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ORIGINAL ARTICLE

Adequacy

Achieving high convective volume in hemodiafiltration: Lessons learned after successful implementation in the HDFit trial

Murilo GUEDES,[1†] Ana Claudia DAMBISKI,[2†] Sinaia CANHADA,[3] Ana Beatriz L. BARRA,[3] Carlos Eduardo POLI-DE-FIGUEIREDO,[4] Américo Lourenço CUVELLO NETO,[5] Maria Eugênia F. CANZIANI,[6] Jorge Paulo STROGOFF-DE-MATOS,[7] Jochen G. RAIMANN,[8] John LARKIN,[1,9] Bernard CANAUD,[9,10] and Roberto PECOITS-FILHO,[1] For the HDFIT Study Investigators

[1]School of Medicine, Pontificia Universidade Catolica do Parana, Curitiba, [3]Fresenius Medical Care Brazil, [7]Clínica de Diálise Ingá, Rio de Janeiro, [4]Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, [5]Hospital Alemão Oswaldo Cruz, [6]Universidade Federal de São Paulo, São Paulo, [2]Irmandade da Santa Casa de Misericórdia de Curitiba, Curitiba, Paraná, Brazil, [8]Renal Research Institute, New York,

Correspondence to: Roberto Pecoits-Filho, MD, PhD, FASN, FACP, School of Medicine, Pontifícia Universidade Católica do Paraná; Imaculada Conceição,1155, Curitiba, PR 80215-901, Brazil. E-mail: r.pecoits@pucpr.br

[†]Co-first authors who contributed equally to the article.

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New York, [9]Fresenius Medical Care, Global Medical Office, Bad Homburg, Germany and [10]Montpellier University, Montpellier, France

Abstract

Background and objectives: High-volume online hemodiafiltration (OL-HDF) associates with improved outcomes compared to hemodialysis (HD), provided adequate dosing is achieved as estimated from convective volume (CV). Achievement of high CV and its impact on biochemical indicators following a standardized protocol converting HD patients to OL-HDF has not been systematically reported. We assessed the success of implementation of OL-HDF in clinics naïve to the modality.

Design, setting, participants, and measurements: We analyzed the results of the implementation of postdilution OL-HDF in patients randomized to the HDF arm of a clinical trial (impact of hemoDiaFIlTration on physical activity and self-reported outcomes: a randomized controlled trial (HDFit) trial [ClinicalTrials.gov:NCT02787161]). The day before randomization of the first patient to OL-HDF at each clinic staff started a 3-day in-person training module on operation of Fresenius 5008 CorDiax machine in HDF mode. Patients were converted from high-flux HD to OL-HDF under oversight of trainers. OL-HDF was performed over a 6-months follow-up with a CV target of 22 L/treatment. We characterized median achieved CV >22 L/treatment record and analyzed the impact of HDF on biochemical variables.

Results: Ninety-seven patients (mean age 53 ± 16 years, 29% with diabetes, and 11% had a catheter) from 13 clinics randomized to the OL-HDF arm of the trial were converted from HD to HDF. Median CV > 22 L/treatment was achieved in 99% (94/95) of OL-HDF patients throughout follow-up. Monthly mean CV ranged from 27.1 L to 27.5 L. OL-HDF provided an increased single pool Kt/V at 3-months (0.2 [95% CI: 0.1–0.3]) and 6-months (0.2 [95% CI: 0.1–0.4]) compared to baseline, and reduced phosphate at 3-months (−0.4 mg/dL [95% CI: −0.8 to −0.12]) of follow-up.

Conclusions: High-volume online hemodiafiltration was successfully implemented with 99% of patients achieving protocol defined CV target. Monthly mean CV was consistently >22 L/treatment during follow-up. Kt/V increased, and phosphate decreased with OL-HDF. Findings resulting from a short training period in several dialysis facilities appear to suggest HDF is an easily implementable technique.

Keywords: Hemodiafiltration, convective volume, end-stage kidney disease, dialysis, dialysis adequacy, quality assurance and improvement

INTRODUCTION

Renal replacement therapies through conventional diffusion methods, such as hemodialysis (HD), have considerably improved end-stage kidney disease (ESKD) patients' survival over the last decades.[1] The accumulation of medium size molecules and toxins bound to proteins, however, is thought to contribute to increased cardiovascular risk and overall mortality in HD patients.[2,3] High-volume online hemodiafiltration (OL-HDF), a technique that combines both convective and diffusion methods, yields an increased overall solute clearance with a broadened spectrum of solute removal for medium and larger molecular weight uremic toxins.[1] High-volume online hemodiafiltration is associated with improved outcomes among ESKD patients, compared to conventional HD.[1,2] However, the clinical benefits of OL-HDF appear to be dose-dependent on the achievement of high CVs.[4]

Despite data supporting clinical benefits of OL-HDF, the global prevalence of use as a renal replacement therapy (RRT) is approximately 10% with the majority of ESKD patients using the modality being distributed across Europe (26%) and Asia (11%). In Latin America, only 1% of dialysis patients utilize OL-HDF as a RRT.[3] One of the potential reasons for limited adoption might be the perception of difficulties in implementation of OL-HDF in clinics who are naïve to this RRT The feasibility of implementing high CV with OL-HDF is debated and has not been systematically explored.[5] We hypothesized adoption of OL-HDF with high CV targets would be easily implementable provided adequate technology and

systematic staff training is provided. Thus, to test this hypothesis, we used data from the OL-HDF treated arm of the impact of hemoDiaFIlTration on physical activity and self-reported outcomes: a randomized controlled trial (HDFit) randomized controlled trial (RCT) conducted in Brazil that used a standardized protocol to convert HD patients to OL-HDF in clinics that were naïve to the OL-HDF modality. We assessed the success of implementation of OL-HDF in the trial by the achievement of high CV and evaluated the impacts on several biomarkers of solute clearance.

MATERIALS AND METHODS

Study design

We performed a post hoc analysis of the HDFit trial limited to patients randomized to the HDF arm of the trial. The HDFit trial was a prospective, multi-centric, unblinded, RCT investigating the impact of postdilution OL-HDF on measured physical activity levels versus high-flux HD (www.ClinicalTrials.gov: NCT02787161). The study design and methodology of the HDFit trial have been previously published.[6] For this study that focused on the implementation of high-volume OL-HDF only patients who were randomized to the HDF arm were included. The main results of the HDFit trial are published elsewhere (REF).[7]

Setting and participants

Fourteen outpatient dialysis clinics across the southern regions of Brazil acted as recruitment sites. Informed consent was obtained from the participants prior to study activities. Adult (age ≥18 years) ESKD patients on HD ≥ 3 and ≤24 months prior to randomization, using a fistula/graft or permanent central venous catheter with adequate flow, presenting a previous Kt/V ≥ 1.2, who were considered clinically stable were included in the study. We excluded patients who were participating in another trial, had a severe limitation in mobility/ambulation, were non-adherent with HD, and/or had a life expectancy of <3 months due to a nonrenal comorbidity.

Assessments

Demographics, comorbidities, and other parameters were captured at baseline. The most recent monthly laboratory results were captured from standard-of-care medical records for pre-/post-HD blood urea nitrogen (BUN) and hemoglobin (Hgb), as well as quarterly values for albumin, potassium, calcium, phosphate, and intact parathyroid hormone. Single-pool Kt/V was calculated from BUN levels.[8]

Dialysis treatment characteristics, dialysis access events/issues, and the occurrence of intra-dialytic hypotension (IDH) events were captured during routine treatments in the interventional period. Patients were defined as having achieved protocol CV targets if the median across all recorded sections was ≥22 L/treatment. Monthly CV data were considered missing if there was less than one record, and all available data were used to estimate the per-patient means.

Table 1 OL-HDF implementation protocol design

Modality	Online postdilution OL-HDF AutoSub *plus*
Dialyzer	FX CorDiax HDF
Anticoagulation	Perclinic protocol (initial bolus and pump infusion)
Needle size	15 G
Arterial pressure	−200 mmHg
Blood flow	400 mL/min
Target convective volume	22 L
Sodium (mmol/L)	138
Potassium (mmol/L)	2
Calcium (mmol/L)	1.5
Bicarbonate (mmol/L)	32
Glucose (mmol/L)	5.5

Dialysis, machines, and equipment

Study site clinics were provided two high-volume OL-HDF. Clinics were provided dialyzers, bloodlines, and concentrates throughout the trial for performing OL-HDF treatments during the 6-months follow-up.

Postdilution high-volume OL-HDF was performed using the AutoSub plus function. The protocol is summarized in Table 1. Centers were allowed to define the heparin adjustment and dosage according to their protocols but were instructed to administer the initial third part of the doses as a bolus in the beginning of the session and the remaining dosage to be infused throughout the rest of the session using infusion pumps.

Staff training protocol

A single nurse certified in OL-HDF by the study sponsor recruited and trained a group of five nurses who were responsible for training staff in the clinics using a

standardized *train-the-trainer* protocol. Each one of the nurses was responsible for the implementation and monitoring of the OL-HDF treatment.

Technicians, registered nurses, and nephrologists from each clinic participated in a standardized in-person 3-day training program, which was performed the day before randomization of the first patient to OL-HDF. The schedule on the first day consisted of lectures containing the basic principles and characteristics of OL-HDF treatment, followed by a hands on training on the use of the OL-HDF machine.

During the second day, clinic health care providers were instructed to setup the OL-HDF machines and start treatments in patients who were randomized to OL-HDF in the trial. Trainers provided oversight of OL-HDF machine setup and monitoring of patients during treatment by clinic staff. This was succeeded by review of clinical research forms and further training in data registration. During the third day, another practical task was performed, and assessment of knowledge was performed using a structured test. All centers receive the same training and evaluation.

The study training teams visited all centers 3- and 6-months later to certify the implementation of the designed protocol, as well as to offer support to any questions related to the OL-HDF technology. Centers were advised to contact study teams with any questions and were provided ad-hoc support.

Statistical analysis

Data distributions were assessed for normality. Continuous variables are summarized as means and standard deviations (SD), or medians and interquartile ranges (IQR). Categorical variables are reported as counts and proportions. When appropriate, Student's t-tests or Mann-Whitney rank-sum-U tests were used. Intra-group comparisons were made using paired t-tests over time periods. Normalized protein catabolic rate (nPCR) and the creatinine index were calculated based on previous validated formulas.[9,10] Considering the low rate of dropout from the trial and the low proportion of overall missing data, missingness for biochemical and body mass composition variables was assumed to be completely at random (MCAR).

RESULTS

HDFit randomized 195 patients (OL-HDF n = 97, HD n = 98) from 13 of the 14 clinics invited to recruit study patients. We used data from patients randomized to the OL-HDF arm in this analysis. The overall population characteristics of HDF patients are shown in Table 2 (mean age 53 ± 15.9 years, 29% with diabetes, 14% with coronary artery disease, and 11% used a tunneled central venous catheter). There was a 8% dropout rate in the OL-HDF arm, which was similar to the rate in HD arm (11%).

Among patients randomized to OL-HDF, 95 patients had CV data recorded (median = 70 treatments recorded per patient) and were included in this analysis. Median effective treatment time (was 235 minutes (25th and 75th quartiles = 233 and 240)). Median CV > 22 L/treatment was achieved in 99% (94/95) of patients during follow-up. The mean time aggregated blood flow was 362 ± 23 mL/min. Monthly mean CV ranged from 27.1 L to 27.5 L (Figure 1). Patient's characteristics stratified by achieved CV are depicted in Table 3. The mean blood flow at baseline across vascular access categories was 345.7 ± 26.2 mL/min, 359.2 ± 11.2 mL/min, and 364.5 ± 22.4 for permanent catheter (n = 11), vascular graft (n = 5), and AV fistula (n = 79), respectively. The mean achieved CVs were 27.2 ± 2.4 L, 27.5 ± 1.3 L, and 27.7 ± 2.5 for permanent catheter, vascular graft, and AV fistula, respectively. Mean blood flow and mean achieved CV did not differ according to vascular access type.

The changes from baseline for laboratory variables are shown in Table 4 and Figures 2 and 3. The predialysis concentration of BUN was reduced by −7.3 mg/dL [95% CI: −10.4 to −4.3] at 3 months and −4.1 mg/dL [95% CI: −7.4 to −0.7] at 6 months compared to baseline. Postdialysis BUN also showed consistent reductions at 3- and 6 months: −4.7 [95% CI: −6.0 to −3.3] and −3.4 [95% CI: −5.2 to −1.6], respectively. Moreover, the single-pool Kt/V increased 0.2 [95% CI: 0.1–0.3] from baseline to 3 months, with sustained differences at 6 months: 0.2 [95% CI: 0.1–0.4]. Phosphate levels were reduced at 3 months (−0.4 mg/dL [95% CI: −0.8 to −0.12]) and had trends to be lower at 6 months (−0.3 mg/dL [95% CI: −0.7 to 0.002]). Additionally, potassium concentrations had trends of a cumulative reduction over time: −0.06 mmol/L [95% CI: −0.2–0.09] at 3 months and −0.14 mmol/L [95% CI: −0.3 to 0.02] at 6 months vs. baseline.

The concentration of hemoglobin showed a tendency to increase at 3 months (0.4 g/dL [95% CI: −0.02 to 0.7]), followed by a slight reduction at 6 months (−0.3 g/dL [95% CI: −0.7 to 0.07]). The proportion of patients with hemoglobin greater or equal than 9 g/dL at baseline, 3 months and 6 months were 90%, 95%, and 86%, respectively. The concentrations of Ferritin and TSAT remained stable over time (Table 4). The proportion of

Table 2 Baseline patient characteristics

Parameters	HDF
Demographics	
Patient number	97
Age (years)	52.6 (15.9)
Male (%)	71 (73.2)
Race White (%)	61 (62.9)
Height (cm)	168.3 (8.7)
Family income level	
>10 minimum wages (%)	7 (4)
Four to 10 minimum wages (%)	26 (13)
Two to Four minimum wages (%)	50 (26)
<2 minimum wages (%)	14 (7)
Transportation type to clinic	
Family car (%)	43 (22)
Public transportation (%)	29 (15)
Ambulance (%)	19 (10)
Taxi (%)	4 (2)
Walk (%)	2 (1)
Clinical Characteristics	
Estimated dry weight (kg)	73.8 (15.2)
BMI (calculated by post-HD weight) (kg/m^2)	26.0 (4.2)
BSA (Dubois calculation by post-HD weight) (m^2)	1.83 (0.2)
Catheter (%)	11 (11.3)
Predialysis weight (kg)	76.2 (15.1)
Postdialysis weight (kg)	73.9 (14.9)
Predialysis SBP (mmHg)	155 (24)
Predialysis DBP (mmHg)	81 (13)
Predialysis pulse (beats per minute)	74 (12)
Postdialysis SBP (mmHg)	151 (25)
Postdialysis DBP (mmHg)	79 (13)
Postdialysis pulse (beats per minute)	73 (12)
Comorbidities	
Diabetes (%)	28 (28.9)
Coronary artery disease (%)	14 (14.4)
Congestive heart failure (%)	5 (5.2)
Laboratory values	
Pre-HD BUN (mg/dL)	58.8 (12.9)
Post-HD BUN (mg/dL)	16.4 (6.3)
Single pool Kt/V	1.6 (0.4)
Albumin (g/dL)	4.0 (0.3)
Potassium (mEq/L)	5.2 (0.7)
Calcium (mg/dL)	9.0 (0.7)
Phosphate (mg/dL)	5.2 (1.4)
Intact parathyroid hormone (pg/mL)	340 (266)
Hemoglobin (g/dL)	11.3 (1.6)

BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; DBP, diastolic blood pressure; DRT, dialysis recovery time; HDF, high-volume online hemodiafiltration; SBP, systolic blood pressure;

patients who were prescribed erythropoiesis stimulating agents (ESA), exclusively EPO-alpha for participating patients, reduced over time from 89% at baseline to 77%

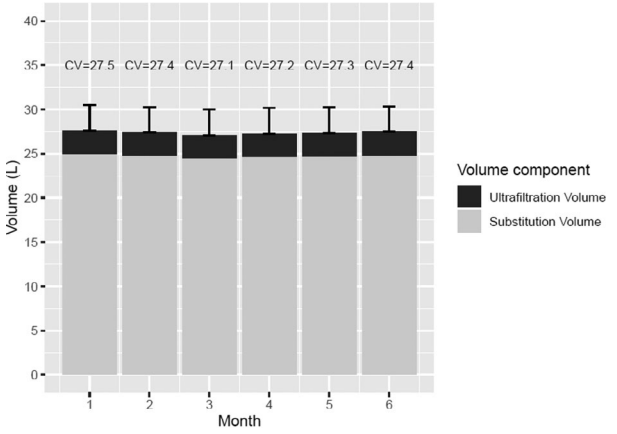

Figure 1 Mean achieved convective volume by components per month. CV: convective volume.

at 6 months (*P*-value = 0.03) (Figure 4). The albumin baseline concentration was 40 g/L and there was a slight reduction over time both at 3 months (−1.0 g/L [95% CI: −1.8 to −0.16]) and at 6 months (−0.8 g/L [95% CI: −0.15 to −0.07]). The proportion of patients with albumin greater or equal than 35 g/L was 92% at baseline, 84% at 3 months, and 88% at 6 months. nPCR was 1.13 ± 0.3 g/kg/day, 1.10 ± 0.30 g/kg/day, and 1.65 ± 0.34 g/kg/day at baseline, 3 and months, respectively. The creatinine index was 13.8 ± 1.0 mg/kg/day, 13.7 ± 1.0 mg/kg/day, and 13.7 ± 1.0 mg/kg/day at baseline, 3 months and 6 months, respectively. Mean body mass index (BMI) was 26.8 ± 4.2 kg/m^2, 27.1 ± 4.1 kg/m^2, and 27.1 ± 4.2 kg/m^2, at baseline, 3 and 6 months, respectively. Consistently, for baseline, 3 and 6 months, lean tissue mass (LTM) was 37.6 ± 10.5 kg, 37.1 ± 10 kg, and 38.6 ± 9.9 kg. Finally, there were no detectable changes in mean CRP over time (Table 4).

There were three serious adverse events that included hospitalization or mortality and two nonserious adverse events reported in patients on OL-HDF, all events were determined to be unrelated to the treatment. The incidence of IDH, as defined by European Best Practice Guidelines criteria,[11] occurred in 12 treatments per 100 patient months.

DISCUSSION

High-volume online hemodiafiltration has increased globally as a mode of RRT due to described superior clinical outcomes when compared to HD,[2,3] but there is still a perception that the clinical implementation of HDF is

Table 3 Patient characteristics by achieved tertiles of convective volume

Achieved convective volume (L)	20.1, 26.7	26.7, 28.7	28.7,32.9
n	32	31	32
Age (years)	50.5 ± 16.6	51.9 ± 16	54.6 ± 16
Diabetes mellitus 2 (%)	8 (25)	12 (39)	7 (22)
White (%)	24 (75.0)	17 (54.8)	18 (56.2)
Cardiovascular disease (%)	6 (19)	8 (26)	7 (22)
Catheter (%)	5 (15.6)	3 (9.7)	3 (9.4)
Male (%)	20 (62.5)	26 (83.9)	23 (71.9)
spKt/V	1.67 ± 0.5	1.46 ± 0.4	1.61 ± 0.4
Hematocrit (%)	34.77 ± 6.0	33.42 ± 4.9	33.37 ± 4.9
Albumin (g/L)	39 ± 3.0	40.3 ± 3.0	39.6 ± 3.0

complex. Herein, we describe the implementation of a protocol to achieve high CVs in a group of clinics that were naïve to HDF participating in a multicentric RCT. The main finding of the present study was that a CV greater than 22 liters per treatment was achieved in the vast majority of patients with no safety concerns and improvement in solute removal efficiency.

We used for the present analysis the experience in implementing high-volume OL-HDF in Brazil, which followed a standardized protocol including a structured approach to training and technical support over a 6-month follow-up period. In our protocol, we actively recommended a high blood flow target (advocating for the selection of patients with optimal vascular access conditions). All sites had 15-gauge needles provided to standardized cannulation of arteriovenous accesses for OL-HDF. Interestingly, our results suggest achievement of high CV was possible across different vascular access types, comorbidities, and baseline biochemical variables.

In fact, we achieved the 22 L/treatment CV target in 99% of patients. Our mean achieved CV was 27 L/treatment throughout the entire study period, which is greater than the reported results of previous RCTs in OL-HDF.[12–14] Some aspects of our protocol and design could explain these results. Compared to the Turkish trial and to the CONTRAST, our achieved blood flows and treatment times were higher, which could partially explain the achievement of higher convection volumes.[12,14] On the other hand, compared to the estudio de supervivencia de hemodiafiltración online (ESHOL) study, our results regarding blood flow and dialysis session time are similar, although our achieved volumes are about 3 L higher per treatment.[13] Population characteristics could explain these results, as we included individuals on average younger than those in ESHOL.[13] The potential impact of the

Table 4 Change from baseline for biochemical variables

Variable	Change from baseline (months)	Estimate	Lower CI	Upper CI	*P* value
BUN Pre (mg/dL)	3	−7.3	−10.4	−4.3	<0.01
	6	−4.1	−7.4	−0.7	0.02
BUN Post (mg/dL)	3	−4.7	−6.0	−3.3	<0.01
	6	−3.4	−5.2	−1.6	0.01
URR	3	5.3	3.3	7.2	<0.01
	6	4.2	2.1	6.4	<0.01
KTV	3	0.2	0.1	0.3	<0.01
	6	0.2	0.1	0.3	<0.01
Phosphate (mg/dL)	3	−0.4	−0.8	−0.1	<0.01
	6	−0.3	−0.7	0.002	0.05
Potassium (mmol/L)	3	−0.1	−0.2	0.1	0.43
	6	−0.1	−0.3	0.02	0.08
Albumin (g/L)	3	−1.0	−1.8	−0.16	0.02
	6	−0.8	−1.5	−0.07	0.03
Hemoglobin (g/dL)	3	0.4	−0.02	0.7	0.06
	6	−0.3	−0.7	0.07	0.11
Ferritin (ng/mL)	3	−31.3	−89.6	26.9	0.29
	6	18.1	−64.9	100.9	0.6
TSAT (%)	3	0.9	−4.1	5.9	0.72
	6	0.03	−3.8	3.9	0.99
CRP (mg/L)	3	−1.8	−6.3	2.6	0.41
	6	0.24	−6.0	6.4	0.93

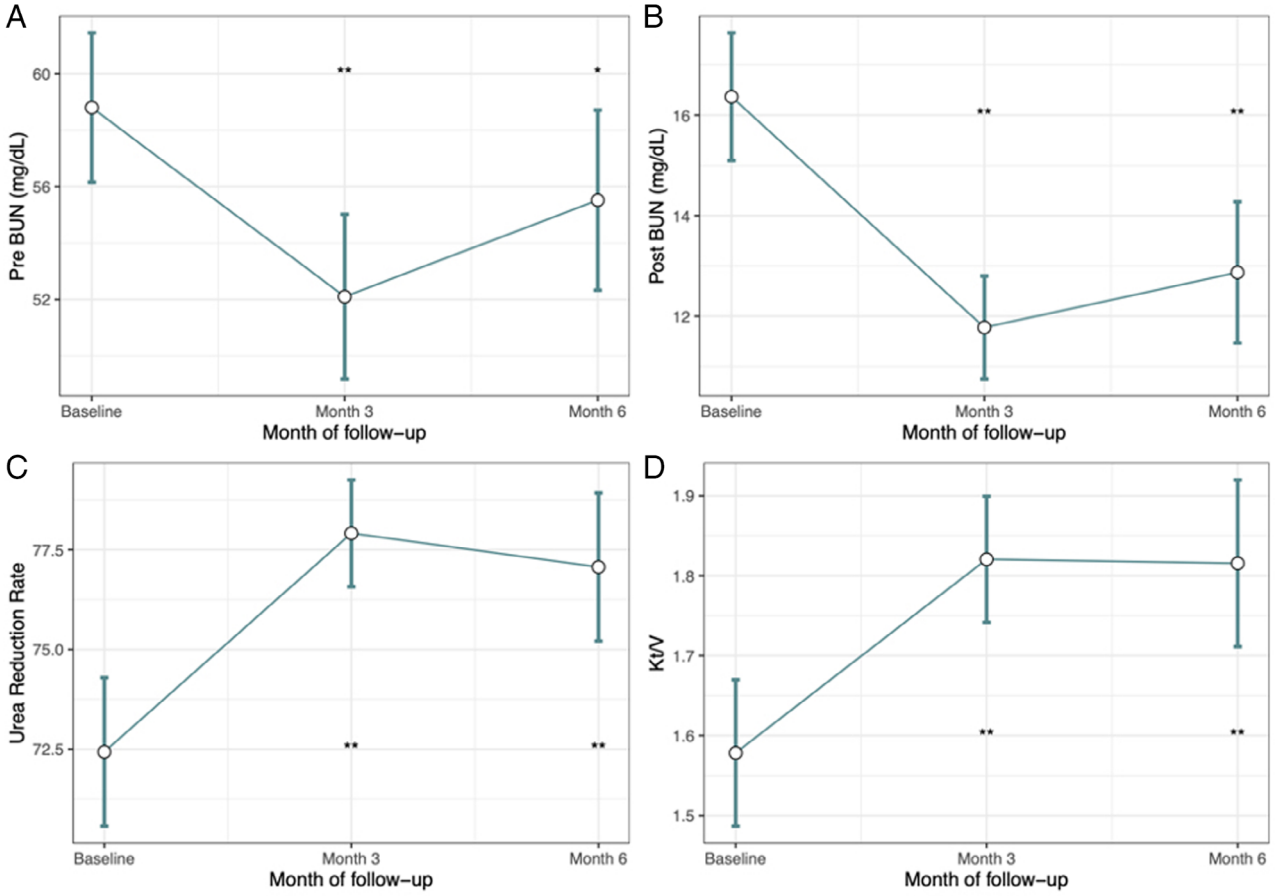

Figure 2 Plots of concentrations of predialysis BUN (A), postdialysis BUN (B), urea reduction rate (C) and Kt/V (D). *P value < 0.05; **P value < 0.01. [Color figure can be viewed at wileyonlinelibrary.com]

achievement of higher CV on clinical outcomes can be projected to be clinically relevant, based on the results on large observational studies and RCTs.[12–15] *Post hoc* analyses of RCTs have shown that patient survival is dose dependent in OL-HDF-treated groups highlighting that higher is the CV better is the outcome.[4,12,14]

Interestingly, we observed that high-volume OL-HDF had a positive impact on the reduction in predialysis concentration of uremic retention molecules, a slight decrease in potassium levels and a decrease in phosphorus levels. There was a reduction of potassium over the 6-months follow-up. Although not statistically significant, the effect sizes within the 95% CI for changes are up to 0.3 mmol/L. Previous studies in chronic hyperkalemia demonstrated the risk of cardiovascular events is continuous for potassium ranges above 5 mmol/L.[16] Therefore, consistent reductions compatible with the effect size we showed could represent a net cardiovascular benefit in this population.

Similar to previous reports, there was a slight reduction in serum albumin, although the proportion of patients with albumin lower or equal than 35 g/L was small. Importantly, our results do not suggest that the changes observed are due to deterioration in nutritional status, since nPCR, creatinine index, BMI and LTM remained unchanged over the time. In fact, these results suggest OL-HDF is neutral regarding nutritional parameters such as catabolic rate and lean body mass, which might represent a benefit in terms of maintenance of nutritional status over time. Our results might be explained by the complex interaction of hemorheological conditions (i.e., high transmembrane pressure, high shear stress, high protocrit) required by HDF, in particular postdilution condition, the high-flux membrane type and dialyzer geometry (i.e., high or low internal blood flow resistance). All these factors contribute to albumin leakage. As previously described, all high-flux dialyzers are not suited for HDF with high albumin loss at all

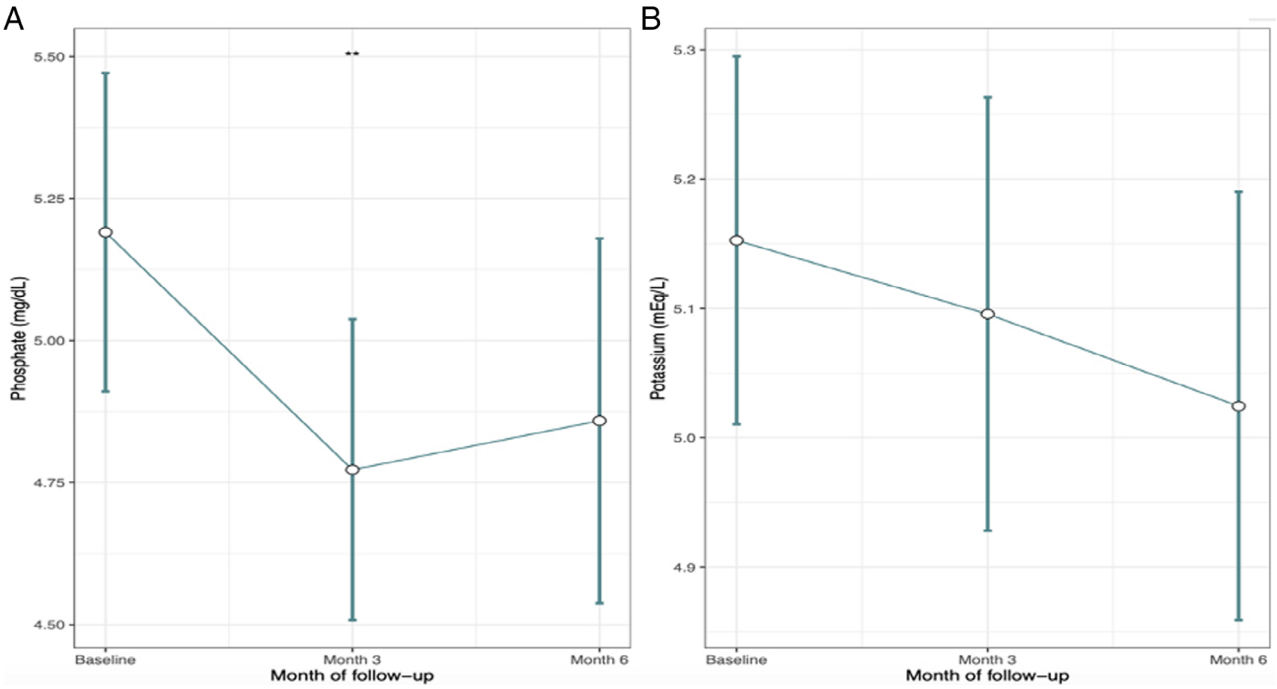

Figure 3 Concentrations of phosphate and potassium over time. ***P* value < 0.01. [Color figure can be viewed at wileyonlinelibrary.com]

operating conditions, but all high-flux dialyzers including Cordiax FX have a potential for albumin leakage at high convective rate.[17] These results also confirm previous findings in observational studies and RCTs with other membranes.[1, 4,18,19]

Interestingly, we observed that ESA prescriptions tended to reduce over time in patients receiving high-volume HDF, while hemoglobin and iron parameters remained relatively stable over time, leading prescribing physicians to discontinue ESA treatment during the study. The findings of lower ESA requirements in HDF are consistent with previous studies.[20–22] There are multiple mechanisms by which HDF could reduce the need for ESA prescriptions over time.[20] Particularly, a potential removal of middle size uremic toxins may reduce systemic inflammation, thereby resulting in better iron utilization and less resistance to ESA action over time.[20] Also, high-volume HDF may lead to better volume management, which can increase hemoglobin levels by reducing the hemodilution observed in fluid overloaded patients leading to a reduction in the need for ESA.[21] In light of the new evidence of the potential ESA-sparing benefit of HDF, these findings may imply that a reduction in the need for ESA observed in the HDF patients may be a potential mediator of the improved cardiovascular outcomes observed in previous trial when compared to conventional hemodialysis.[23] Additionally, the observed reduction in the ESA prescription may have implications regarding the pharmaco-value of HDF.[24] Finally, we reported few adverse events in this study and none of them were adjudicated to be related to OL-HDF. Additionally, our incidence of IDH was lower than previously reported in OL-HDF RCTs.[13]

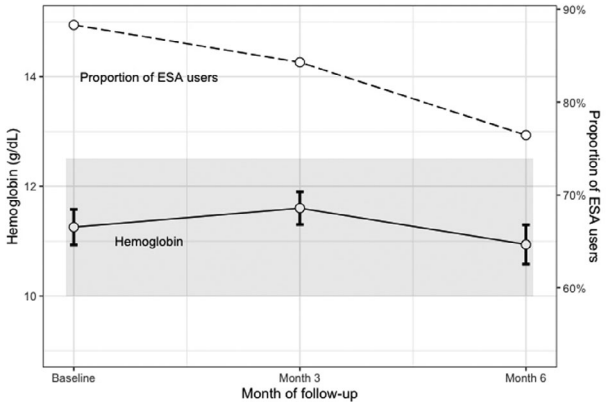

Figure 4 Mean hemoglobin and proportion of ESA users over follow-up. Shaded areas refer to treatment hemoglobin targets according to the KDIGO Guidelines.

The main limitation of this study is that this is a uncontrolled single-arm post hoc analysis, with the inherent limitations associated with such design. However, in the original trial published elsewhere similar trends in solute removal were observed. In addition, we included individuals with optimal vascular access conditions, who were younger and presented less comorbidities that the typical HD population. Also, we did not collect information on residual kidney function. On the other hand, our study has several strengths. We successfully implemented a protocol in naïve clinics in multiple centers resulting in optimal achievement of high CV. By protocol, we provided detailed information to the centers regarding HDF prescription and monitored the performance during the visits throughout the study. We therefore provide evidence showing OL-HDF implementation can be done in a relatively simple manner, given that technical training and monitoring are provided, which generalizes and confirms results from observational studies evaluating the feasibility of high-volume OL-HDF.[5]

In summary, in this post hoc analysis of the intervention arm of a RCT, we showed that HDF was successfully implemented in naïve clinic with 99% of patients achieving the protocol CV target, which was consistently >22 L/treatment during the entire follow-up. HDF provided high Kt/V throughout the follow-up and led to lower phosphate levels at 3 months compared to baseline, as well as lower ESA requirements over time and stability for nutritional parameters. These findings resulting from a short period of systematic training, suggesting that the implementation of high-volume HDF is an simple and feasible in clinics that are naïve to the modality.

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STATEMENTS OF ETHICS

The trial was managed by the Center for Epidemiology and Clinical Research (EPICENTER), an academic clinical research organization (ACRO) at Pontifícia Universidade Católica do Paraná (PUCPR). Informed consent was obtained from the participants prior to study activities. The trial was conducted in adherence with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the design and interpretation of the data, as well as revised critically the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work, including its accuracy and integrity. M.G. and A.C.D. participated in the design, analysis, and interpretation of the data for the current study and were primarily responsible for the written content in the manuscript. M.G. was responsible for the data analysis in the study. S.C. participated was responsible for the design and implementation of the training protocol in the trial and provided the content for the manuscript. A.B.B., C.E.P.F., A.L.C.N., M.E.F.C., and R.P.F. were primarily responsible for the study design and implementation and actively participated in the review process. J.G.R., J.L., J.P.S.M., and B.C. participated in the design, contributed considerably to the content of the manuscript and revised critically the analysis and the drafts. R.P.F. was responsible for design and implementation of the trial and for the current sub analysis, contributed to data analysis interpretation, wrote, revised and supervised the process for the final draft.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix A: HDFIT Study Site Investigators and Trial Leadership.
Appendix B: EPICENTER ACRO HDFIT Key Leadership and Affiliates.