NARRATIVE REVIEW

OPEN

Safety Summary of the Selective Cytopheretic Device: A Review of Safety Data Across Multiple Clinical Trials in ICU Patients With Acute Kidney Injury and Multiple Organ Failure

H. David Humes, MD[1]
Stuart L. Goldstein, MD[2]
Lenar T. Yessayan, MD[1]
David A. Catanzaro, PharmD[3]
Emily C. Scribe, PharmD[3]
Sai Prasad N. Iyer, PhD[3]
Kevin K. Chung, MD[3]

OBJECTIVES: Acute kidney injury (AKI) requiring continuous kidney replacement therapy is a significant complication in ICU patients with mortality rates exceeding 50%. A dysregulated immune response can lead to systemic inflammation caused by hyperactivity of pro-inflammatory neutrophils and monocytes leading to tissue damage. The selective cytopheretic device (SCD) is an investigational medical device in a new class of cell-directed extracorporeal therapies distinct from cytokine adsorbers or filters, as it targets activated leukocytes. These leukocytes are the cellular sources driving this hyperinflammatory process. The objective of this report is to summarize the safety experience from clinical studies of the SCD in ICU patients with AKI or acute respiratory distress syndrome (ARDS) and multiple organ dysfunction (MOD).

DATA SOURCES AND STUDY SELECTION: The studies included in this report represent all relevant trials of the SCD conducted in patients with AKI or ARDS and MOD. Adverse event data, clinical laboratory data and mortality rates were described and summarized in this report.

DATA EXTRACTION AND DATA SYNTHESIS: Five clinical studies were included in this report, including four adult studies of AKI and/or ARDS and one pediatric AKI study, which involved 151 patients treated with the SCD in an ICU setting. Over 800 SCD sessions were deployed with an estimated 19,000 exposure hours with no device-related infections or attributable serious adverse events. Furthermore, there were no safety signals of leukopenia, thrombocytopenia, or other indications of immunodepletion or immunosuppression.

CONCLUSIONS: The SCD has shown to be a promising extracorporeal therapy with promising clinical results and a favorable safety profile. These studies support that the SCD can be added as a therapeutic intervention in critically ill AKI patient populations with multiple organ failure without adding additional safety risks.

KEYWORDS: acute kidney injury; immunomodulation; monocytes; multiple organ failure; neutrophils

Acute kidney injury (AKI) is a frequent and serious complication in critically ill patients, occurring at a rate of one in five adults and one in three children hospitalized with acute illness (1). AKI requiring kidney replacement therapy (KRT) is a significant complication in ICU patients with mortality rates exceeding 50% (2–5). Damage resulting from hyperinflammation associated with AKI frequently progresses to other organs, such as the heart, lung, or liver (6, 7). A dysregulated immune response can lead to systemic inflammation caused by a hyperactivity of pro-inflammatory neutrophils and monocytes leading to tissue damage (8). Approaches to diminish or

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KEY POINTS

Questions: This report will summarize the safety data of the selective cytopheretic device (SCD) used in critically ill patients with acute kidney injury or acute respiratory distress syndrome and multiple organ dysfunction.

Findings: Across five clinical trials, more than 150 ICU patients were treated with over 800 sessions of the SCD with a favorable safety profile, including no device-related infections or device-related serious adverse events.

Meanings: The SCD is a promising immunomodulatory extracorporeal therapy that can be safely added to existing continuous kidney replacement therapy circuits with the potential for clinical benefit without increasing safety risks.

modulate this excessive inflammatory response may have a major impact on improving clinical outcomes.

The selective cytopheretic device (SCD) is an investigational medical device in a new class of cell-directed extracorporeal therapies distinct from cytokine adsorption columns or filters. It is intended to function in conjunction with continuous KRT (CKRT) in the treatment of AKI in both adult and pediatric patients. The SCD cartridge is an extracorporeal device containing hollow polysulfone fibers; blood is directed through the side ports and enters the extracapillary space (ECS) to flow along the extraluminal sides of the membranes. Blood flow directed to the ECS promotes a low shear environment approximating capillary shear. The system requires an infusion with regional citrate anticoagulation (RCA) to maintain an ionized calcium (iCa) concentration less than 0.4 mmol/L to both maintain patency of the blood circuit and enable SCDs immunomodulatory effect. The unique combination of a low shear and low iCa environment mimics the physiologic conditions seen in capillary beds which enables the SCD to selectively target the most highly activated neutrophils and monocytes. Highly activated neutrophils are deactivated and programmed for apoptosis, and monocytes are shifted toward a less inflammatory, and reparative phenotype within the SCD and released back to the systemic circulation. The immunomodulated cells are released back into systemic circulation allowing for the natural reparative process of the body to progress toward immune homeostasis and recovery (9, 10).

Over the last several years, the SCD has been studied in a variety of critically ill ICU patient populations with AKI and multiple organ dysfunction (MOD) showing promising and consistent signals of clinical benefit with a favorable safety profile (9, 11–14). This report summarizes the safety data from those clinical studies.

DATA SOURCES AND STUDY SELECTION

The clinical studies included in this report were adult and pediatric clinical trials investigating the safety and efficacy of adding the SCD with RCA to an existing CKRT circuit in a critically ill population with AKI or acute respiratory distress syndrome (ARDS) with MOD, of whom a majority were also septic. All clinical studies described herein were conducted according to Good Clinical Practice guidelines. Study protocols were approved by local institutional review boards and all patients or parents/guardians provided written informed consent prior to study participation.

DATA EXTRACTION

Safety was assessed through the monitoring and collection of adverse events (AEs) and serious AEs (SAEs) and were categorized by investigators based on severity and related causality to the device. An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medicine (or device) and whether anticipated or unanticipated. An AE is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes: death, life-threatening illness or injury, permanent impairment of a body structure or a body function, including chronic diseases, inpatient or prolonged hospitalization, medical or surgical intervention required to prevent life-threatening illness/injury or permanent impairment to a body structure or function, fetal distress, fetal death, a congenital anomaly or birth defect, including physical or mental impairment, important medical event. Clinical laboratory results were also collected and will be shared where relevant. All-cause

mortality was also collected and thus will be reported for each study.

DATA SYNTHESIS

The five studies included in this report are summarized in **Table 1**.

Study 1 (China Pilot Study)

This was a prospective, single-arm, single-center pilot study in China to evaluate the safety and efficacy of SCD treatment on clinical outcomes in AKI requiring KRT in the ICU (11). Patients enrolled in the trial were compared with historical case-matched controls with respect to age and Sequential Organ Failure Assessment score. These controls came from the Program to Improve Care in Acute Renal Disease dataset. The primary endpoint was in-hospital all-cause mortality.

The study enrolled 9 patients evaluated on SCD treatment. The mean age was 59.3 ± 13.9 years. There were eight AEs of hypercalcemia, two AEs of hypophosphatemia, and one each of the following: thrombocytopenia, hypocalcemia, allergic reaction, and hypernatremia. None of the reported AEs was deemed attributed to the device. No neutropenic events were reported; mean WBC counts remained normal throughout treatment with a mild decline noted upon initiation of therapy which rebounded by day 7. There were no reports of subsequent infections noted. No bleeding events occurred, and mean platelet counts remained above 50,000 throughout treatment, although the one patient with a thrombocytopenia event did require a platelet transfusion due to a platelet count below 20,000. There were no SAEs reported in the study. The mortality in the SCD group was 22.2% vs. 77.8% for case-matched controls ($p = 0.027$).

Study 2 (Acute Renal Failure-002; Adult AKI Study)

The next study was a prospective, single-arm, multicenter U.S. study to evaluate the safety and efficacy of SCD treatment in adults with AKI requiring CKRT in the ICU (12). The primary endpoint was all-cause mortality at day 60.

The study enrolled 35 adult patients. The mean age was 56.3 ± 15 years. A total of 199 AEs were observed in 33 of the 35 patients. Most AEs (> 85%) were either mild or moderate in severity. Twenty-eight SAEs were observed in 23 patients (which include 11 deaths); there were no device-related AEs reported in the study. There were approximately 10 infections reported during the study, none were attributed to the device. The AEs observed were those that were expected for a critically ill patient population

TABLE 1.
Summary of Clinical Studies Included in This Report

Study No. (Descriptor)	Patient Population	Severity of Illness Score[a]	Sepsis at Baseline	Requiring Mechanical Ventilation	No. of SCD-Treated Patients
Study 1 (China Pilot Study)	Adult AKI	11	NR	44.4%	9
Study 2 (ARF-002 Pilot Study)	Adult AKI	11.3	80%	88.6%	35
Study 3 (SCD-003)	Adult AKI	13.8	65.2%	88.4%	69
Study 4 (SCD-PED-01)	Pediatric AKI	7	37.5%	NR	16
Study 5 (SCD-005)	Adult COVID-19 AKI/ acute respiratory distress syndrome	11.8	100%	100%	22
Total number of patients across all studies					151

AKI = acute kidney injury, ARF = acute renal failure, study 2, NR = not reported, PED = pediatric study, SCD = selective cytopheretic device.

[a]For adult studies, mean Sequential Organ Failure Assessment score was reported. For pediatric study, median Pediatric Risk of Mortality II score was reported.

with AKI and/or in an ICU setting. All-cause mortality at day 60 was 31.4%.

Study 3 (SCD-003; Adult AKI Study)

This study was a multicenter, randomized, open-label, controlled pivotal study in adults with AKI to evaluate the safety and efficacy of CKRT + SCD with RCA (treatment) vs. CKRT alone (control) (13). The primary endpoint was all-cause mortality at day 60.

The study was targeted to enroll 344 patients across 21 U.S. medical centers. During the time of study enrollment, a national calcium shortage occurred in the United States due to manufacturing issues of the major U.S. supplier. Due to the reliance of the SCD on a narrow intra-circuit iCa range for functional efficacy and the concern that patients randomized to the SCD were not getting effective therapy, the interim analysis was performed early after enrollment of only 134 patients.

Of the 134 patients in the analysis, 69 received SCD therapy and 65 received CKRT alone (control). The mean age was 55.4 ± 14.0 years. Overall, AEs did not differ between treatment and control groups in the intent-to-treat (ITT) analysis. No difference was found between SAEs of the control and treatment groups. The frequency of SAEs did not differ between treated and control groups (65% [45/69] vs. 63% [40/65]; $p = 0.86$), respectively. Furthermore, none of the SAEs was considered "definitely" device-related per study investigators. Infections were reported in 27 of 69 patients (39.1%) treated with the SCD; of these, 14 events were serious in 12 patients. In the control group, infections were reported in 23 of 63 patients (36.5%); 11 events were serious in 10 patients. As noted, none of the SAEs (including infections) were considered device-related. The AEs observed were those expected for a critically ill patient population with AKI and/or in an ICU setting. There was no statistically significant difference found between the treated and control groups in all-cause mortality at day 60 (39% vs. 36%; $p = 0.23$), respectively. However, in the Per Protocol group that received adequate RCA and achieved target iCa levels to less than 0.4 mmol/L, there was a signal of mortality benefit in the SCD vs. control group (16% vs. 41%; $p = 0.11$), respectively.

Study 4 (SCD-pediatric-01; Pediatric AKI Study)

This was a prospective, multicenter, single-arm, open-label pilot study to evaluate the safety and efficacy of the SCD in pediatric patients with AKI being treated with CKRT with RCA (14). The primary endpoint of the study was safety of the SCD (as determined with AEs) up to 60 days following SCD initiation.

The study enrolled 16 pediatric patients. Mean age was 12.3 ± 5.1 years. There were a total of 47 AEs reported in the study; none of these were attributed to the SCD device. There were 12 SAEs that occurred in eight patients; none of the SAEs were device related and none were related to the study. There were no device-related infections reported in the study; all but one patient were on antibiotics at baseline. Regarding infection risk, one patient was never initiated on antibiotics during their entire SCD treatment while another patient was on antibiotics at baseline and discontinued antibiotics on day 5 of 7 days of SCD treatment, suggesting little risk of infection. Fifteen of the 16 patients survived to the end of SCD therapy; 12 of 16 patients survived to hospital discharge. Of the 12 survivors, ten were dialysis independent at day 28 and all 12 were dialysis independent with a normal serum creatinine at day 60, resulting in a survival rate of 75% (as compared with 50% in a contemporary case-matched pediatric registry [15]).

Study 5 (SCD-005; Adult COVID-19 AKI/ARDS Study)

The final study was a prospective, single-arm, multicenter U.S. study to evaluate the safety and efficacy of the SCD in patients developing AKI or ARDS associated with COVID-19 infection; all but one patient had concomitant AKI (9). The primary endpoints of the study were all-cause mortality at day 60 and dialysis dependency at day 60 (day 90 post hoc).

The study enrolled 22 adult patients. The mean age was 53 ± 17.7 years. A total of 70 AEs were observed in 19 of 22 patients. None of the AEs or SAEs were considered device-related. There were no events related to leukopenia, neutropenia, or thrombocytopenia. Additionally, there were no SCD-related clotting events or events related to citrate in the study. There were 24 nosocomial and/or opportunistic infections reported during and after treatment, however, an independent safety review committee evaluated and confirmed that all infections were related to underlying medical conditions or corticosteroid treatment. All-cause mortality at 60 days post-initiation of the

SCD was 50% for the ITT group, and 31% in patients treated for at least 96 hours compared with 81% for the contemporaneous control group ($p = 0.102$ and $p = 0.012$, respectively).

Table 2 summarizes the cumulative SCD exposure across the five studies in this report. There were over 150 patients in these studies treated with an average of 5.3 daily SCD sessions running 24 hours each. This accounts for more than 800 total devices used and an estimated greater than 19,000 total therapy hours with the SCD in trial experience.

Table 3 quantifies the overall AEs and SAEs reported across the five studies in this report. The AEs reported in each of these studies were consistent with those expected in a critically ill ICU patient population. Across five clinical studies and 151 patients treated with the SCD, there have been no unanticipated serious device-related events. In the single study that used a control group (study 3), there were no significant differences between the safety of the of the device vs. control.

A summary of mortality rates in patients on SCD therapy vs. observed (or historical) controls from each study is shown in **Table 4**. These data would indicate that the SCD device is not adding any additional safety risks that could have a deleterious effect on survival. Although none of the studies were powered to show a mortality benefit, the trend of higher survival rates in patients treated with the SCD is compelling and suggests a possible favorable risk-benefit relationship.

CONCLUSIONS

The SCD has been studied in a variety of patient populations, including adults and pediatric patients with AKI, multiple organ failure, sepsis, as well as COVID-positive patients. The SCD has consistently shown to be a promising extracorporeal therapy with no

TABLE 2.
Cumulative Exposure of Selective Cytopheretic Device Use Across Studies

Study (Descriptor)	No. of SCD-Treated Patients	No. of SCD Used per Patient (Mean)	Total No. of SCD Used	Total SCD Exposure Time (hr)
Study 1 (China Pilot)	9	3.9	34	816
Study 2 (ARF-002)	35	4.3	150	3,508[a]
Study 3 (SCD-003)	69	5.2	359	8,611.2
Study 4 (SCD-PED-01)	16	5	80	1,936[b]
Study 5 (SCD-005)	22	8.2	181	4,344
Totals	151	5.3	804	19,215.2

ARF = acute renal failure, study 2, PED = pediatric study, SCD = selective cytopheretic device.
[a]Study ARF-002 reported total duration hours (minus therapy interruptions).
[b]Study SCD-PED-01 reported the actual total hours of therapy for each patient.

TABLE 3.
Summary of Adverse Events From Studies

Study (Descriptor)	SCD-Treated Patients (*n*)	No. of Adverse Events	No. of SAEs	No. of Device-Related SAEs	No. of Device-Related Infections
Study 1 (China Pilot Study)	9	14	0	0	0
Study 2 (ARF-002)	35	199	28	0	0
Study 3 (SCD-003)	69	354	80	0	0
Study 4 (SCD-PED-01)	16	47	12	0	0
Study 5 (SCD-005)	22	70	50	0	0
Total	151	684	170	0	0

ARF = acute renal failure, study 2, PED = pediatric study, SAEs = serious adverse events, SCD = selective cytopheretic device.

TABLE 4.
Selective Cytopheretic Device Mortality Rates Versus Active or Historical Controls Across Studies

Study (Descriptor)	Patient Population	Analysis	SCD Tx, *n*	Control Tx, *n*	SCD Mortality Rate	Control Mortality Rate	*p*
Study 1 (China Pilot)	Adult AKI	ITT	9	Hx	22.2%	77.8%[a]	$p = 0.027$
Study 2 (ARF-002)	Adult AKI	ITT	35	Hx	31.4%	50%[b]	NR
Study 3 (SCD-003)	Adult AKI	ITT	69	65	39.1%	35.6%	$p = 0.23$
		PP	19	27	15.8%	40.7%	$p = 0.11$
Study 4 (SCD-PED-01)	Pediatric AKI	ITT	16	Hx	25%	50%[c]	NR
Study 5 (SCD-005)	Adult COVID-19 AKI/acute respiratory distress syndrome	ITT	22	Hx	50%	81%[d]	$p = 0.102$
		PP	16		31.3%		$p = 0.012$

AKI = acute kidney injury, ARF = acute renal failure, study 2, CRRTnet = Continuous Renal Replacement Therapy Network, Hx = historical control, ITT = intent-to-treat analysis, NR = not reported, PED = pediatric study, PP = per protocol analysis, SCD = selective cytopheretic device, Tx = treatment.

[a]Case-matched controls based on Sequential Organ Failure Assessment scores and age.

[b]Hx (16, 17).

[c]Hx (18).

[d]Contemporaneous controls from CRRTnet registry (19).

attributed SAEs in these critically ill ICU patients. The SCD uses a novel mechanism of action which leads to immunomodulation without the immunosuppression which can be seen with drugs, such as corticosteroids. As shown in previous studies (9, 11), the SCD was able to deactivate hyperinflammatory immune effector cells allowing the body to return to a naturally reparative process and recovery. This is supported by clinical studies showing SCD treatment without producing leukopenia, thrombocytopenia, no device-related infections, or SAEs with over 800 devices used and an estimated greater than 19,000 exposure hours from the five studies summarized in this report.

We believe there are two key attributes of the mechanism of action of the SCD that are possible explanations for the lack of immunosuppression or related infection AEs observed thus far. The first is that unlike adsorbent filters, the SCD does not sequester or retain any immunomodulated cells. Rather, deactivated leukocytes are released back into circulation (in a process that is termed "catch-and-release"), thereby minimizing any chances for immunodepletion. The second attribute is the actual process of binding and deactivation itself; specifically of neutrophils. For neutrophils, the binding event fully activates the neutrophils with release of constituents from exocytotic vesicles through degranulation. These vesicles contain multiple degradative enzymes and antimicrobial substances, specifically evolved to destroy invading pathogens. Therefore, the extracorporeal space during SCD use is a confined space full of toxic moieties to combat microbes of all varieties, potentially creating an antimicrobial environment within the device and the extracorporeal circuit. This is a key point of the SCD to highlight within the context of the type of acutely ill patients that have been treated in the ICU with the SCD, since these are in critical conditions and thus have an absolute requirement for minimizing any possible infectious exposure.

One of the key attributes of this report is that this is a comprehensive safety summary of all the major studies of the SCD device with over 150 critically ill adult and pediatric patients with AKI and multiple organ failure treated in an ICU setting, a majority of whom were septic. AEs and clinical laboratory values were collected and reported in each study. Additionally, all-cause mortality was reported for each study, offering a very comprehensive review of the safety of this extracorporeal device.

There are a few limitations with this report. Notably, without a single safety database used consistently

across all studies, we were not able to pool patient data for further analyses. This could have assisted with identifying broader signals in safety data, although there were no clear trends in events reported across each study. Additionally, a central laboratory database would have assisted with a deeper analysis of trends in laboratory values across studies. The studies were also not powered to show statistical differences in all-cause mortality. Despite this limitation, the overall trend in survival vs. control groups across these studies is still encouraging.

Perhaps the most critical development in establishing the safety and efficacy of the SCD will come from the ongoing NEUTRophil and monocyte deActivation via the seLective cytopheretIc device: a randomiZEd clinical trial in Acute Kidney Injury-AKI pivotal study which is currently enrolling adult patients with AKI and at least one other life-threatening organ dysfunction (ClinicalTrials.gov Identifier: NCT05758077) (Yessayan et al(20)). In this randomized, open-label, controlled, multicenter study, up to 200 adults in the ICU requiring CKRT with stage 2 or greater AKI and at least one additional life-threatening organ dysfunction will be randomized to CKRT + SCD vs. CKRT alone. Patients will receive KRT ± SCD treatment for up to 10 consecutive days. The primary endpoint is the composite of all-cause mortality or dialysis dependence at 90 days. Secondary outcome measures include major adverse kidney events at 90 days, dialysis dependence at 1 year, ICU-free days in the first 28 days, and mortality at 28 days. This study is expected to complete in late 2025.

In summary, these studies support that the SCD can be added as a therapeutic intervention in critically ill AKI patient populations with additional multiple organ failure without adding additional safety risks. Any intervention with the potential to improve survival in conditions and patient populations with such a high mortality rate would be a welcome addition to the acute care setting.

1 *Department of Nephrology, Weil Institute for Critical Care Research & Innovation, University of Michigan, Ann Arbor, MI.*

2 *Center for Acute Care Nephrology, Cincinnati Children's Hospital, Cincinnati, OH.*

3 *SeaStar Medical; Denver, CO.*

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For information regarding this article, E-mail: kchung@seastarmed.com

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