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The Brophy Kit: A Manual Hemodialysis Device for Neonates

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Introduction: Acute kidney injury (AKI) is common in critically ill neonates, including very and extremely low birth weight (VLBW, ELBW) neonates. In severe cases, kidney replacement therapy (KRT) may be warranted. Currently, available KRT devices are only indicated for those weighing $\geq$ 2.5 kg and require a double lumen or 2 separate single lumen catheters. We miniaturized the Kirpa Kit manual dialysis device, naming it the Brophy Kit, and we assessed its *in vitro* clearance and ultrafiltration (UF) performance.

Methods: We diluted packed red blood cells to a normal hematocrit (Hct: 31.1%–36.8%) and conducted 12 clearance and 3 UF experiments. A cycle consisted of aspirating 10 ml of blood from the blood bag, passing it through a hemofilter, and returning it in a circular path. For clearance experiments, we tested 4 configurations, with varied timing and volume of saline flushes to refresh the dialysis compartment, then measured blood urea nitrogen (BUN) and potassium concentrations every 5 cycles. For each UF cycle, 1 ml of ultrafiltrate was removed, and Hct was measured every 10 cycles.

Results: Median BUN and potassium reduction were 31.0% (interquartile range [IQR]: 17.6–37.9) and 35.0% (IQR: 26.9–41.7), respectively, after 30 clearance cycles. Median Hct increased to 52.6% (IQR: 52.5–53.8) after 60 UF cycles, more than the expected Hct (47.7%).

Conclusion: The Brophy Kit performs *in vitro* clearance efficiently and UF consistently. The Brophy Kit may address a technological KRT gap for small neonates because of its minimal extracorporeal volume and ability to function with single lumen access.

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Neonatal AKI is common and associated with increased morbidity and mortality. VLBW and ELBW neonates, weighing <1500 g and <1000 g, respectively, are at the highest risk,[1,2] and AKI prevalence and associated mortality in these populations have increased in recent years. Advancements in neonatal care have focused primarily on lung, heart, gut, and neurodevelopmental outcomes, with kidney outcomes less of a priority. Thus, less attention has been placed on advancing kidney support devices.

In the past 10 years, the only hemodialysis-based device approved for neonatal and infant KRT is the Carpediem (Mozarc Medical, Mirandola, Italy).[3] However, this device is not approved for patients weighing <2.5 kg, excluding those with the highest AKI burden, and requires large dual-lumen catheter or 2 venous access points, which can be challenging to place and more prone to complications in small patients.[4–6] Other centers have described adaptation of adult platforms, such as the Aquadex UF machine (Nuwellis Inc, Eden Prairie, MN), with the addition of prereplacement fluid to provide clearance. This device is not cleared for neonates, requires a dual-lumen catheter or 2 venous access points, and has an extracorporeal volume that is too large (33 ml) for use without blood priming in VLBW or ELBW neonates.[7] The Newcastle Infant Dialysis and Ultrafiltration System (NIDUS) was recently developed and can perform single-lumen KRT in low-weight infants[8]; however, it is not approved by either the European Medicines

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Agency or the US Food and Drug Administration. Peritoneal dialysis remains an option in VLBW or ELBW neonates; however, inadequate skin integrity, a weak abdominal wall, and concerns for necrotizing enterocolitis make this modality technically challenging. Thus, VLBW or ELBW neonates with AKI and/or fluid overload have no approved treatment options available.

A manual hemodialysis device has the potential to address many limitations to providing KRT to this patient population. The manual single-lumen alternating micro-batch dialysis device can provide clearance and UF with single-lumen access and does not depend on a certain blood flow rate for its operation.[9,10] The modified version, the Kirpa Kit (Stavro Medical, Golden, CO), has a much smaller extracorporeal volume, can accommodate very small batch volumes to limit fluid shifts that neonates might not tolerate and has blood flow that is tightly controlled with syringe push-pull.[11] We have miniaturized the Kirpa Kit to create the Brophy Kit, designed with smaller tubing for a reduced extracorporeal volume (4 ml), syringes, and a structure that allows connection to smaller hemofilters. The lack of a pump and electrical connections and overall compact design (30 cm length × 10 cm width, 150 g) provides the added benefit of fitting it into the neonatal incubator. Herein, we sought to test the efficacy of the Brophy Kit in an *in vitro* setting. Our aims were 2-fold: to determine the clearance rates of 4 different dialysis fluid configurations to optimize clearance efficiency, and to evaluate the reliability and accuracy of UF.

METHODS

The Brophy Kit Experimental Set-Up

The set-up of the device and the steps to perform clearance and UF are the same as for the Kirpa Kit, described recently,[11] with the main difference being its smaller size. In Table 1, we summarize the differences between the devices; and in Figure 1a and b, we show the set-up for and steps to use the Brophy Kit. We conducted 2 sets of experiments, the first to test clearance (clearance study) and the second to study UF (UF study). The characteristics of the 2 studies are summarized in Table 2. Our blood bag consisted of expired packed red blood cells diluted with 0.9% sodium chloride solution to achieve a normal Hct and a total volume of 220 ml, 500 units of heparin, and 1 g of urea (454 mg/dl). This blood bag was attached to the Brophy Kit, and 2 ml samples were drawn from the blood bag for determination of BUN, potassium, and Hct, depending on the experiment type. All baseline samples were drawn in duplicate to further ensure accurate starting concentrations. Institutional review board approval was not necessary because this study protocol is classified as non-Human Subjects Research, by Cincinnati Children's Hospital Medical Center's institutional guidelines.

Table 1. Sizes and volumes of the components of the different manual devices

Device Component	mSLAMB	Kirpa Kit	Brophy Kit
Tubing volume (ml)	48	8	4
Blood syringe volume (ml)	60	60	10
Dialysis fluid syringe (ml)	n.a.	60	20
Effluent syringe (ml)	n.a.	60	10
Length (cm)	80	60	30
Width (cm)	100-180	25	10
Weight (g)	520	230	150

mSLAMB, manual single lumen alternating micro batch, n.a., not applicable.
For the mSLAMB device, dialysis fluid and effluent fluid volumes were determined by gravity flow and thus less precisely controlled.

Clearance Study

The clearance study consisted of 12 experiments with 30 cycles each. Each cycle consisted of drawing 10 ml of blood from the blood bag through the bypass tube using syringe 1 (step 1), filling syringe 2 with 10 ml or 20 ml of 0.9% sodium chloride as dialysis fluid (step 2), refreshing the dialysis side of the hemofilter at a different frequency depending on the configuration (step 3), and then returning the blood into the blood bag through the hemofilter with syringe 1 (step 4) (Figure 1a). For our clearance study, UF was not removed; thus, syringe 3 was not necessary.

We tested 4 configurations in triplicate, all using diffusive clearance. Configurations varied by frequency or volume of the dialysis flushes; however, 0.9% sodium chloride was used for each flush. In configuration 1, we flushed the hemofilter every 5 cycles with a 10 ml flush. In configuration 2, we flushed every 2 cycles with 10 ml. In configuration 3, we flushed every cycle with 10 ml. And in configuration 4, we flushed with 20 ml every 2 cycles. To assess clearance, we measured BUN and potassium concentrations (mg/dl and mmol/l, respectively) at baseline and every 5 cycles from the blood bag. BUN and potassium concentrations were measured using a Roche c311 clinical chemistry analyzer (Roche Diagnostics, Indianapolis, IN) per manufacturer protocols in the Cincinnati Children's Hospital Medical Center's Nephrology Research Laboratory. BUN and potassium reduction

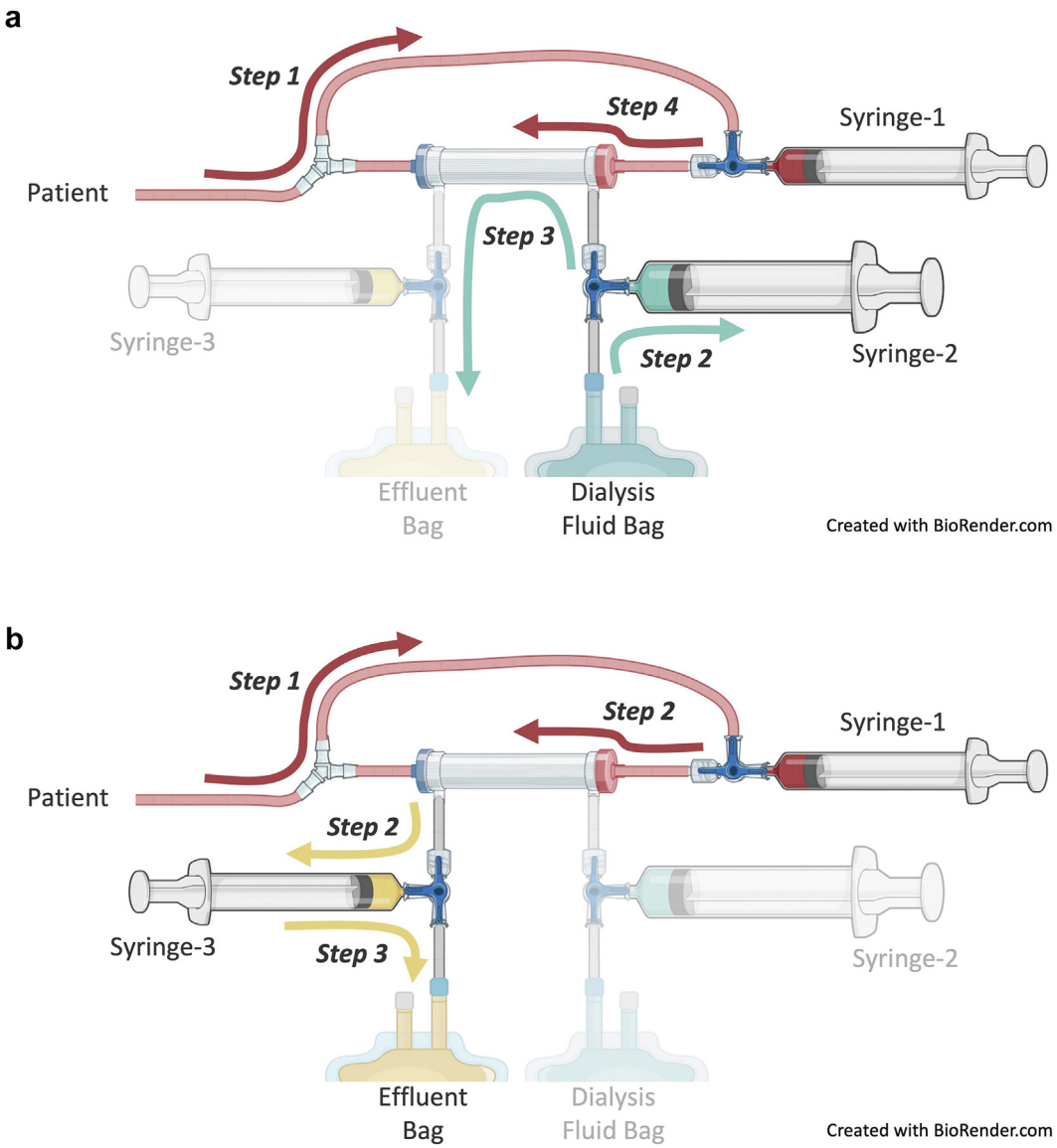

Figure 1. Schematic representation of the Brophy Kit. Steps are labeled. (a) Shows the procedure to perform clearance with the following steps: step 1 - blood is pulled from the access point through the bypass tubing into syringe 1; step 2 - dialysis fluid is pulled into syringe 2; step 3 - dialysis fluid is pushed out of syringe 2 into the filter to refresh the compartment; step 4 - blood is pushed through the filter with syringe 1. (b) The figure shows the procedure to perform ultrafiltration with the following steps: step 1 - blood is pulled from the access point through the bypass tubing into syringe 1; step 2 - while blood is pushed through the filter with syringe 1, ultrafiltrate is removed via syringe 3; step 3 - Ultrafiltrate is pushed into effluent bag by pushing syringe 3.

percentages were calculated using the following formulas:

$$\text{BUN reduction \% after cycle N} = \left(\text{BUN}_{\text{baseline}} - \text{BUN}_{\text{cycleN}}\right) \div \text{BUN}_{\text{baseline}} \times 100$$

$$\text{Potassium reduction \% after cycle N} = \left(\text{Potassium}_{\text{baseline}} - \text{Potassium}_{\text{cycleN}}\right) / \text{Potassium}_{\text{baseline}} \times 100$$

UF Study

The UF Study consisted of 3 experiments with 60 cycles each. Each cycle consisted of drawing 10 ml of blood from the blood bag through the bypass tube using syringe 1 (same as step 1 above), then returning it to the blood bag via the hemofilter (step 4 of the clearance experiment). Simultaneously, 1 ml of ultrafiltrate (UF) was aspirated into syringe 3, then emptied into the effluent bag (Figure 1b). For pure UF, syringe 2 was not necessary. The primary outcome was Hct measured after every 10 cycles from the blood bag. Hct determinations were performed using a Stat Profile Prime+ (Nova Biomedicals, Waltham, MA) as per manufacturer protocols. The Hct values measured were compared with the expected Hct values in all 3 experiments to assess the accuracy of the

Table 2. Description between clearance and ultrafiltration studies and summary of results

Characteristic	Clearance study	Ultrafiltration study
Number of experiments	12	3
Cycles per experiment	30	60
Batch volume (ml)	10	10
Hemofilter type	Polyflux 2H	Stavro XR 11
Hemofilter volume (ml)	17	8
Tubing volume (ml)	4	4
Total volume (ml)	21	12

Measure	Blood Urea Nitrogen[a]	Potassium[b]	Hematocrit
Starting, median (IQR)	47.9 (34.0–77.6)	8.3 (7.0–10.7)	34.1% (33.4–34.9)
Final, median (IQR)	37.8 (23.2–52.8)	5.7 (4.4–7.8)	52.6% (52.5–53.8)
Configuration 1, median (IQR)			
Baseline	47.0 (43.1–52.2)	9.1 (8.0–10.9)	n.a.
Final Reduction %	41.8 (37.8–47.1) 11.0 (9.9–12.4)	7.4 (6.5–8.9) 18.3 (18.1–18.5)	
Configuration 2, median (IQR)			
Baseline	76.5 (51.4–85.8)	9.1 (8.2–11.0)	n.a.
Final Reduction %	53.9 (36.4–65.5) 28.1 (23.5–28.8)	6.1 (5.6–7.6) 31.5 (30.6–32.4)	
Configuration 3, median (IQR)			
Baseline	80.9 (64.9–106.0)	10.0 (7.7–13.8)	n.a
Final Reduction %	50.6 (40.1–68.2) 37.5 (36.0–38.4)	5.8 (4.5–8.3) 41.6 (40.1–41.7)	
Configuration 4, median (IQR)			
Baseline	22.6 (18.4–29.6)	7.1 (5.6–7.3)	n.a.
Final Reduction %	13.3 (10.8–19.0) 40.9 (36.7–41.1)	4.0 (3.1–4.3) 44.7 (40.8–45.4)	

IQR, interquartile range; n.a., not applicable.
[a]Blood urea nitrogen concentrations reported in mg/dl.
[b]Potassium concentrations reported in mmol/l.
Configuration 1 – filter refreshed with 10 ml every 5 cycles; configuration 2 – filter refreshed with 10 ml every 2 cycles; configuration 3 – filter refreshed with 10 ml each cycle; configuration 4 – filter refreshed with 20 ml every 2 cycles.

technique. Expected Hct was calculated using the equation:

$$\text{Expected Hct}_{\text{post}}\ (\%) = \left(\left[\text{Hct}_{\text{pre}} \div 100 \times \text{blood volume}_{\text{pre}}\right] - \left[\text{sample volume} \times \text{Hct}_{\text{pre}} \div 100\right]\right) \div (220 - \text{UF volume} - \text{sample volume}) \times 100$$

The expected Hct (percentage of red blood cell volume relative to blood volume) after a cycle was calculated by dividing the red blood cell volume at the end of the cycle (which changed only because of the small sample volume at the end of the previous cycle) by the total blood volume at the end of the cycle. This total volume results from the removal of the plasma component via UF and the small volume taken by the previous cycle's blood draw.

Statistical Analysis

Statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were shown as median and IQR. The final median reductions in BUN and potassium of the 4 configurations were compared in pairs using the Mann-Whitney U test. The Wilcoxon signed-rank test for paired samples was used to compare the measured and expected Hct increase in the UF study.

RESULTS

Clearance Study

The median baseline BUN was 47.9 mg/dl (IQR: 34.0–77.6), which decreased to a median BUN of 37.8 mg/dl (IQR: 23.2–52.8) after 30 cycles. Median baseline potassium was 8.3 mmol/l (IQR: 7.0–10.65), which decreased to 5.7 mmol/l (IQR: 4.4–7.8) after 30 cycles. In Supplementary Table S1, we show all BUN and potassium concentrations and reduction percentages. However, BUN and potassium reduction varied by configuration. BUN and potassium reduction percentages were 11.0% (IQR: 9.9–12.4) and 18.3% (IQR: 18.1–18.5) for configuration 1, 28.1% (IQR: 23.5–28.8) and 31.5% (IQR: 30.6–32.4) for configuration 2, 37.5% (IQR: 36.0–38.4) and 41.6% (IQR: 40.1–41.7) for configuration 3, and 40.9% (IQR: 36.7–41.1) and 44.7% (IQR: 40.8–45.4) for configuration 4, respectively (Table 2). Configurations 3 and 4 had greater reduction percentages compared with configurations 1 and 2 ($P = 0.049$), and configuration 2 had greater reduction percentages compared with configuration 1 ($P = 0.049$). No statistically significant difference was observed in reduction percentages between configurations 3 and 4 ($P = 0.513$) (Figures 2a and b).

UF Study

The median baseline Hct was 34.1% (IQR: 33.4–34.9). In Supplementary Table S2, we report on the cycle-by-cycle Hct increase observed in each of the 3 experiments. Hct should have increased from 34.1% to 47.7% (IQR: 46.8–48.9). After 60 cycles, with a removal of 60 ml of UF, the median Hct increased to 52.6% (IQR: 52.5–53.8). The median percentage variation between measured and expected Hct after 10, 20, 30, 40, 50, and 60 cycles were 0.6 (IQR: 0.0–0.8), 3.0 (IQR: 2.3–3.2), 2.9 (IQR: 2.6–4.2), 6.0 (IQR: 4.2–8.3), 8.0 (IQR: 6.5–11.4), and 9.3 (IQR: 6.9–12.9), respectively. The measured Hct did not differ from the calculated Hct in Experiment 1 ($P = 0.06$), but did in experiments 2 and 3, accounting for UF removed and sample volumes ($P = 0.04$ for both experiments) (Figure 3). In Supplementary Figure S1, we show the Bland-Altman

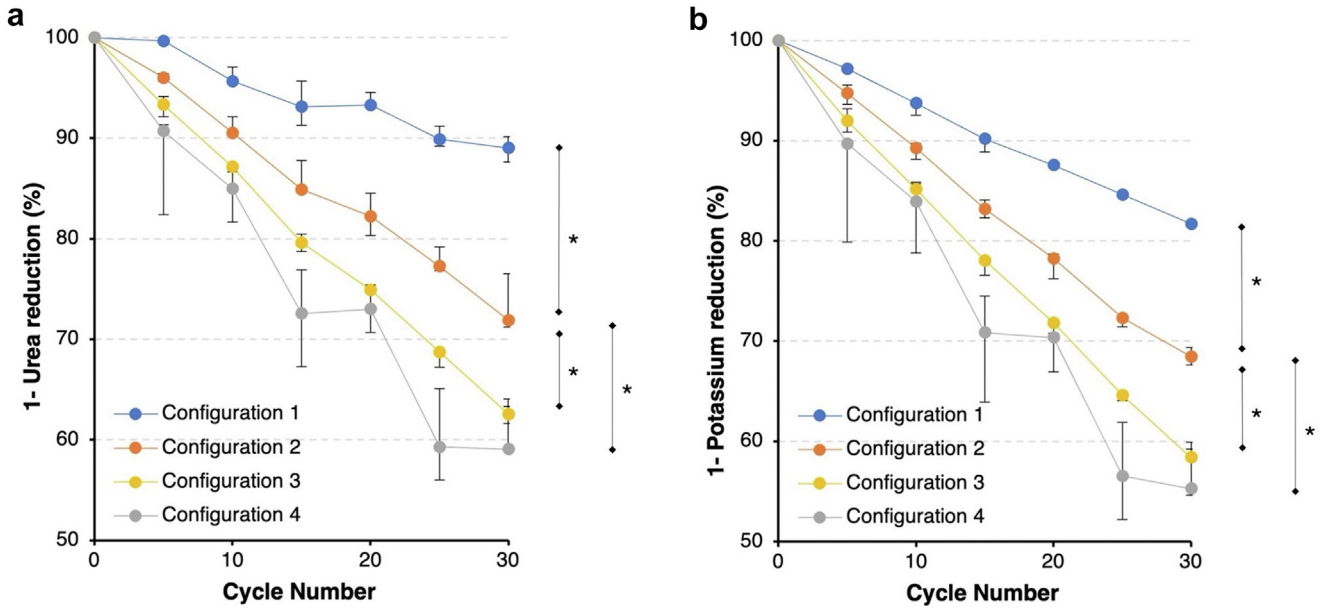

Figure 2. (a)Urea and (b) potassium reduction by configuration. *Indicates a comparison with a P value < 0.05.

plot depicting the difference between the measured and the expected Hct.

DISCUSSION

In this study, we have shown that the Brophy Kit, a miniaturized version of the Kirpa Kit, can perform clearance and UF *in vitro* with a very small extracorporeal volume (12 ml) and precise and small fluid shifts. We have demonstrated an optimal configuration to achieve 40% BUN and potassium reduction in the span of 15 to 20 minutes and we were able to reliably remove 1 ml UF volumes with each cycle. For these reasons, along with its single-lumen access and compact design that allows the circuit to fit into a neonatal incubator, we believe the Brophy Kit has the potential to be a salvage therapy for neonates without other KRT options.

Great progress has been made in the understanding and management of neonates with life-threatening congenital kidney failure or acquired conditions that lead to severe AKI.[4] About 30 years ago, Coulthard and Sharp were able to dialyze 1 VLBW and 2 ELBW neonates using a single-lumen manual syringe-driven technique.[12] Although this device is similar to the Brophy Kit in its extracorporeal volume and structure, technical differences make them quite different, such as the path of blood flow (forward and backward in theirs and circular in ours) and the use of a mechanical

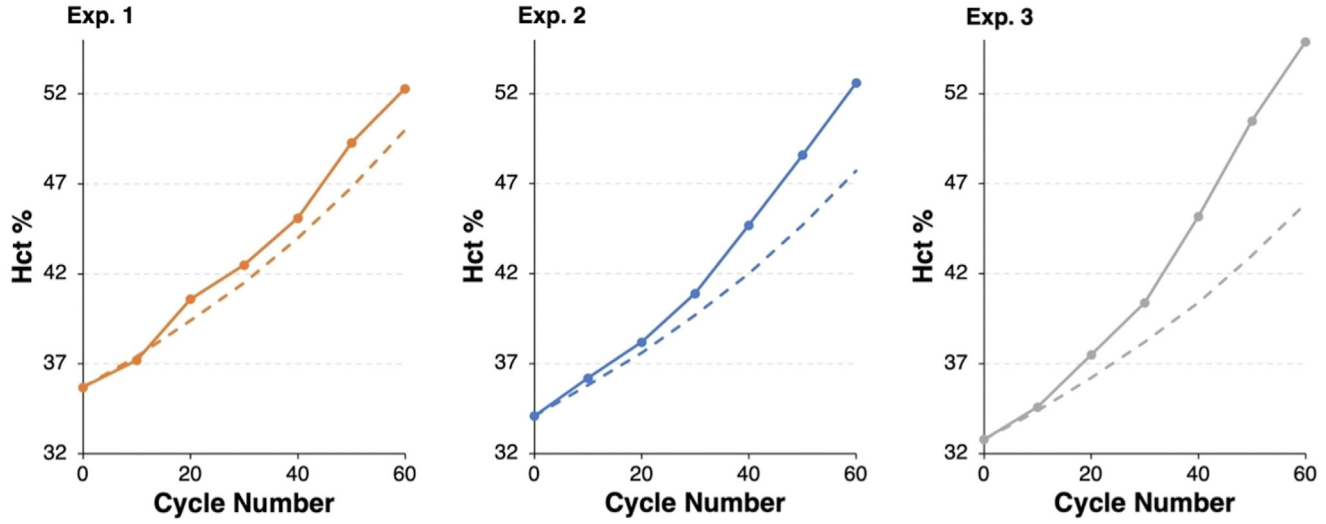

Figure 3. Difference between the measured versus calculated hematocrits in the 3 ultrafiltration study experiments. Expected hematocrit was calculated using the equation: Expected Hct_{post} (%) = ([Hct_{pre} ÷ 100 × blood $volume_{pre}$] – [sample volume × Hct_{pre} ÷ 100]) ÷ (220 – UF volume – sample volume) × 100. Exp, experiment.

dialysis fluid pump that makes their system only partially manual. These authors subsequently automated this device, creating the NIDUS, which provided higher dialysis clearance and more precise UF than peritoneal or conventional hemodialysis to 10 infants and neonates who weighed < 8 kg.[8] However, as stated earlier, NIDUS has not been approved by medical/regulatory agencies. Other differences between these devices are important to note. Whereas their manual version was never commercialized, representing an initial phase in the development of the NIDUS, the Brophy Kit is a finalized design that makes its rudimentary nature an innovation. The NIDUS is intended to provide continuous KRT, whereas the Brophy Kit is intended to be performed intermittently, for a few hours a day, for the purpose of stabilization.

Despite its manual design, we believe the Brophy Kit can provide clearance capabilities like other available pediatric dialysis devices, including Carpediem, modified continuous veno-venous hemofiltration using the Aquadex UF device, and NIDUS, as displayed in Table 3.[7,8,13] Clearance is shown as a range (minimum and maximum) based on data from *in vitro*, animal, and early human studies of these devices.[7,8,13] The urea clearance range of the Brophy Kit shown in Table 3[7,8,13] includes extrapolated values. The duration of 1 cycle during the clearance study was about 8 seconds, a value by which we determined the "measured clearance" (Supplementary Table S3). However, although 8 seconds to pull and push 10 ml of blood may be sufficient in an *in vitro* experiment, it may not be sufficient in a clinical setting, particularly with young children who have small venous catheters and potentially hemodynamic instability. We therefore extrapolated the theoretical clearance values that would be obtained by extending the cycle time (Supplementary Table S3 and Supplementary Figure S2). Owing to the operational mechanism of the Brophy Kit, both blood flow rate and dialysis fluid flow rate are directly proportional to the cycle rate. Therefore, if the cycle time decreases, blood flow rate, and dialysis fluid flow rate increase proportionally. Even if the cycle time increased to 60 seconds, which could be feasible with a 3.5 French 30 cm umbilical vein catheter, this would produce a blood flow rate, of 10 ml/min, a dialysis fluid flow rate of 600 ml/h (using configuration 3), and result in a urea clearance of 4.8 ml/min, in fact comparable with the characteristics and capabilities of these other devices.

We tested 4 different dialysis configurations to identify the optimal volume and frequency of hemofilter refreshes. BUN and potassium clearance increased significantly with larger flush volumes, and did not vary if the same volume was divided and administered every cycle or concentrated and administered every 2 cycles (configuration 3 vs. configuration 4). We chose the flush volume for configuration 4 to be the volume of the dialysis fluid compartment of the filter (20 ml), to replace the "depleted" dialysis fluid in the hemofilter with clean fluid to maintain the concentration gradient that drives diffusive clearance. Given similar clearance as in configuration 3, a flush volume equal to the volume of the dialysis fluid compartment of the filter appears reasonable.

With the UF study, we were able to remove a set volume of fluid without technical issues. Despite an increase in Hct, we did not experience hemofilter clogging (obstruction of the capillaries of the filter due to red blood cell stacking), likely because of removing only 10% of the blood batch volume with each cycle (1 ml UF per 10 ml of blood). The median increase in Hct we observed was higher than expected, 18.5% instead of 13.6%, based on our expected Hct calculations. In experiments 2 and 3, the increase in Hct was greater than expected, whereas in experiment 1, the measured Hct values were not different from those expected. We

Table 3. Urea clearance performances and device specifications of neonatal/infant dialysis platforms described in different experimental models compared to the Brophy Kit

Characteristic	Carpediem[13]	mCVVH with Aquadex[7]	NIDUS[8]	Brophy Kit
Urea clearance, range (ml/min)	2.5–11.9	0.5–2.2	1.0–2.5	2.4–59.4
Experimental model	Human plasma (urea added) *in vitro*	Neonates *in vivo*	Piglets *in vivo*	Human pRBC (saline, urea added) *in vitro*
BFR, range (ml/min)	17–50	10–40	20	5–125
Qd range (ml/h)	300–900	n.a.	n.a.	300–7500
Access line required	Double lumen central catheter	Double lumen central catheter	Single lumen central catheter	Single lumen catheter (central or peripheral)
Priming volume (ml)	32–41	35	10[a]	6.5–12
Filter Surface area (m^2)	0.16–0.29	n.a	0.045	0.023–0.09
Minimum Patient Weight (kg)	2.5	5	n.a.	n.a.

BFR, blood flow rate; Carpediem, Cardiorenal Pediatric Emergency machine; mCVVH, modified continuous venovenous hemofiltration with Aquadex machine; n.a., not available; NIDUS, Newcastle Infant Dialysis and Ultrafiltration System; pRBC-packed red blood cells; Qd, dialysis fluid flow rate.
Brophy Kit values are based on calculations described in Supplemental Table 3 using Configuration 3, and the wide range of values reflects varying blood flow rates. The minimum patient weight provided is what has been approved by the European Medicines Agency or US Food and Drug Administration.
[a]Not confirmed.

believe our syringe size did not allow for the accuracy necessary for such small volumes; an extra 0.2 ml of UF each cycle would result in a Hct of 51.9%, very similar to that measured (52.6%). We used a 10 ml syringe, which only has a sensitivity of 0.2 ml, whereas a 3 ml syringe would have allowed us a sensitivity of 0.1 ml. Another potential source of error was our sampling procedure. Although we attempted to homogenize the blood bag by mixing it before sampling, this may not have been enough. Given that the greatest differences were noted after cycle 30, it is possible that user fatigue contributed to that. Future experiments should test the optimal number of cycles to be performed by a single user, because UF accuracy is key to the reliability and safety of this device.

Our study has several limitations. This device does not overcome the limitations of other manual devices[11]: the efficacy demonstrated *in vitro* is likely not translatable to clinical practice because of the higher ratio of batch volume to total blood volume in our studies; the higher volume of distribution of BUN and the constant generation of BUN and potassium via metabolism *in vivo*; the inability to account for blood flow resistance of the intravenous catheter; and anticoagulation strategies, which have not been addressed (as we used blood without plasma and platelets). There is a risk of hypothermia any time an extracorporeal circuit is used, and VLBW or ELBW neonates are at greatest risk for this. Although our set-up does not include insulation, we propose placing the circuit inside the incubator, for which its small size should allow. In VLBW and ELBW neonates, even a few milliliters of fluid can be hemodynamically significant; thus, the accuracy of UF must be improved. Next steps involve studies using smaller syringes (2–3 ml) to address UF accuracy as well as smaller filters to reduce extracorporeal volumes. This is because the Brophy Kit can work with hemofilters of different sizes, for example the Hemoconcentrator D025 (Medica S.p.a, Medolla, Modena, Italy; extracorporeal volume 2.5 ml), which would allow for dialysis of a 900 g child without exceeding 10% of its total blood volume.

In conclusion, the Brophy Kit can provide clearance and remove volume with very small batch volumes and within a small circuit that utilizes a single-lumen access point. *In vivo* animal experiments with this device are underway to study its safety, efficacy, and a suitable anticoagulation protocol, so that the Brophy Kit can be brought to the bedside for VLBW and ELBW neonates who previously had no other extracorporeal option.

DISCLOSURE

CLS is a consultant for AM Pharma, Mozarc Medical, and BioPorto Diagnostics. JM is a consultant for Mozarc Medical. AS is a consultant for Mozarc Medical. EP is an employee of ExThera Medical and co-inventor of the Brophy Kit. SLG reports receiving personal fees from Baxter Healthcare, BioPorto Diagnostics, Calcimedica, Fresenius, Novartis, Nuwellis, Ostuka, MediBeacon, and Mozarc Medical. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Bland-Altman plot showing the difference between the measured and the expected hematocrit in the 3 ultrafiltration study experiments.

Figure S2. Theoretical urea clearance as a function of the blood flow rate and the configuration.

Table S1. Urea and potassium reduction by experiment and configuration.

Table S2. Hematocrit increases by cycle.

Table S3. Urea clearance, measured and extrapolated by blood flow rate.

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