ORIGINAL ARTICLE

CARPEDIEM® for continuous kidney replacement therapy in neonates and small infants: a French multicenter retrospective study

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Abstract

Background The Cardio-Renal Pediatric Dialysis Emergency Machine (CA.R.P.E.D.I.E.M.®) device is a continuous kidney replacement therapy (CKRT) equipment dedicated to neonates and small infants. This study aimed to assess the effectiveness, feasibility, outcomes, and technical considerations relating to CARPEDIEM® use.

Methods This retrospective multicenter study included 19 newborns and six infants receiving CARPEDIEM® in five French pediatric and neonatal intensive care units. Laboratory parameters were collected at the initiation and end of the first CARPEDIEM® session. Results are presented as median [IQR] (range).

Results At initiation, age was 4 days [2–13] (1–1134) with a body weight of 3.3 kg [2.5–4] (1.3–11.1). Overall, 131 sessions and 2125 h of treatment were performed. Treatment duration per patient was 42 h [24–91] (8–557). Continuous venovenous hemofiltration (CVVH) was performed in 20 children. Blood flow rate was 8 mL/kg/min [6–9] (3–16). The effluent flow rate for CVVH was 74 mL/kg/h [43–99] (28–125) and net ultrafiltration (UF) 6 mL/kg/h [2–8] (1–12). In the five children treated by hemodialysis, the blood and dialysate flow rates were 6 mL/kg/min [5–7] (4–7) and 600 mL/h [300–600] (120–600), respectively, while session duration was 8 h [6–12] (2–24). Most infants required a catheter between 4.5 and 6.5 French. Hemodynamic instability with a need for volume replacement occurred in 31 sessions (23%). Thrombocytopenia was observed in 29 sessions (22%). No hemorrhage occurred; all the patients survived the sessions, but only eight patients (32%) were alive at hospital discharge.

Conclusions These data confirm that the use of CARPEDIEM® is safe and effective in critically ill neonates and infants.

Keywords Neonate · CARPEDIEM® · Continuous kidney replacement therapy

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Introduction

Acute kidney injury (AKI) is a common complication in neonatal intensive care and is associated with higher mortality, particularly in neonates (31.3%) and children requiring dialysis (27.1%) [1, 2]. When conservative measures fail, AKI management requires kidney replacement therapy (KRT) to control fluid overload (FO) and metabolic abnormalities. The modality choice for dialysis is based on the patient's characteristics, the performance of the dialysis type, and the local institutional resources [3]. Since 1986, continuous kidney replacement therapy (CKRT) is performed in neonates with AKI, to treat severe FO that cannot be optimally managed by peritoneal dialysis (PD) and to allow higher ultrafiltration (UF) [4].

In 2012, Ronco et al. reported the development of new CKRT equipment which has recently been approved by the Food and Drug Administration (FDA): the Cardio-Renal Pediatric Dialysis Emergency Machine (CA.R.PE. DI.E.M.®) [5]. This machine was developed for newborns and small infants weighing 2.0–9.9 kg [6], and the flow rate of the miniaturized blood pump varies from 2 to 50 mL/min. The use of CARPEDIEM® in continuous veno-venous hemodialysis (CVVHD) mode rather than in continuous veno-venous hemofiltration (CVVH) seems to enhance the purification of small solutes [7]. To date, two studies have reported the use of CARPEDIEM® in neonates and small infants.

In CVVHD, successful blood purification for small solutes was obtained in 95 consecutive treatments in 13 neonates and small children [8]. A similar result was reported in 26 neonates and small children having received 165 CVVH sessions [9].

This study aimed to retrospectively assess the effectiveness, feasibility, outcomes, and technical considerations relating to the use of CARPEDIEM® in French pediatric and neonatal intensive care units.

Methods

Patients

This multicenter retrospective study consists of a case series of 19 newborns and six infants recruited in five French pediatric/neonatal intensive care units (Nice $n = 9$, Paris-Saclay $n = 7$, Lyon $n = 4$, Bordeaux $n = 4$, Toulouse $n = 1$). All children who received CARPEDIEM® treatments between December 2018 and January 2022 were included.

Laboratory data collection

Serum creatinine, serum potassium, blood urea nitrogen, hemoglobin, and platelet levels were regularly assessed as part of the routine follow-up of these patients with multiple organ dysfunctions. Estimated glomerular filtration rate (eGFR) was estimated using the 2009 Schwartz formula [10]. Laboratory parameters were collected at two time points during the follow-up of each patient: initiation and end of the first CARPEDIEM® session. The percentage of FO (% FO) was calculated for each patient using the method described by Goldstein et al. (% FO = (CKRT initiation weight − baseline weight) × 100) [11]. The Sethi Tibrewal Agrawal Raina waZir (STARZ) neonatal score was used to quantitatively calculate the risk of AKI in neonates [12]. Due to the retrospective nature of the study, chemical clearances were not measured.

CARPEDIEM®

The CARPEDIEM® machine (Medtronic, Inc., Dublin, Ireland) was used for all treatments, and each center followed its local practices for dialysis prescription. The dialysis modality and the use of CARPEDIEM® machine were decided at the physician's discretion.

Several circuits were available with different surface areas (0.075, 0.147, and 0.245 m^2) and extracorporeal volumes (27.2 mL, 33.5 mL, and 41.5 mL), which were chosen according to weight and body surface area. CARPEDIEM® circuits were changed every 24 h. Different modalities were performed: CVVH, CVVHD, and prolonged intermittent KRT. HbioFluids + ® (Medtronic) containing 32 mmol/L of sodium bicarbonate and 2.5 mmol/L of potassium was used as replacement solution. The potassium concentration was adapted in some patients according to their needs. The dialysis downtime (%) was calculated for treatment duration of 24 h, by calculating the number of prescribed hours/delivered hours using the following formula: [Treatment duration achieved (hours)/24 h] × 100. The net UF (mL/kg/h) was calculated using the following formula: Total UF volume/(Hospital admission weight (kg) × CKRT duration (hours)).

Statistical analysis

Results are presented as medians with inter-quartile range [IQR] and range (min–max) for patient characteristics and laboratory routine parameters. Statistical Mann–Whitney tests were used to compare patient characteristics of the survivor and non-survivor groups. Survival was defined as survival at hospital discharge. The laboratory parameters at initiation and end of the first session were compared using a

Wilcoxon test (non-parametric paired tests). The Chi-square test was used to evaluate complications (clotting and circuit dysfunction) according to catheter size, catheter localization, anticoagulation, blood flow, and platelet transfusion variables. In all cases, p-values below 0.05 were considered statistically significant using GraphPad Prism software 9.3.1 (GraphPad, La Jolla, CA, USA).

Results

Patient characteristics

Relevant demographic and clinical features of the 25 patients (15 males) at the time of CARPEDIEM® initiation are presented in Tables 1 and 2. Nine neonates were preterm (36%), and two were very preterm (25 and 28 weeks of gestational age). Six neonates presented a birth weight of less than 2 kg, three of whom had in utero growth restriction.

CARPEDIEM® initiation

CARPEDIEM® was initiated at a median [IQR] (range) age of 4 days [2-13] (1–1134) in children with a body weight of 3.3 kg [2.5–4.0] (1.3–11.1). CARPEDIEM® was prescribed to treat AKI with FO in 15 patients (60%), chronic kidney disease (CKD) stage 5 in five patients (20%), inborn error of metabolism (IEM) with hyperammonemia in three patients (12%), and electrolyte abnormalities in two patients (8%). FO was 18% [7-25] (4–32) (Table 1). The CKD stage 5 group included three children with polycystic kidney disease, one with an oxalosis, and one with hemolytic-uremic syndrome. For two of them, CARPEDIEM® was initiated before the peritoneal dialysis catheter implantation. For the others, CARPEDIEM® was used as a replacement therapy after peritoneal dysfunction, until the switch to hemodialysis. For the patient weighing 11 kg, the CARPEDIEM® machine was used because the conventional device was not available. For these children, CKRT was performed with

Table 1 Patient characteristics and clinical and laboratory data at CARPEDIEM® initiation: comparison between survivors and non-survivors

Patient characteristics	Overall ($n=25$)	Survivors ($n=8$)	Non-survivors ($n=17$)	p
Birth weight (kg)	2.7 [2.0–3.2]	2.9 [2.5–3.1]	2.6 [2.0–3.1]	0.18
Gestational age (weeks)	37 [34–39]	39 [35–39]	37 [32–39]	0.34
Sex (males, %)	15 (60%)	4 (50%)	11 (65%)	0.66
Primary diagnosis				
- Hypoxic-ischemic encephalopathy	$n=9$ (36%)	$n=1$ (12%)	$n=8$ (47%)	**0.0004**
- Sepsis	$n=4$ (16%)	$n=0$ (0%)	$n=4$ (23%)	**0.03**
- Kidney disease	$n=5$ (20%)	$n=4$ (50%)	$n=1$ (6%)	0.20
- Metabolic disease	$n=4$ (16%)	$n=2$ (25%)	$n=2$ (12%)	>0.99
- Miscellaneous[a]	$n=3$ (12%)	$n=1$ (12%)	$n=2$ (12%)	>0.99
CARPEDIEM® Initiation				
Age (days)	4 [2-13]	78 [6–162]	3 [1-9]	**0.02**
Weight (kg)	3.3 [2.5–4.0]	3.9 [3.2–5.5]	2.8 [2.4–3.6]	0.06
CKRT Indication				
- AKI with fluid overload	$n=15$ (60%)	$n=2$ (25%)	$n=13$ (76%)	**0.0001**
- CKD stage 5	$n=5$ (20%)	$n=4$ (50%)	$n=1$ (6%)	0.21
- Hyperammonemia	$n=3$ (12%)	$n=2$ (25%)	$n=1$ (6%)	>0.99
- Electrolyte abnormality	$n=2$ (8%)	$n=0$ (0%)	$n=2$ (12%)	0.33
Urine output (mL/kg/h)	0.1 [0.0–1.4]	2.0 [0.2–4.5]	0.1 [0.0–0.6]	0.1
Fluid overload (%)	18 [7-25]	6 [− 2 to 15]	14 [6-25]	0.5
Furosemide before CKRT initiation	$n=11$ (44%)	$n=1$ (12.5%)	$n=10$ (59%)	**0.001**
Vasoactive medications	$n=20$ (80%)	$n=4$ (50%)	$n=16$ (94%)	**< 0.0001**
Mechanical ventilation	$n=21$ (84%)	$n=4$ (50%)	$n=17$ (100%)	**< 0.0001**
eGFR (mL/min/1.73 m^2)	13 [11-17]	14 [11-17]	13 [12-17]	0.67
STARZ score (0–100)	60 [52–72]	49 [32–63]	66 [57–74]	0.12

Survival was defined as survival at hospital discharge. Data are presented as median and [IQR]. Mann–Whitney tests were used to compare characteristics between survivors and non-survivors. p-values below 0.05 were considered statistically significant and presented in bold emphasis

CKRT continuous kidney replacement therapy, *AKI* acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

[a]Twin-to-twin transfusion syndrome — cardiac and pulmonary disease

Table 2 Individual characteristics of the infants included in the study, the circuits used, and the complications observed

Case	GA (weeks)	Birth weight (kg)	Primary diagnosis	Weight at initiation (kg)	Age at initiation (days)	CKRT modality	Effluent flow (mL/kg/h) or dialysis flow (mL/h)	Catheter size (French)	Membrane surface area (m²)	Circuit size (mL)	Priming	HD instability (session number)	Replacement	Survival
1	28+1	1.1	TTTS syndrome	1.3	1	CVVH	60	4.5	0.147	33.5	NaCl 0.9%	1	Albumin/NaCl	No
2	30	1.1	Sepsis	1.6	13	CVVH	112	4.5	0.147	33.5	NaCl 0.9%	1	Albumin/NaCl	No
3	38	1.9	Metabolic disease	2.4	4	CVVH	80	6.5	0.245	41.5	NaCl 0.9%	1	Albumin	No
4	37	2.4	EAI	2.4	1	CVVH	125	4.5	0.245	41.5	NaCl 0.9%	1	Albumin/NaCl	No
5	33+5	2.5	Cardiac disease	2.5	8	CVVH	NA	5.5	0.245	41.5	Albumin/CGR/isofundine	9	Ringer/NaCl/isofundine	Yes
6	32	1.9	EAI	2.5	1	CVVH	105	5.5	0.147	33.5	NaCl 0.9%	2	Albumin/NaCl	No
7	25+3	0.8	Sepsis	2.5	72	CVVH	67	6	0.245	41.5	NaCl 0.9%	0	–	No
8	39+4	2.8	Hyperammonemia	2.5	3	CVVH	104	6	0.245	41.5	NaCl 0.9%	0	–	Yes
9	35+5	2.1	CKD stage 5	2.7	9	CVVH	49	4.5	0.147	33.5	Albumin	0	–	No
10	37	2.7	EAI	2.8	4	CVVH	85	5.5	0.245	41.5	NaCl 0.9%	0	–	No
11	32	2.0	Pulmonary disease	2.8	10	CVVH	94	4.5	0.147	33.5	NaCl 0.9%	2	Albumin/NaCl	No
12	36	2.9	EAI	2.9	1	CVVH	28	4.5	0.147	33.5	Albumin	0	–	No
13	36+5	2.9	EAI	3.3	1	CVVH	46	6	0.245	41.5	NaCl 0.9%	1	Albumin	No
14	38+5	3.8	Hyperammonemia	3.3	3	CVVH	81	6.5	0.245	41.5	NaCl 0.9%	1	NaCl	No
15	39	4.0	Hyperammonemia	3.5	7	CVVHD	120	4.5	0.147	33.5	Albumin	0	–	Yes
16	38+1	2.6	Sepsis	3.6	66	CVVH	NA	5.5	0.245	41.5	NaCl 0.9%	5	Albumin	No
17	38	2.9	EAI	3.6	3	CVVH	100	5.5	0.245	41.5	NaCl 0.9%	1	NaCl	Yes
18	39+5	3.5	EAI	3.8	3	CVVH	33	4.5	0.147	33.5	Albumin	0	–	No
19	39+6	3.1	Sepsis	3.9	2	CVVH	35	6.5	0.245	41.5	NaCl 0.9%	2	Albumin/NaCl	No
20	40+1	3.6	EAI	4.5	2	CVVH	42	6	0.147	33.5	NaCl 0.9%	0	–	No
21	39	3.7	EAI	4.9	4	CVVHD	300	5.5	0.245	41.5	NaCl 0.9%	1	Albumin	No
22	NA	NA	CKD stage 5	5	148	CVVHD	600	6.5	0.245	41.5	Albumin/NaCl 0.9%	0	–	Yes

Table 2 (continued)

Case	GA (weeks)	Birth weight (kg)	Primary diagnosis	Weight at initiation (kg)	Age at initiation (days)	CKRT modality	Effluent flow (mL/kg/h) or dialysis flow (mL/h)	Catheter size (French)	Membrane surface area (m²)	Circuit size (mL)	Priming	HD instability (session number)	Replacement	Survival
23	34 + 2	1.2	CKD stage 5	5.2	159	CVVH	40	6.5	0.245	41.5	Albumin/NaCl 0.9%	2	PRBC	Yes
24	NA	NA	CKD stage 5	7	172	CVVHD	600	6.5	0.245	41.5	Albumin/NaCl 0.9%	1	Albumin	Yes
25	40 + 5	3.2	CKD stage 5	11.1	1134	CVVHD	600	8	0.245	41.5	NaCl 0.9%	0	–	Yes

Hemodynamic instability refers to hypotension lower than gestational age for neonates and lower than 50 mmHg for infants. Volume replacement was performed with fluid replacement following local protocols in case of hypotension

GA gestational age, *NA* not available, *PRBC* packed red blood cells, *EAI* encephalopathy-anoxic-ischemic, *NaCl 0.9%* normal saline, *CKD* chronic kidney disease

CVVHD modality for three of them, and with CVVH modality for the two others.

Most of the children were critically ill with a need for mechanical ventilation in 21 patients (84%), vasoactive medications in 20 (80%), and intravenous furosemide in 11 (44%) (Table 1).

CARPEDIEM® circuits and parameters

A total of 131 sessions and 2125 h of treatment were realized. The duration of treatment per patient was 42 h [24–91] (8–557), and the duration of one session was 19 h [8-24] (2–24) (Table 3). A trend toward a longer treatment duration was found in the CKD stage 5 group (50 h [30–192] (11–215)) compared to the AKI group (40 h [24–77] (8–557)), $p = 0.56$.

CVVH was used in 20 children (80%; predilution $n = 8$; postdilution $n = 12$), with a blood flow rate of 8 mL/kg/min [6-9] (3–16), an effluent flow rate of 74 mL/kg/h [43–99] (28–125), and a net UF flow of 6 mL/kg/h [3-9] (1–12). Supplemental Table 1 provides details on the CARPEDIEM® circuits and parameters used according to the primary diagnosis.

In the five children treated in hemodialysis mode, the blood and dialysate flow rates were 6 mL/kg/min [5-7] (4–7) and 600 mL/h [300–600] (120–600), respectively, and session duration was 8 h [6–12] (2–24). The net UF flow was 9 mL/kg/h [8-11] (8–12).

For patients with IEM, the effluent flow rate was 82 and 104 mL/kg/h for those treated with CVVH, and the dialysis flow rate was 120 mL/h for the patient treated with CVVHD.

Vascular access was obtained through the internal jugular vein in 18 patients (72%), the left subclavian vein in five patients (20%), the umbilical vein in one patient (4%), and the femoral vein in another patient (4%). The French line sizes of the catheters used were 4.5 Fr (32%), 5.5 Fr (24%), 6 Fr (16%), 6.5 Fr (24%), and 8 Fr (4%). To prevent filter clotting, circuits were anticoagulated using continuous heparin therapy at a dose of 10 UI/kg/h [8-12] (3–19) in 22 patients (Table 3). For the three other patients, one did not have any anticoagulation, and two benefitted from a loading dose of heparin at CARPEDIEM® initiation.

The circuit was primed with normal saline in 54 sessions (41%), 4% albumin or isofundine in 69 sessions (52%), and packed red blood cells in 8 sessions (in one patient weighing 2.5 kg). In children for whom the extracorporeal circuit exceeded 10% of the infant's total blood volume, crystalloid or colloid was used to prime the circuit for all but one patient for whom packed erythrocytes were used. For the patients who did not receive blood priming, packed erythrocytes could be used before the CKRT initiation according to the transfusion indication protocol to prevent or treat anemia.

Table 3 CARPEDIEM® circuits and parameters: comparison between survivors and non-survivors

CARPEDIEM® circuit	Overall ($n=25$)	Survivors ($n=8$)	Non-survivors ($n=17$)	p
Number of sessions	131	68	63	0.07
Total treatment duration (h)	2125	1002	1123	0.50
Duration of treatment/patient (hours)	42 [24–91]	49 [28–116]	39 [24–72]	0.59
CKRT modality				
- Convective (CVVH)	$n=20$ (80%)	$n=4$ (50%)	$n=16$ (94%)	**0.0004**
- Diffusive (CVVHD)	$n=5$ (20%)	$n=4$ (50%)	$n=1$ (6%)	0.20
Vascular access				
- Internal jugular vein	$n=18$ (72%)	$n=6$ (75%)	$n=12$ (71%)	0.09
- Left subclavian vein	$n=5$ (20%)	$n=1$ (12.5%)	$n=4$ (23%)	0.21
- Femoral vein	$n=1$ (4%)	$n=1$ (12.5%)	–	–
- Umbilical vein	$n=1$ (4%)	–	$n=1$ (6%)	–
Catheter size (Fr)				
- 4.5	$n=8$ (32%)	$n=1$ (12.5%)	$n=7$ (41%)	
- 5.5	$n=6$ (24%)	$n=2$ (25%)	$n=4$ (23%)	0.57
- 6	$n=4$ (16%)	$n=1$ (12.5%)	$n=3$ (18%)	0.49
- 6.5	$n=6$ (24%)	$n=3$ (37.5%)	$n=3$ (18%)	>0.99
- 8	$n=1$ (4%)	$n=1$ (12.5%)	–	–
Anticoagulation with heparin (UI/kg/h)	10 [8-12]	10 [9-12]	10 [7-11]	0.6
Priming circuit (number of sessions)				
- Normal saline	$n=54$ (41%)	$n=20$ (29%)	$n=34$ (54%)	**0.01**
- Albumin/isofundine	$n=58$ (44%) // 11(8%)	$n=29$ (43%) //11 (16%)	$n=29$ (46%) // –	>0.99//–
- Packed red blood cells	$n=8$ (7%)	$n=8$ (12%)	–	–
Filter (m^2)				
- 0.15	$n=9$ (36%)	$n=2$ (25%)	$n=7$ (41%)	0.06
- 0.25	$n=16$ (64%)	$n=6$ (75%)	$n=10$ (59%)	0.29
CVVH modality				
- Anticoagulation with heparin (UI/kg/h)	10 [8-12]	12 [10-14]	10 [7-11]	0.21
- Blood flow (mL/kg/min)	8 [6-9]	9 [7-10]	7 [6-8]	0.51
- Effluent flow rate (mL/kg/h)	74 [43–99]	100 [70–102]	67 [44–89.5]	0.41
Hemodialysis modality				
- Anticoagulation with heparin (UI/kg/h)	9 [8-10]	9 [8-10]	10	–
- Blood flow (mL/kg/min)	6 [5-7]	7 [7-10]	5	–
- Dialysis flow (mL/h)	600 [300–600]	600 [482–600]	300	–

Data are presented as median and [IQR]. Mann–Whitney tests were used to compare characteristics between survivors and non-survivors; p-values below 0.05 were considered statistically significant and presented in bold emphasis

CKRT continuous kidney replacement therapy, *CVVH* continuous veno-venous hemofiltration, *Fr* French

CARPEDIEM® outcomes

All patients survived the CARPEDIEM® sessions, but 17 (68%) died from their primary severe disease. The proportion of patients who survived was higher in the CKD stage 5 group (50%) than in the AKI group (13%). After the first CARPEDIEM® session, creatinine and urea plasma levels decreased significantly from 131 [98–181] (46–216) to 82 μmol/L [62–104] (14–185) ($p<0.0001$) and 8.3 mmol/L [5.4–11.7] (2.3–19.0) to 5.1 [2.9–7.1] (0.8–16.4) ($p<0.0001$), respectively (Fig. 1A and B). Serum potassium levels decreased significantly from 4.9 [4.1–6.3] (2.8–9.6) to 4.2 mmol/L [3.8–4.7] (3.1–5.6) ($p=0.002$). Hyperkaliemia management was possible using CARPEDIEM®, and kaliemia remained stable in normal ranges (Fig. 1C). For the patients treated for hyperammonemia (two with CVVH and one with CVVHD), a minimum of tenfold decrease in ammonia was found in each patient after 24 h of treatment (Fig. 1D). Two of them were still alive at hospital discharge.

CARPEDIEM® complications

Over the 131 sessions, UF was stopped momentarily and infusion was administered in 31 sessions (23%) due to

Fig. 1 Comparison of serum creatinine (**A**), blood urea nitrogen (**B**), serum potassium (**C**), and ammonia (**D**) levels between the initiation and end of the first CARPEDIEM® session. Each dot on the graph represents the laboratory parameter of each patient at the initiation and the end of the first treatment session with CARPEDIEM®. The red line corresponds to the median of all patients. Statistical analyses were performed using Wilcoxon test: $*p < 0.05$; $**p < 0.01$; $***p = 0.001$; $****p < 0.0001$
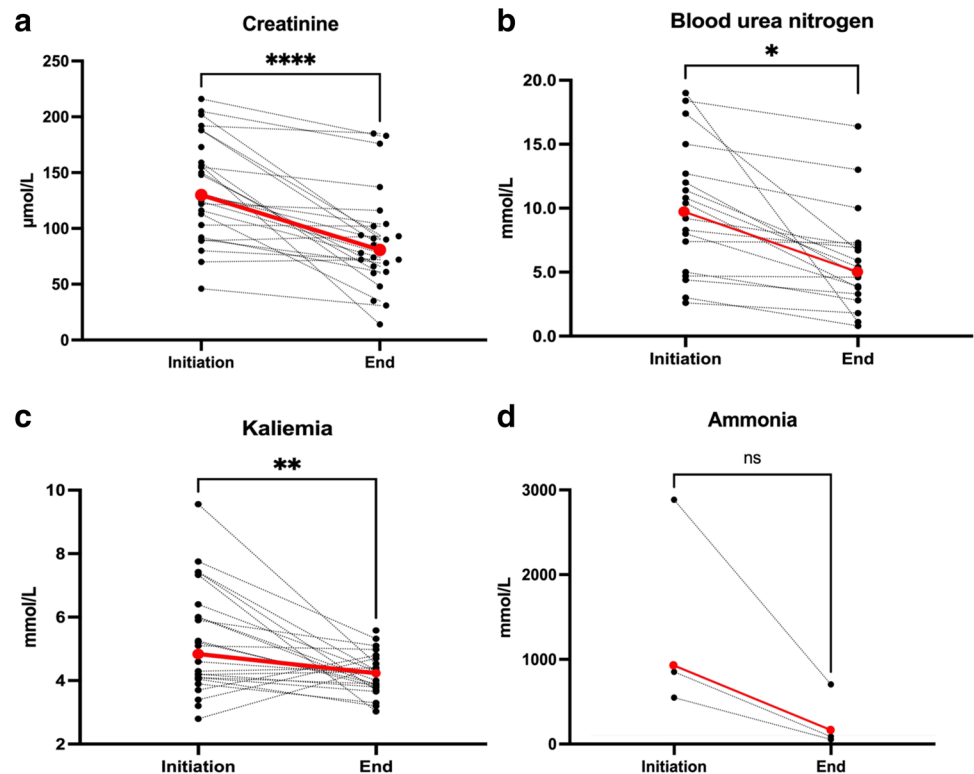
hemodynamic instability. The dialysis downtime was 79% [54–91] (33–100). Clotting was observed in 25 sessions (19%), catheter dysfunction in three sessions (2%), pressure dysfunction due to a machine pressure pod issue in seven sessions (5%), and restitution failure in four sessions (3%). Table 4 reports complications according to catheter localization and size, anticoagulation, and blood flow rate. Thrombocytopenia was observed in 29 sessions (22%) representing 20 patients but was already present before treatment initiation in 15 patients due to their primary disease. No hemorrhage was reported.

Discussion

This French cohort study evaluating CARPEDIEM® use in 19 newborns and six small infants showed that blood purification, FO, and metabolic disorders such as hyperammonemia can be managed successfully, without severe complication, using this machine.

Herein, the survival rate at hospital discharge was low, but all patients survived the CARPEDIEM® course. The high mortality rate can be explained by the severity of the primary disease, a majority of patients presenting with multi-organ failure and neurological symptoms secondary to hypoxic ischemic encephalopathy. Ronco et al. reported that a weight over 3 kg was associated with survival [9], a result that could not be confirmed in the current study.

However, CARPEDIEM® initiation occurred at a significantly older age in the survivors of the present cohort, likely due to the relatively high number of CKD stage 5 patients present in the survivor group. Although elevated FO% has been shown to be correlated with high mortality [13–15], the FO% herein, which was close to the 14% previously reported [9], was not significantly different between survivors and non-survivors, likely due to missing data.

In the current study, the CVVH modality was used for the majority of sessions and induced a significant decrease in blood creatinine, urea nitrogen, and hyperkaliemia after the first session. The effluent flow rate required during CVVH has not been defined and remains controversial [16–18]. Although the international KDIGO statements and the French Society of Intensive Care and Pediatric Emergency recommend an effluent volume of 25–35 mL/kg/h [19, 20], the CVVH substitution range used herein was larger. The median effluent flow rate was higher for patients with IEM in order to achieve a higher and faster removal of toxic metabolites. Such high flow rates may be associated with electrolyte complications although none were found in the present study. Based on these results, it appears that the effluent flow rate must be adapted to the primary diagnosis. The blood flow rate, however, was consistent with the recommended blood flow of 3–10 mL/kg/min obtained from animal studies [21], which seems to be more appropriate than the higher blood flow rates (10–12 mL/kg/min) reported when using adult devices in neonates [22].

Table 4 Circuits used and complications observed during the 131 CARPEDIEM® sessions performed in the 25 infants included in the study

| | Overall (131 sessions) | Complications | | p |
| | | Clotting | Circuit dysfunction | |
		(25/131 sessions)	(11/131 sessions)	
Catheter size, Fr				0.09
4.5	$n=47$	$n=5$	$n=6$	–
5.5	$n=37$	$n=4$	$n=1$	–
6	$n=8$	$n=2$	$n=1$	–
6.5	$n=35$	$n=12$	$n=3$	–
8	$n=4$	$n=2$	0	–
Catheter localization				0.43
Jugular	$n=103$	$n=16$	$n=8$	–
Subclavian	$n=11$	$n=4$	$n=2$	–
Femoral	$n=15$	$n=4$	$n=1$	–
Umbilical	$n=2$	$n=1$	0	–
Anticoagulation with heparin				**0.02**
<10 UI/kg/h	$n=22$	$n=3$	0	–
10 UI/kg/h	$n=13$	$n=7$	$n=2$	–
>10 UI/kg/h	$n=76$	$n=15$	$n=6$	–
Loading dose/none	$n=20$	$n=0$	$n=3$	–
Blood flow (mL/kg/min)				0.07
<5 mL/kg/min	$n=43$	$n=6$	$n=6$	–
>5 mL/kg/min	$n=88$	$n=19$	$n=5$	–
Platelet transfusion				0.70
Yes	$n=29$	$n=6$	$n=2$	–
No	$n=102$	$n=19$	$n=9$	–

Circuit dysfunction included pressure dysfunction ($n=7$) and restitution failure ($n=4$). Complications with hemodynamic instability, thrombocytopenia, and vascular malfunction are not described in this table. The chi-square test was used to evaluate complications (clotting and circuit dysfunction) according to catheter size, catheter localization, anticoagulation, and blood flow variables; p-values below 0.05 were considered statistically significant and presented in bold emphasis

Fr French

In the present study, most infants required lines between 4.5 Fr (Vygon®, 6 cm) and 6.5 Fr while one required an 8 Fr line, located mainly in the internal jugular vein. Previous studies showed better outcomes in CKRT when using large catheters [23]. However, in a recent in vitro study, higher blood flow rates were obtained when using small 4 French and 5 French catheters with a small three-roller CARPEDIEM® pump (13 and 29 mL/min, respectively) rather than with an adult two-roller pump (10 and 20 mL/min, respectively) [24]. The present results and those from the Italian cohort confirm that purification can be obtained successfully using small catheters and pumps in a dedicated pediatric device [9].

Devices other than CARPEDIEM® are currently in use or being developed for dialysis in infants and neonates. The Newcastle Infant Dialysis and Ultrafiltration System (NIDUS® Allmed, England) was designed in the UK for CKRT and is currently only available for research purposes. It can be used in infants weighing 0.8 to 8 kg with a single lumen vascular access [25]. In a comparative study evaluating dialysis in 10 children weighing 1.8 to 5.9 kg, Coulthard et al. reported that using NIDUS® in CVVHD mode provided higher clearances and allowed for better UF control compared to PD and intermittent hemodialysis using an adult device [25]. Before the approval of CARPEDIEM® by the FDA, the adult machine Aquadex® (Baxter Corporation, Minneapolis, Minnesota) was adapted to children in the USA. The UF pump has a range of 0 to 500 mL/h and an accuracy of ± 10% [26]. In a case series of 12 children using Aquadex®, Askenazi et al. reported a blood priming of the circuit in 79% of the sessions according to the size of the extracorporeal volume of 33 mL, with few complications [26]. Compared to previous adult devices, Goldstein et al. reported a higher survival in infants treated with CARPEDIEM® [11].

In urea cycle disorders and organic acidemia, ammonia serum levels > 200 µmol/l (341 µg/dl) are associated with poor neurological outcomes and can lead to hepatic

encephalopathy and irreversible cerebral damage. In such cases, KRT should be quickly considered when medical treatment fails. Guidelines for hyperammonemia management recommend using high-dose CVVHD with Qb 30–50 mL/min as first-line treatment, when available [27]. In metabolic diseases, CVVHDF and CVVHD have been shown to enable a more rapid elimination of toxic metabolites than PD, and the usual dose for CVVHD or CVVHDF in patients with IEM is a dialysis flow of 460 mL/kg/h or an effluent volume of 8000 mL/1.73m2/h [27–29]. For most infants, CARPEDIEM® may not be able to achieve those high doses and as fast an epuration as intermittent dialysis devices [30]; however, the risk/effectiveness balance, taking into account age and weight, should be considered. Herein, there was at least a tenfold decrease in ammonia in the three neonates with hyperammonemia at the end of the first CARPEDIEM® session which lasted 17, 23, and 24 h. In these three patients, CKRT modality did not seem to affect treatment effectiveness or survival.

It is important to note that, although destabilization with a need for volume replacement was the most common complication that required intervention herein, it is difficult to conclude if this was due to an imprecise UF control or to the clinical severity of the patients (80% had vasoactive treatment), even though the smallest extracorporeal circuit is applied when using CARPEDIEM®. Moreover, thrombocytopenia was the second most common complication reported. Although no hemorrhagic complication was noted, patients received platelet transfusions in about a fifth of the sessions. In CKRT, thrombocytopenia is a frequent complication and has been reported in 42.9% of sessions in neonates [31]. When using other extracorporeal circuits such as extracorporeal membrane oxygenation, a recent meta-analysis reported thrombocytopenia in 21% of adults [32]. Although the etiology of thrombocytopenia during extracorporeal treatment is multifactorial, the presence of inflammatory stress and oxidative mediators is likely to contribute to decreased platelet counts and increase the risk of thrombocytopenia. Other factors including medication, sepsis, and use of anticoagulation with heparin, which are found in critically ill patients such as those herein, have also been associated with an increased risk of thrombocytopenia [33]. Such risk factors could explain the high proportion of thrombocytopenia observed in the present cohort. Moreover, in CKRT, a possible destruction or retention of platelets in the hemofilter may also induce thrombocytopenia. Indeed, although using a larger filter and a higher blood flow, Mulder et al. measured platelet levels in adults before and after the CKRT filter and estimated that 625×10^9 platelets were lost daily across the filter [34]. Importantly, recent studies have shown that thrombocytopenia due to CKRT is associated with poor outcomes such as higher mortality, lower kidney recovery, and increased risk of secondary infections [35–37].

When considering the use of CARPEDIEM®, physicians thus need to consider such possible complications. More broadly, ethical considerations based on comorbidities should be discussed among neonatologists and nephrologists and communicated to parents prior to CARPEDIEM® initiation [38].

The present study represents the first French national cohort evaluating the CARPEDIEM® machine and the first to assess its use in such low-birth-weight premature neonates. The study, however, has some limitations, particularly due to the small number of patients and the presence of missing data due to its retrospective design. These are classical limitations when working in the field of pediatric orphan diseases, and even more so when assessing an off-label use of novel therapies (CARPEDIEM® use in infants under 2 kg).

Conclusion

The present data confirm that the use of CARPEDIEM® is safe and effective in neonates and infants. Long-term kidney assessment remains to be evaluated, and studies comparing the efficacy of CARPEDIEM® with that of PD and other adult devices are needed.

Declarations

Ethics The study was approved by an ethics committee (Comité d'Ethique des Recherches non Interventionelles Université Côte d'Azur, session 23 September 2020, approval N°2020–68) and respected all local and European relevant regulations. This study was performed with the appropriate participants' informed consent in compliance with the Helsinki Declaration.

Conflict of interest The authors declare no competing interests.

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