower adjacent values, and dots the outlier values. IQR, interquartile range; SCD, selective cytopheretic device; WBC, white blood cell.

Table 2. Serious adverse events

Subject	Description of SAE	Severity	Device Related	Causality to Study	Outcome
1	Cardiorespiratory arrest	Severe	No	Unrelated	Resolved without sequelae
2	Pneumoperitoneum	Severe	No	Unrelated	Resolved with sequelae[a]
2	Nephrolithiasis	Moderate	No	Unrelated	Resolved without sequelae
3	Stevens-Johnson Syndrome	Severe	No	Unrelated	Resolved without sequelae
4	Cardiac arrest	Severe	No	Unrelated	Death
5	Junctional tachycardia	Severe	No	Unrelated	Resolved with sequelae[b]
5	Vascular graft occlusion	Moderate	No	Unrelated	Resolved without sequelae
5	Worsening respiratory failure	Severe	No	Unrelated	Death
6	Cerebral hemorrhage	Severe	No	Unrelated	Not resolved[c]
7	Cardiac arrest	Severe	No	Unrelated	Resolved without sequelae
8	Pulmonary hemorrhage	Severe	No	Unrelated	Not resolved[c]
8	Adrenal insufficiency	Severe	No	Unrelated	Not resolved[c]

SAE, serious adverse event.
[a]Patient underwent subtotal colectomy with placement of an ileostomy.
[b]Patient required insertion of a pacemaker.
[c]Not resolved events were ongoing at the time of the patient's death but did not cause the patient's death.

the circuit iCa^{2+} concentration at <0.40 mmol/l at the prespecified rate of more than 90% of the time, and subjects' iCa^{2+} were maintained above >1.0 mmol/l 97.5% of the time CKRT-SCD therapy was delivered using an established pediatric RCA protocol. Thus, provision of SCD therapy did not require substantial technical alteration to standard CKRT therapy in children.

The integration of the additional SCD device into the CKRT circuit raises a potential to cause thrombocytopenia by platelet aggregation on the membranes. This concern is magnified in pediatric patients, who have a lower blood volume compared with adults. Two studies have reported thrombocytopenia associated with CKRT provision to neonates.[37,38] We only observed 2 instances of thrombocytopenia (one of which was due to systemic heparinization verified by the presence of an antiheparin antibody). Although we did not enroll patients <15 kg in this study, we are currently developing an SCD with a smaller ECV for lower-weight children, to be incorporated with the CARPEDIEM (Bellco-Medtronic, Inc., Mirandola, Modena, Italy)[39] or Prismaflex/PrisMax HF20 (Baxter Healthcare)[40] CKRT system, each of which are indicated for a subset of patients <10 kg. Interestingly, evidence of hemolysis (anemia, thrombocytopenia) reversed within 24 hours of SCD therapy initiation in the 2 subjects with hemolysis, including 1 subject with HUS whose platelet count had not yet nadired.

The precise mechanism of action of the SCD is becoming better understood and appears to be an immunomodulatory process that inhibits leukocyte activation, a critical component of the SIRS leading to MOD. The modulation of the dysregulated inflammatory state also allows recovery of renal function in AKI and other associated organ failures. The cartridge acts as an SCD in the presence of citrate anticoagulant to

Table 3. Adverse events

Adverse Events by Category	Severity			Total
	Mild	Moderate	Severe	
Blood and lymphatic system disorders	1	2		3
Thrombocytopenia		1		1
Thrombocytosis	1			1
Heparin-induced thrombocytopenia		1		1
Cardiac disorders	2		2	6
Cardiac arrest			1	1
Junctional tachycardia			1	1
Tachycardia	3			3
Ventricular arrhythmias and cardiac arrest			1	1
Gastrointestinal disorders			1	1
Pneumoperitoneum			1	1
General disorders and administration site conditions	5			5
Hypothermia	3			3
Pyrexia	2			2
Infections and infestations		1	1	2
Postprocedure pneumonia (hospital-acquired)		1		1
Stevens-Johnson syndrome			1	
Injury, poisoning, and procedural complications		1		1
Subcutaneous emphysema		1		1
Metabolism and nutritional disorders		3		6
Adrenal insufficiency			1	1
Hyperglycemia		3		3
Hypokalemia	1	1		2
Nervous system disorders			1	1
Cerebral hemorrhage			1	1
Psychiatric disorders		1		1
Intensive care unit delirium		1		1
Renal and urinary disorders		1		1
Nephrolithiasis		1		1
Respiratory, thoracic, and mediastinal disorders		2	2	4
Acute respiratory failure		2	1	3
Cardiorespiratory arrest			1	1
Surgical and medical procedures		1		1
Vascular Graft Occlusion		1		1
Vascular disorders	6			8
Hypertension	1			1
Hypotension	5		1	6
Pulmonary hemorrhage			1	1
Total	17	13	10	40

bind and immunomodulate potentially damaging circulating leukocytes. This perspective is based on evolving data from *in vitro* bench studies, preclinical animal models, and human clinical trials using measurements of inflammatory biomarkers and leukocyte cell sorting, cytometric analysis.

The low iCa^{2+} environment during RCA and the low shear stress along the blood pathway within the SCD promotes a selective binding of the most activated neutrophils and monocytes to the membranes of the device.[24,28,41] This selectivity is due to the calcium dependency of leukocyte-binding processes. Once bound, the activated neutrophils are promoted in the low iCa^{2+} environment to transition from delayed apoptosis to an apoptotic program and released back to the systemic circulation.[42–44] The transition of these neutrophils to apoptosis and release results in the clearance of these previously highly activated inflammatory cells via well-described pathways of phagocytosis and digestion within macrophages in the bone marrow and liver.[45] A continuous process of binding, apoptotic conversion, release, and clearance from the circulation of the most activated circulating neutrophils results in immunomodulation of the systemic inflammatory process to a less proinflammatory state.[41] For monocytes, the most activated, proinflammatory circulating monocyte pool is selectively bound to the SCD. The binding and sequestration of this monocyte subset promotes a shift of the circulating pool of the

proinflammatory monocytes to a patrolling, reparative phenotype. This shift thereby promotes immunomodulation of circulating monocytes from a degradative phenotype to a reparative, recovery subset,[24,46] enhancing tissue repair and functional recovery.

Given the limited sample size of 16 subjects agreed on with the FDA to establish safety for a Humanitarian Device Exemption application, we can make no claims about the efficacy of the SCD on patient-related outcomes. However, the 75% survival rate observed compares favorably to published CKRT studies in critically ill children with MOD. The largest multicenter study assessed 116 children in the ppCRRT Registry who received mechanical ventilation or a vasoactive agent, which were identical inclusion criteria to the current study, yet the survival rate to ICU discharge was 51.7%.[16] A more recent single-center study of children receiving CKRT reveals a strikingly similar survival rate in 130 patients receiving a vasoactive medication (50.0%) or mechanical ventilation (50.7%) on CKRT.[15]

In addition, similar to results seen in adult clinical studies evaluating SCD treatment, none of the survivors in this pediatric study was dialysis dependent at 60 days. In fact, all 12 survivors had normal kidney function at 60 days. Prior experience in pediatric patients with AKI has reported a CKD incidence rate of 10% to 60% of long-term CKD.[17–19,47] Also, the 2 subjects who were treated with SCD with integration of a CKRT circuit into ECMO support had no SCD-related AEs. Although both subjects did not survive, these safety data are important to acknowledge as a recent report showed rapid improvements in respiratory and inflammatory indices in SCD-treated adults with COVID-19–related acute respiratory distress syndrome requiring ECMO support.[48]

In summary, we demonstrated a high level of safety of SCD therapy in pediatric patients with AKI and MOD receiving CKRT standard of care. Although we cannot make efficacy claims, the 75% survival rate and 100% renal recovery/normal kidney function rate in surviving children suggest a favorable benefit-to-risk ratio in this critically ill pediatric population. Further studies will be required to establish safety in smaller children, feasibility of integration with other CKRT platforms, and to demonstrate improved patient outcomes compared with current supportive therapy, which is associated with a high rate of CKD in survivors. We plan to develop a larger-scale SCD efficacy trial once we have received the Humanitarian Device Exemption from the US FDA.

DISCLOSURES

SLG receives consulting fees from SeaStar Medical, Inc., to assist with their application for a Humanitarian Device Exemption from the US FDA for the SCD technology. SeaStar Medical was not involved in the execution of this study including patient enrollment, data acquisition, data analysis, or development of this manuscript. HDH's relevant disclosures include Innovative Biotherapies, Inc.: shareholder, officer, director; SeaStar Medical: shareholder, scientific advisor, consultant; and Silicon Kidney: scientific advisor.

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These data were presented as an oral abstract at the at the American Society of Nephrology Annual Conference, October 2020.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. List of study exclusion criteria.

Table S2. Listing of inclusion criteria not met and exclusion criteria met.

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