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Point-of-Care Chemistry-Guided Dialysate Adjustment to Reduce Arrhythmias: A Pilot Trial

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Introduction: Excessive dialytic potassium (K) and acid removal are risk factors for arrhythmias; however, treatment-to-treatment dialysate modification is rarely performed. We conducted a multicenter, pilot randomized study to test the safety, feasibility, and efficacy of 4 point-of-care (POC) chemistry-guided protocols to adjust dialysate K and bicarbonate (HCO3) in outpatient hemodialysis (HD) clinics.

Methods: Participants received implantable cardiac loop monitors and crossed over to four 4-week periods with adjustment of dialysate K or HCO3 at each treatment according to pre-HD POC values: (i) K-removal minimization, (ii) K-removal maximization, (iii) Acidosis avoidance, and (iv) Alkalosis avoidance. The primary end point was percentage of treatments adhering to the intervention algorithm. Secondary endpoints included pre-HD K and HCO variability, adverse events, and rates of clinically significant arrhythmias (CSAs).

Results: Nineteen subjects were enrolled in the study. HD staff completed POC testing and correctly adjusted the dialysate in 604 of 708 (85%) of available HD treatments. There was 1 K $\leq$3, 29 HCO3 $<$20 and 2 HCO3 $>$32 mEq/l and no serious adverse events related to study interventions. Although there were no significant differences between POC results and conventional laboratory measures drawn concurrently, intertreatment K and HCO3 variability was high. There were 45 CSA events; most were transient atrial fibrillation (AF), with numerically fewer events during the alkalosis avoidance period (8) and K-removal maximization period (3) compared to other intervention periods (17). There were no significant differences in CSA duration among interventions.

Conclusion: Algorithm-guided K/HCO3 adjustment based on POC testing is feasible. The variability of intertreatment K and HCO3 suggests that a POC-laboratory-guided algorithm could markedly alter dialysate-serum chemistry gradients. Definitive end point-powered trials should be considered.

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Approximately half of cardiovascular deaths in the end-stage kidney disease population are due to sudden cardiac arrest, which kills 1 in 20 HD patients annually and occurs at a rate 20 times greater than in the general population.[1] In addition, overt AF is present in 11.6%[2,3] whereas subclinical AF is present in up to 41% of patients receiving maintenance HD.[4] Both overt and subclinical forms of AF have been associated with mortality and stroke.[2,3,5,6] Therefore, a continuum of CSAs characterizes HD and underlies the extraordinarily high incidence of cardiovascular morbidity and mortality in this population.

Cardiovascular events and arrhythmias have been observed to consistently cluster around HD sessions, and there is increasing evidence that both overly rapid and insufficient correction of electrolyte disorders underlie the excess peri-dialytic cardiovascular risk.[7–12] The rate of removal of K and HCO3 during HD is governed by the serum-to-dialysate concentration gradient,

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which can be modified by changing the dialysate prescription. However, in outpatient dialysis clinics, treatment-to-treatment dialysate modification is not performed primarily because pretreatment serum K and HCO3 levels are not routinely measured. The purpose of this pilot and feasibility trial was to test the hypothesis that an algorithm for dialysate prescription adjustment according to (POC) pre-HD serum electrolyte testing results could be effectively and safely deployed in real-world outpatient dialysis clinics. In addition, we sought to examine the effect of 4 different dialysate K and HCO3 adjustment algorithms on the incidence of CSAs.

METHODS

Population

The RADAR-Electrolytes trial (clinicaltrials.gov NCT03519347) was a multicenter, randomized double-blinded crossover trial enrolling individuals between 18 and 85 years old on maintenance HD for end-stage kidney disease for >30 days. Participants between 18 and 40 years were additionally required to have a history of heart failure, diabetes, coronary or peripheral vascular disease, or arrhythmia. Participants were enrolled from 2 HD units in New York City and 1 in Durham, North Carolina.

Key exclusion criteria included the following: (i) expected survival <6 months; (ii) kidney transplant, transfer to home or peritoneal dialysis, or to nonstudy HD facility anticipated within 6 months; (iii) prisoners or cognitive disability preventing consent; (iv) chronic skin conditions or frequent infections increasing the likelihood of implantable loop recorder infection; (v) bleeding disorders or inability to reverse anticoagulants for loop recorder placement; (vi) existing pacemaker, implantable monitor or defibrillator precluding device placement; (vii) chronic persistent AF; (viii) hemoglobin <8 g/dl; and (ix) serum K >6.5 or <3.5 mEq/l within 30 days.

Trial Design and Interventions

Eligible participants underwent subcutaneous implantation of an implantable loop recorder (Medtronic LINQ, Medtronic Inc., Minneapolis, MN) in the left chest followed by 1 month of usual care. After the 1-month observation period, participants were randomized to cross-over in random order to 4 consecutive 4-week treatment periods with 1 week of usual care washout between each period. A balanced, uniform crossover design stratified by site in blocks of 4 was utilized (Figure 1). The study statistician generated the randomized intervention sequence for each participant and communicated the intervention sequence via the electronic trial data collection system to the site research coordinators for implementation; however, the study investigators were blinded to the intervention sequence throughout the trial.

Clinic personnel were trained by research coordinators to obtain serum chemistry levels using whole-blood drawn from the dialysis access and a POC serum chemistry analyzer (Abbott i-STAT, Abbott Point-of-Care, Orlando, FL). After training, clinic personnel conducted POC testing prior to each dialysis treatment during the intervention periods and adjusted the dialysate K or HCO3 according to 1 of 4 different algorithms (2 for K and 2 for the HCO3 prescription). K algorithms (Supplementary Table S1) included one that prioritized higher dialysate K levels to avoid hypokalemia and minimized the serum-to-dialysate gradient (K Max) and one prioritizing lower dialysate K levels to avoid hyperkalemia (K Min). Similarly, HCO3 algorithms (Supplementary Table S2) included one prioritizing acidosis avoidance by maximizing the serum-to-dialysate HCO3 gradient (B Max) and one prioritizing alkalosis avoidance (B Min) using lower dialysate HCO3 levels. In the event of predialysis K levels <3 or >7 mEq/l, or HCO3 <15 or >35 mEq/l, investigators were contacted, and the prescription was adjusted according to clinical judgment. If participants missed more than

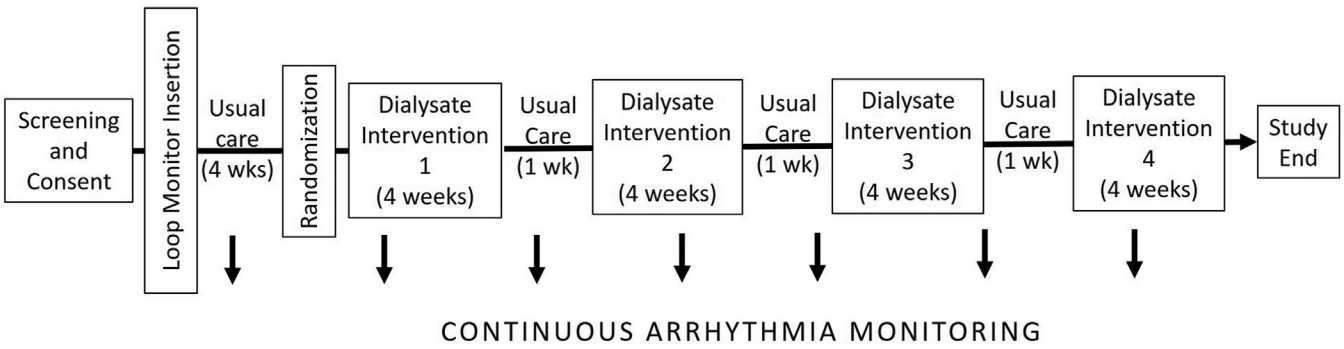

Figure 1. Study design. Each dialysate intervention lasted for 4 weeks and was followed by 1 week of usual care. Dialysate interventions were delivered in a random order using the following 4 randomized sequences: B Max/B Min/K Max/K Min ($n = 5$), B Min B Max K Min K Max ($n = 4$), K Max K Min B Max B Min ($n = 4$), K Min K Max B Min B Max ($n = 6$).

half of the treatments during a treatment period (>6), the treatment period was extended so that a minimum of 6 treatments were conducted using the assigned intervention. Participants and investigators were blinded to treatment assignments that were implemented by unblinded clinic staff and research coordinators.

Data Collection

Adverse events, dialysis records, and standard-of-care laboratory measures were reviewed monthly. Implantable loop recorders were set to automatically detect all ventricular tachycardia episodes ≥130 beats per minute lasting for at least 32 beats, all >3-second pauses, bradycardia of ≤40 beats per minute at least 4 beats long, and all episodes of AF. In addition, participants were able to trigger an electrocardiogram recording in the event of symptoms suggestive of arrhythmia.

Tracings were adjudicated by a blinded physician investigator every other week. In the event of *de novo* sustained ventricular tachycardia, serious bradycardia or asystole, new onset, sustained AF or frequent paroxysmal AF, participants and a responsible clinician were notified to allow for clinical management such as institution of anticoagulation or referral for a pacemaker. A survey with questions about barriers to following the protocol was also administered to dialysis nursing staff.

Outcomes

The primary outcome was adherence to the prescribed intervention algorithm defined by the percent of dialysis treatments attended within each intervention period for which the appropriate POC testing was performed and the dialysate prescription was adjusted per protocol. Recruitment feasibility was assessed as the achievement of a recruitment rate of 1 patient per month. Safety endpoints assessed during intervention periods included the incidence of severe K or HCO3 abnormalities and unscheduled HD or hospitalizations for electrolyte abnormalities in the absence of a missed treatment.

The secondary exploratory efficacy end point was the total duration of CSAs during the intervention periods, indexed to adherence with trial intervention. CSA was defined as AF, asystole ≥3 seconds, bradycardia ≤40 beats per minute lasting ≥6 seconds, and sustained ventricular tachycardia ≥130 beats per minute lasting ≥30 seconds. Although no data exist on the potential effect of dialysate adjustments on CSA incidence rates, using a mean duration of CSAs of 356 minutes/month observed in prior monitoring studies,[4] we estimated that a sample size of 20 subjects would provide 80% power for detection of change in CSAs duration of 140 minutes/month given within-subject correlation of 0.9. Exploratory outcomes included a comparison of the results of POC testing results with monthly laboratory measures; comparisons of how often the algorithms directed changes to the dialysate prescription; and associations of prescription with clinical outcomes including all-cause and cardiovascular mortality, hospitalization, arrhythmia subtypes.

Power and Statistical Analysis

The primary purpose of the study was to assess feasibility and adherence to the study protocol. As a secondary exploratory outcome, we estimated the power to detect CSA differences among the study arms. On the basis of a mean duration of CSAs in the Monitoring in Dialysis trial[4] of 356 ± 1765 minutes, a sample size of 20 subjects was anticipated to provide 80% power for detection of change in CSA duration of 140 minutes/month given within-subject correlation of 0.9, 370 minutes for within-subject correlation of 0.7, and 470 minutes for within-subject correlation of 0.5.

Baseline characteristics are described as mean ± SDs, median (interquartile range) or *N* (%) as appropriate according to the distribution. Adherence was estimated as percentage (95% confidence interval) of attended dialysis sessions without protocol deviation. Safety events were assessed as the incidence rate (complications per unit follow-up time). The duration of CSAs in seconds was logarithmically transformed to account for nonnormality, and then compared across interventions using a linear regression model adjusted for intervention adherence. A Wald-based test for proportion was used to test differences in proportions.[13] $P < 0.05$ was considered significant in all analyses. Given the pilot and hypothesis-generating nature of this study, no adjustments were made for multiple comparisons. All analyses were completed in R version 4.1.2 (R Foundation for Statistical Computing, https://www.R-project.org/).

RESULTS

Patient Characteristics

Ninety-four patients were screened and approached, 26 patients consented to participate and were enrolled between September 25, 2019 and December 28, 2021, with a final study visit completed on October 14, 2022 (Figure 2). Additional details about recruitment metrics are provided in the Supplementary Appendix. Seven patients dropped out prior to device implantation (screening failure $n = 2$, withdrawal of consent $n = 3$, withdrawn by the principal investigator due to medical issues $n = 1$, moved to nonparticipating dialysis clinic $n = 1$). Nineteen patients were ultimately included in the study and assessed for end points. Baseline

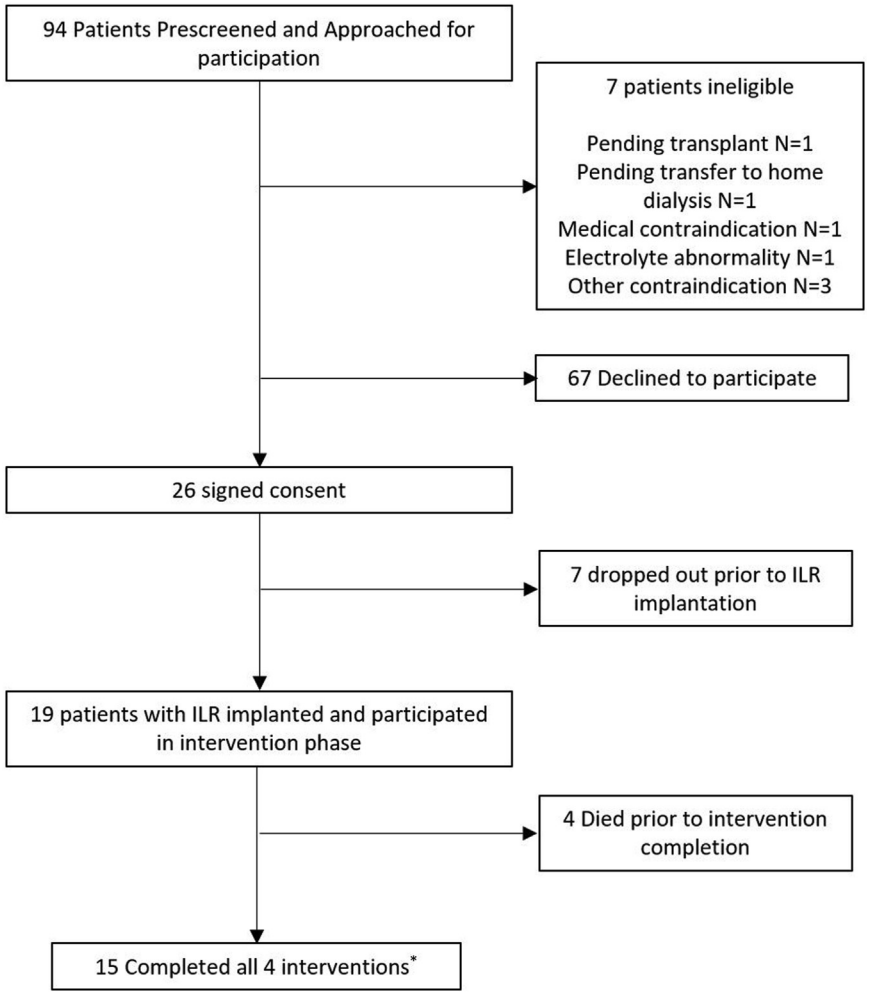

Figure 2. Study flow: *There was 1 additional subject death after completing the 4th intervention. ILR, implantable loop recorder.

characteristics of the patients are summarized in Table 1. Mean age of the patients was 59.4 years, 15.8% were female, and 42.1% were Black. The median dialysis vintage was 2.6 years, At baseline, dialysate K prescription was 2 mEq/l in 63.2% and 3 mEq/l in 36.8% of the patients. The mean dialysate HCO3 prescription was 33.6 mEq/l. Baseline predialysis serum K and HCO3 levels were 4.9 and 24.1 mEq/l, respectively.

Adherence to Study Intervention

The majority (79%) of participants completed all interventions, but 4 died prior to completing the study. The mean number of eligible dialysis sessions attended per subject during each intervention month was 10.3 (95% confidence interval 9.5–11.2), and the mean number of interventions successfully delivered per intervention month was 8.0 (95% confidence interval 7.1–9.8) for an overall adherence rate of 85% (95% confidence interval 83%–88%). Details according to intervention month are provided in Supplementary Table S3. The primary reason for nonadherence was missed POC testing prior to dialysis treatments ($n = 86$ treatments), followed by failure to correctly adjust the dialysate per protocol ($n = 5$). A survey of participating dialysis unit staff revealed that time constraints were most often cited as the main barrier to following the study intervention (Supplementary Table S4).

Adverse Events and Safety

There were no complications resulting from implantable loop recorder implantation. Only 3 significant dyskalemias were observed: 1 K $\geq$6.5 during the B Min intervention and 2 K $\leq$3.0 during the B Max and K Min intervention periods, respectively. Acid-base abnormalities were more frequent. We observed 38 predialysis HCO3 levels of $<$20 mEq/l, primarily during the B Min intervention period ($n = 23$ compared to 6 during B Max period, $P < 0.001$). In contrast, only 6 predialysis HCO3 levels $>$32 mEq/l occurred, 4 of which occurred during the K Max/K Min interventions. There were no hospitalizations for dyskalemias or acid-base disturbances in the absence of missed dialysis.

The rate of other adverse events was evenly balanced (Supplementary Table S5). The low frequency

Table 1. Baseline characteristics of the study cohort

Variable	Values, $N = 19$
Demographics	
Age, yrs	59.4 (11.5)
Female gender	3/19 (15.8%)
Race	
White	7/19 (36.8%)
Black	8/19 (42.1%)
Other	4/19 (21.1%)
Ethnicity	
Hispanic/Latino	4/19 (21.1%)
Years on dialysis	2.59 [0.4-28]
Highest level of education	
Less than high school or equivalent	4/19 (21.1%)
Technical or vocational school degree	2/10 (10.5%)
Some college education	4/19 (21.1%)
College graduate or above	5/19 (26.3%)
Missing	2/19 (10.5%)
Employment status	
Employed	1 /19 (5.3%)
Permanently disabled	9/19 (47.4%)
Retired or unemployed	9/19 (47.4%)
Comorbidities at baseline	
Cause of ESKD	
Glomerular disease	1/19 (5.3%)
Diabetic nephropathy	7/19 (36.8%)
Hypertensive nephrosclerosis	5/19 (26.3%)
Unknown/Other	5/19 (26.3%)
Missing	1/19 (5.3%)
Prior kidney transplantation	4/19 (21.1%)
Coronary artery disease	5/18 (27.8%)
Heart failure	3/19 (15.8%)
Past history of atrial fibrillation or atrial flutter (resolved)	1/18 (5.6%)
Ventricular arrhythmia	0/19 (0.0%)
Stroke or TIA	4/19 (21.1%)
Peripheral vascular disease	5/19 (26.3%)
Hypertension/high blood pressure	18/19 (94.7%)
Hyperlipidemia	11/17 (64.7%)
Diabetes	11/19 (57.9%)
History of cancer	6/19 (31.6%)
Asthma or reactive airway disease	4/19 (21.1%)
Chronic obstructive pulmonary disease	2/19 (10.5%)
Hepatitis B or C infection	3/19 (15.8%)
HIV	0/19 (0%)
Lupus	1/19 (5.3%)
Gout	2/19 (10.5%)
Current smoker	4/19 (21.1%)
Medication usage at baseline	
ACEI/ARB	2/17 (11.8%)
Potassium binder	5/16 (31.3%)
Beta-blocker	8/17 (47.1%)
Antiarrhythmic	0/16 (0.0%)
Laboratory values at enrollment	
Potassium (mEq/l)	4.9 (0.9)
Bicarbonate (mmol/l)	24.1 (3.6)
Sodium value (mEq/l)	138 (3.7)
Urea nitrogen (mg/dl)	59.3 (20.3)
Creatinine (mg/dl)	10.2 (3.1)
Albumin (g/dl)	3.9 (0.3)
Corrected calcium (mg/dl)	8.8 (1.4)
Phosphorus (mg/dl)	6.9 (1.5)
Parathyroid hormone (pg/ml) (Median [IQR])	618 [12, 5140]
Hemoglobin (g/dl)	10.5 (1.0)
Single pool Kt/V	1.5 (0.3)
Vitals at enrollment	
Weight (kilograms)	93.1 (22.1)
Systolic blood pressure (mm Hg)	136 (23)
Diastolic blood pressure (mm Hg)	75 (14)
Baseline dialysis prescription data	
Target weight (kg)	84.2 (24)
Hemodialysis time prescribed (min)	224 (23.7)
Dialysate potassium (mEq/l)	
2	12/19 (63.2%)
3	7 (36.8%)
Dialysate calcium (mEq/l)	
2.25	9/19 (47.4%)
2.5	7/19 (36.8%)
3	3/19 (15.8%)
Dialysate bicarbonate (mEq/l)	33.6 (5.1)

ACEI/ARB, ACE inhibitor/angiotensin receptor blocker; ESKD, end-stage kidney disease; IQR, interquartile range; kg, kilograms; mEq/lL, milliequivalents per liter; mg/dl, milligrams per deciliter; mm Hg; millimeters of mercury; mmol/lL, millimoles per liter; TIA, transient ischemic attack.
Proportion or Mean (SD)/Median [interquartile range] reported as applicable.

of events precluded formal testing for differences in incidence rates. Two subjects were hospitalized for new onset AF with rapid ventricular response, which was specified *a priori* as a serious adverse event of interest. Both occurred during the B Min intervention period; however, neither were deemed to be related to the intervention by the investigators or the independent data safety monitoring board. A total of 5 subjects died during the trial (4 prior to intervention completion and 1 following the conclusion of the last intervention period); 1 sudden death occurred several hours following a dialysis treatment during the K Min intervention. None of the deaths were assessed as related to the intervention by the investigators or the independent data safety monitoring board.

Accuracy and Variability of POC Testing

Mean differences between POC testing and standard of care laboratory testing on the same day were nonsignificant and were −0.2 mEq/l and +0.6 mEq/l for serum K and HCO3 respectively (Supplementary Table S6). Within-subject variability of serum K and HCO3 through the course of each intervention month, analyzed as the difference between the value of each predialysis POC test and the first POC test value of the month, was high (Figure 3). As shown in Table 2, 34% to 44% of all K levels differed by ≥0.5 mEq/l compared to the initial level of the month, and 7% to 13% differed by ≥1.0 mEq/l. Predialysis HCO3 levels were also highly variable; 14% to 44% of all HCO3 levels differed by ≥3.0 mEq/l compared to the first level of the month, and 1% to 10% were different by at

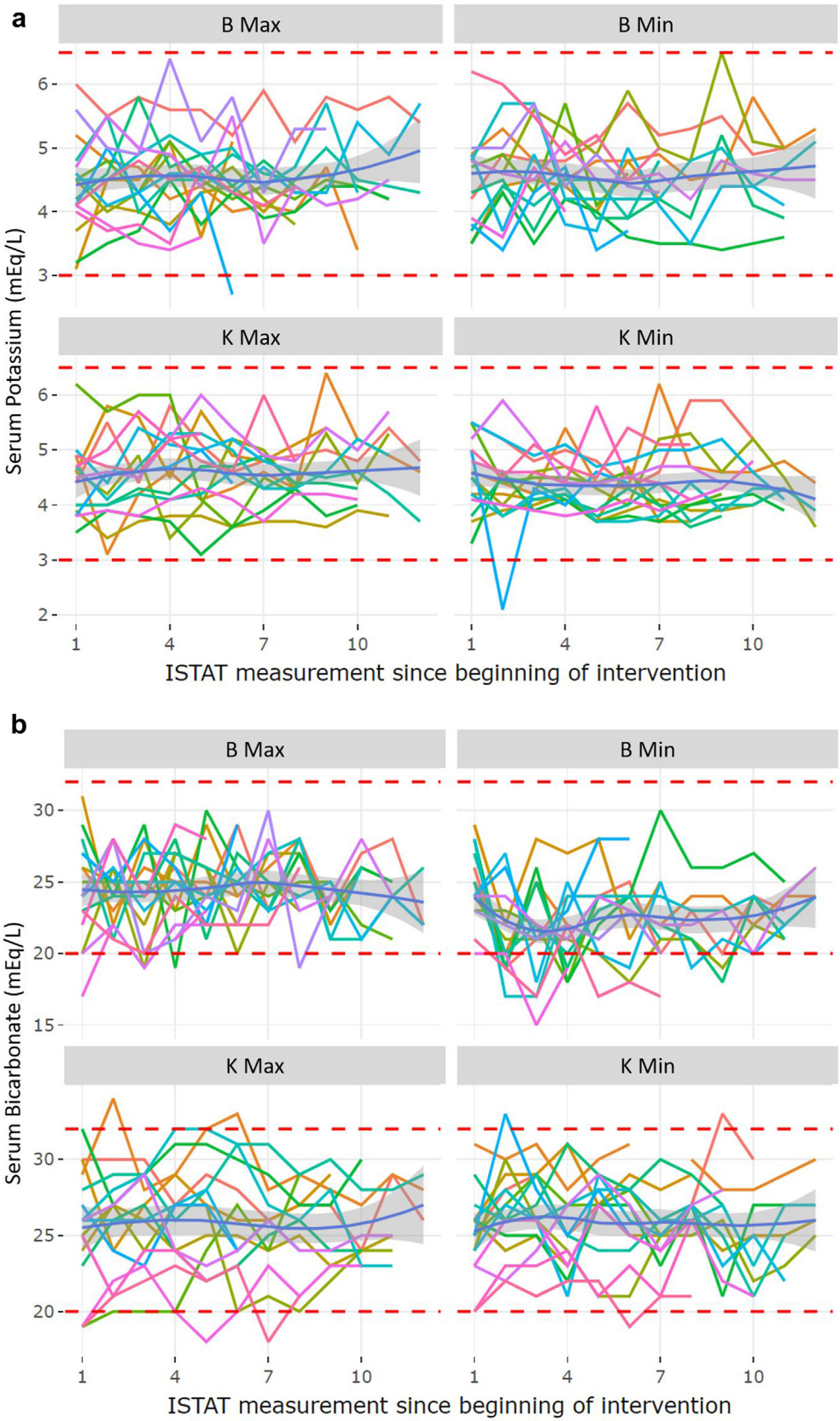

Figure 3. Variability of predialysis serum potassium (a) and serum bicarbonate (b) levels across the intervention periods. Each colored line represents the longitudinal results from an individual subject.

Table 2. Variability of serum electrolyte values within intervention periods

Intervention	Percentage of predialysis chemistry values outside of listed range of the monthly laboratory value within individual subjects (95% confidence interval)		
Serum potassium values	± 0.5 mEq/l	± 1.0 mEq/l	<3.5 or >6 mEq/l
B Max	38% (29–46)	13% (8–20)	3% (1–7)
B Min	44% (35–54)	12% (7–19)	3% (1–8)
K Max	35% (27–43)	11% (6–17)	4% (1–8)
K Min	34% (26–42)	7% (3–13)	1% (0–5)
Serum bicarbonate values	± 3 mEq/l	± 6 mEq/l	<20 or >30 mEq/l
B Max	33% (25–41)	8% (4–14)	3% (1–7)
B Min	44% (35–53)	10% (5–16)	18% (12–26)
K Max	22% (15–30)	1% (0–5)	9% (5–15)
K Min	14% (8–20)	1% (0–5)	5% (2–10)

least ≥6.0 mEq/l. There were no significant differences in variability between intervention periods.

Effects on Serum and Dialysate Potassium and Bicarbonate

In Table 3, we show the mean serum and dialysate K and HCO3 values according to intervention periods. As expected, K Max resulted in higher mean prescribed dialysate K (3.0 mEq/l) compared to K Min (2.2 mEq/l) and a smaller serum-dialysate gradient (1.6 vs. 2.2 mEq/l, respectively). The K Max intervention utilized primarily 3 mEq/l dialysate and required a change to 2 mEq/l dialysate in only 2% of recorded treatments according to POC testing results. Dialysate changes were more frequent during K Min with a change from 2 to 3 mEq/l required in 19% of treatments.

The mean dialysate HCO3 prescribed during B Max was 34.7 compared to 30.8 mEq/l for the B Min, with mean serum HCO3 of 24.5 and 22.4 mEq/l for B Max and B Min interventions, respectively. The mean number of unique HCO3 prescriptions utilized per subject for B Max was 3.1 versus 2.7 for B Min.

CSAs

Overall, there were 45 CSAs detected, including 18 events during prerandomization usual care, during washout, or after the end of intervention but before device explant. New-onset AF accounted for the majority (63%), followed by bradycardia (25%). In Tables 4 and 5, we show the distribution of detected arrhythmias during intervention periods in terms of number (Table 4) and event duration (Table 5). There were fewer CSAs during B Min and K Min periods compared with B Max and K Max, but a longer total duration of CSAs during B Max and K Min interventions. After accounting for the level of intervention adherence, there were no significant differences in the secondary exploratory efficacy outcome (total duration of CSAs) between the B Max and B Min or K Max and K Min arms ($P > 0.05$). Additional analyses examining for sequence effects due to the cross-over study design were performed; there were no significant interactions between chronological study period and the interventions, indicating no evidence of carry-over effects between interventions.

DISCUSSION

In this randomized controlled pilot trial, we examined feasibility of utilizing POC devices in real-world dialysis clinics to direct dialysate prescription adjustment according to 4 different intervention algorithms. We found that clinical staff were able to utilize devices without difficulty and appropriately adjusted the dialysate prescription in 85% of available treatments. POC measurements were accurate compared with conventional laboratory values, however, K and HCO3 measurements drawn throughout the month varied widely compared to the monthly measurements obtained with standard-of-care. Accordingly, POC testing-guided interventions achieved the expected and clinically relevant changes in serum-dialysate concentration gradients without major differences in adverse events among treatment arms. Lastly, we did not observe significant differences in CSAs between the various K and HCO3 arms, most likely due to the rarity of events.

Multiple continuous arrhythmia monitoring studies have shown that the timing of arrhythmic events tracks the intermittent hemodialysis cycle closely.[4,7] Further, the amount and rate of dialytic solute

Table 3. Serum and dialysate potassium and bicarbonate values during the trial

Variable	B Max (n = 166)	B Min (n = 144)	K Max (n = 155)	K Min (n = 165)	Overall (n = 693)
Serum K	4.5 (0.6)	4.6 (0.7)	4.6 (0.7)	4.4 (0.6)	4.5 (0.6)
Dialysate K	2.4 (0.5)	2.4 (0.5)	3.0 (0.1)	2.2 (0.4)	2.5 (0.5)
Serum-dialysate K gradient	2.1 (0.8)	2.3 (0.71)	1.6 (0.7)	2.2 (0.9)	2.0 (0.8)
Serum HCO3	24.5 (2.7)	22.4 (2.9)	25.8 (3.3)	25.8 (2.8)	24.7 (3.2)
Dialysate HCO3	34.7 (4.4)	30.8 (4.1)	36.6 (0.8)	36.6 (0.8)	34.7 (3.8)
Serum-dialysate HCO3 Gradient	−10.1 (7.0)	−8.31 (6.4)	−10.8 (3.0)	−10.7 (2.6)	−10.0 (5.2)

HCO3, bicarbonate; K, potassium.
Values represent means (SD), and units are in mEq/l.

Table 4. Clinically significant arrhythmias detected according to the type and intervention period

Event type	B Max (n = 11)	B Min (n = 8)	Baseline (n = 5)	K Max (n = 5)	K Min (n = 3)	After intervention before ILR removal (n = 6)	During washout (n = 7)	Overall (N = 45)
Atrial fibrillation <24 hours	5 (45.5%)	7 (87.5%)	3 (60.0%)	2 (40.0%)	1 (33.3%)	6 (100%)	4 (57.1%)	28 (62.2%)
Atrial fibrillation ≥24 hours or ≥12 hours over consecutive days	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (14.3%)	2 (4.2%)
Ventricular tachycardia with heart rate ≥130 for ≥30 seconds	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bradycardia with heart rate ≤40 for ≥6 seconds	3 (27.3%)	0 (0%)	2 (40.0%)	2 (40.0%)	2 (66.7%)	0 (0%)	1 (14.3%)	10 (22.2%)
Asystole ≥3 seconds	2 (18.2%)	1 (12.5%)	0 (0%)	1 (20.0%)	0 (0%)	0 (0%)	1 (14.3%)	5 (11.1%)
Interruption in data	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Any clinically significant arrhythmias	11 (100%)	8 (100%)	5 (100%)	5 (100%)	3 (100%)	6 (100%)	7 (100%)	45 (100%)

ILR, implantable loop recorder.

removal, governed by the choice of dialysate composition and the resulting serum-to-dialysate gradient, has been linked to arrhythmic risk. In the case of K, lower dialysate K concentrations and higher serum-to-dialysate K gradients have been associated with higher risks of hospitalization[14] and sudden death.[15,16] Higher serum and dialysate HCO3 levels have also been associated with sudden death, perhaps due to the tendency for alkalosis to promote hypokalemia.[17,18] Conversely, hyperkalemia and acidosis from insufficient removal also contribute to cardiac events.[18,19] Although the specific benefits of alternative approaches to serum-dialysate gradient prescribing need to be validated in randomized trials, current standard practices regarding predialysis serum electrolyte level monitoring may also amplify the cardiac risks associated with dialysis. First, laboratory results are typically not available until days after the treatment, obviating opportunity for real-time, tailored dialysate prescribing. Second, predialysis chemistries are usually measured on a monthly basis, and the dialysate prescription is written for the entire month on the basis of a single measure without knowledge of treatment-to-treatment variability.

Our findings demonstrate that predialysis serum K and HCO3 have marked treatment-to-treatment variability and differ substantially from monthly values. Therefore, uniform monthly dialysate prescriptions based on a single chemistry measurement are likely to cause wide variations in serum-to-dialysate gradients which are unobserved and likely unintended. Given the rapid flux in serum chemistry during dialysis, POC testing would also seem to be an appropriate application to reduce risk in outpatient dialysis clinics where central laboratory access is limited. POC testing has the potential to transform dialysis prescriptions from a currently crude, essentially unguided clinical practice to an example of "precision medicine." Despite wide availability, to our knowledge, this is the first study to examine POC chemistry devices in the setting of maintenance HD. Our results show that this technology and algorithms incorporating the results can be adopted with relative ease and precision without substantial disruptions to clinic workflow.

Our POC testing-guided K algorithms were limited by the general availability of only 2 dialysate K concentrations; however, the algorithms succeeded in achieving a change in the concentration gradient (0.6 mEq lower in K Max vs. K Min). Despite the differential gradients, changes in predialysis serum K were minimal. Neither algorithm was associated with increased rates of dyskalemia or other adverse events. Based on this data, it appears that either K algorithm may be reasonable to employ without significant safety concerns until more definitive data is obtained.

Dialysate HCO3 concentration is determined by on-board proportioning and concentration choice is much less limited compared to dialysate K. Therefore, the B Max and B Min algorithms resulted in a greater diversity of dialysate HCO3 concentrations and serum-dialysate gradients in the expected directions. This also resulted in wider differences in predialysis serum

Table 5. Duration of clinically significant arrhythmia (seconds) according to the intervention period

Event duration	B Max (n = 11)	B Min (n = 8)	K Max (n = 5)	K Min (n = 3)
Duration of event: seconds				
Mean (SD)	7950 (26,000)	1020 (2060)	61 (56)	497 (817)
Median [Min, Max]	105 [3, 86,400]	120 [3, 6000]	44 [3, 120]	38 [12, 1440]
Log duration (s)				
Mean (SD)	4.4 (2.8)	5.3 (2.2)	3.5 (1.6)	4.5 (2.5)
Median [Min, Max]	4.7, [1.1, 11.4]	4.8 [1.1, 8.7]	3.8 [1.1, 4.8]	3.6 [2.5, 7.3]

Clinically significant arrhythmias included atrial fibrillation, ventricular tachycardia ≥130 beat per minute for ≥30 seconds, asystole ≥3 seconds and bradycardia at rate ≤40 beat per minutes for ≥6 seconds. Pairwise comparisons of log duration between intervention arms (B Max vs. B Min, K Max vs. K Min) did not reveal any significant differences.

HCO3 levels, with more concentrations <20 mEq/l during B Min. Although our algorithms were designed based on published observational data to avoid extremes,[18] our results suggest that higher dialysate HCO3 concentrations than the mean levels used in the protocol (31 mEq/l) are needed to consistently avoid acidosis; it also illustrates the potential tradeoffs between minimizing serum-dialysate gradients and achieving target predialysis serum levels. As with K, there were no obvious adverse clinical sequelae of abnormal HCO3 concentrations and no hospitalizations attributed to acid-base abnormalities in this short term study.

Similar to other monitoring studies, we detected a higher frequency of AF and bradycardias compared to ventricular arrhythmias. Although there were small, numerical differences in the number or duration of arrhythmia among arms, none achieved statistical significance. Our results are compatible with differential effects of the 4 algorithms on the risk of arrhythmia; however, the small number of events precludes meaningful conclusions about efficacy. Larger hypothesis testing trials are needed to detect meaningful differences in clinically important outcomes.

Several limitations should be acknowledged. This trial was designed as a pilot and feasibility trial. Although the limited sample size and enrollment at 2 academic centers and 3 HD units (1 owned by a large dialysis organization, 2 privately owned) were sufficient to demonstrate that POC testing-guided dialysate prescriptions could be implemented with high fidelity in the context of typical United States dialysis practices, success in this context does not rule out additional challenges to implementation more broadly across the landscape of dialysis organizations in the United States or elsewhere. Due to subject dropouts and challenges in recruitment due to the COVID-19 pandemic, we approached but did not achieve the target of 20 subjects as planned for our secondary arrhythmia efficacy outcome of CSAs, which diminished our ability to detect differences. Women were underrepresented; therefore, generalizability may be affected. Despite ongoing questions about its safety, we were unable to incorporate <2 mEq/l K dialysates into the algorithms because use of <2 mEq/l K concentrates is strictly regulated and often banned outright by dialysis facilities in the United States. Lastly, we did not check postdialysis chemistries or account for differences in other prescription parameters such as ultrafiltration rate or dialysate sodium, calcium, and magnesium concentrations. Each of these would have provided additional information about effect modifiers of the tested interventions but is likely to be better studied in well-powered definitive trials.

In conclusion, in this pilot randomized trial, we demonstrated that a POC chemistry-guided approach to the dialysate K and HCO3 prescription can be readily implemented in the outpatient setting. With the exception of the HCO3 minimization algorithm, the tested K and HCO3 algorithms appeared to be safe, were associated with a low incidence of clinically important electrolyte abnormalities, and resulted in markedly different dialysate-serum concentration gradients. Definitive studies to test whether the use of these algorithms in place of once-monthly, standard HD prescriptions reduces the rate of sudden death or CSAs are warranted.

DISCLOSURE

PHP has received investigator-initiated research funding from Medtronic; honoraria from the American Society of Nephrology and the National Kidney Foundation; and consulting fees from Fresenius Kidney Care North America, AstraZeneca, Janssen, Relypsa, and Ardelyx. SMA received modest research funding that has ended from Medtronic and Boston Scientific paid to her institution. DMC has received investigator initiated funding from Medtronic as well as consulting fees from Medtronic, Eli Lilly, Boehringer Ingelheim, Astra Zeneca, Allena Pharmaceuticals, Gilead, Novo Nordisk, Glaxo Smith Kline, Merck, Amgen, CSL Behring, Zogenix, and Renalytix, and research funding, Gilead, NovoNordisk, and Amgen. All the other authors have declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Appendix: Recruitment Metrics results.

Table S1. Intervention treatment algorithm for dialysate potassium.

Table S2. Intervention treatment algorithm for dialysate bicarbonate.

Table S3. Summary of available treatments and adherence according to intervention period.

Table S4. Results of staff survey on acceptability/barriers to intervention delivery.

Table S5. Summary of serious and nonserious adverse events.

Table S6: Comparison of point of care-obtained laboratory values and standard laboratory values obtained predialysis on the same day.

CONSORT Checklist.

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