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Expanded Hemodialysis and Its Effects on Hospitalizations and Medication Usage: A Cohort Study

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Keywords
Colombia · Kidney failure · Hemodialysis · Expanded hemodialysis · Hospitalization · Medium cut-off membranes

Abstract
Introduction: Expanded hemodialysis (HDx) effectively removes large middle molecular uremic toxins (>25 kDa) while still retaining albumin, potentially reducing their adverse effects. We compare the clinical laboratory parameters, hospitalization rates, and medication use in a cohort of patients switched from high-flux HD to HDx. ***Methods:*** This is a multicenter, observational cohort study of 81 adult patients, across 3 clinics, with end-stage kidney disease (ESKD) on chronic hemodialysis (HD). Patients received high-flux HD for at least 1 year and then switched to HDx and were followed up for 1 year. Patients were excluded if they discontinued therapy, changed provider, underwent kidney transplant, recovered kidney function, or changed to peritoneal dialysis, another dialyzer, or renal clinic. ***Results:*** Twelve months after switching to HDx, the rate of hospitalization events per patient-year decreased from 0.77 (95% CI: 0.60–0.98, 61 events) to 0.71 (95% CI: 0.55–0.92, 57 events) (p = 0.6987). The hospital day rate per patient-year was significantly reduced from 5.94 days in the year prior to switching compared with 4.41 days after switching (p = 0.0001). The mean dose of erythropoiesis-stimulating agent (SC epoetin-α) and intravenous iron also significantly decreased (p = 0.0361 and p = 0.0003, respectively). ***Conclusion:*** Switching to HDx was associated with reductions in hospital day rate and medication use, suggesting HDx has the potential to reduce the burden of ESKD on patients and healthcare systems.

Introduction

Worldwide, the number of patients with chronic kidney disease (CKD) [1] and end-stage kidney disease (ESKD) [2] is large and expanding. Recent years have seen improved patient outcomes [3] including reduced mortality rates [4], improved 5-year survival [5], and reduced morbidity [6, 7]. However, ESKD continues to place a substantial burden on healthcare systems and patients worldwide. A contributing factor to this process is the retention of a group of large uremic toxins (>25 kDa), now referred to as large middle molecules [8].

In a systematic review of the role of large middle molecules in ESKD, Wolley and Hutchison [8] identified

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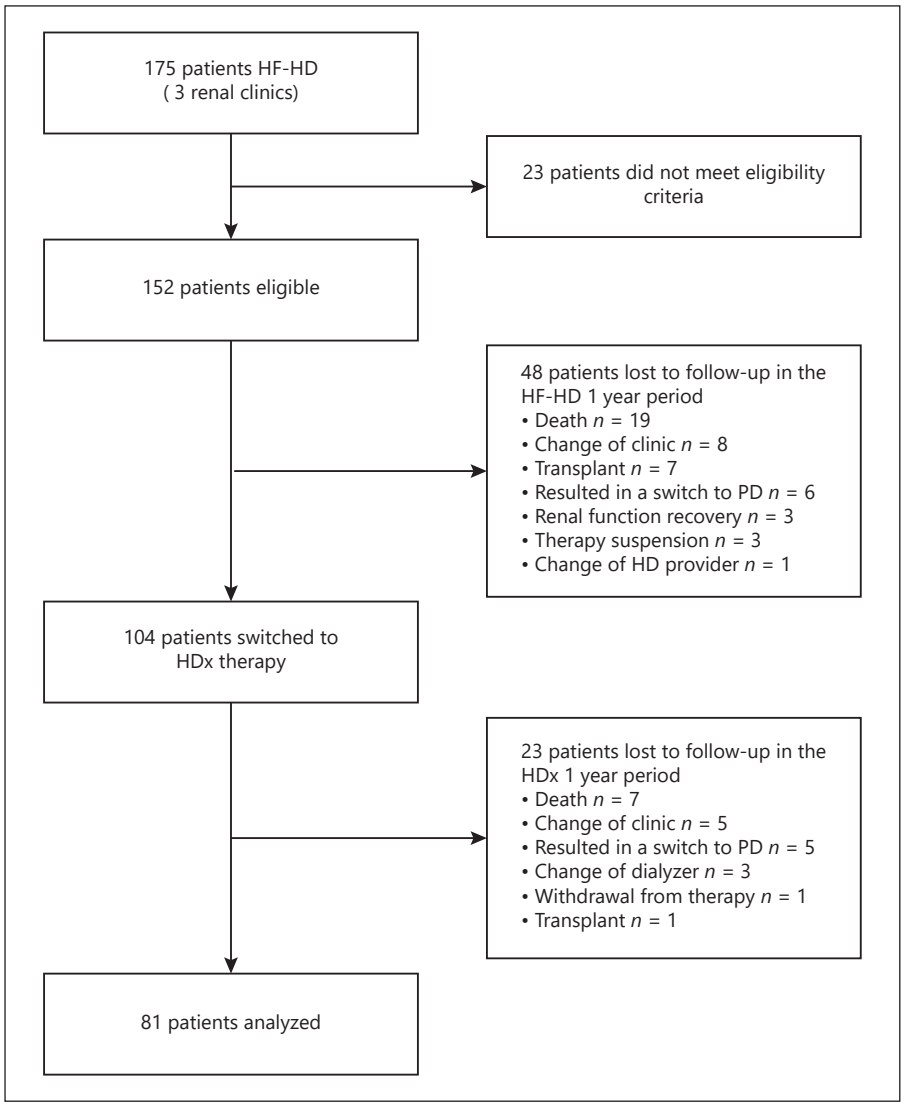

Fig. 1. Flowchart of the patients in the study: consort diagram showing the flow of patients in the study. Of the 175 patients originally recruited, 23 did not meet the eligibility criteria. Prior to switching, 48 patients were lost during the high-flux HD potion of the study and 23 were lost during the HDx portion, leaving 81 patients eligible for analysis. HF-HD, high-flux hemodialysis; HDx, expanded hemodialysis; PD, peritoneal dialysis.

these historically difficult-to-remove-uremic toxins are involved in several key biological pathways which drive adverse outcomes. These include chronic inflammation, secondary immunodeficiency, atherosclerosis, left ventricular hypertrophy, and kidney anemia. Of these processes, chronic inflammation has been particularly well described for its role in adverse outcomes for patients with ESKD through mechanisms such as protein-energy wasting, decline in cognition, disturbed mineral metabolism, cardiovascular disease, and overall mortality [9, 10]. The link between large middle molecules and secondary immunodeficiency largely results from the suppression of normal activation of neutrophils by these toxins. The impact of large middle molecules on cardiovascular outcomes, both left ventricular hypertrophy and atherosclerosis, results from approximately 50% of described large middle molecules affecting numerous biological pathways. Finally, kidney anemia and erythropoiesis-stimulating agent (ESA) resistance are in part linked to the poor clearance of hepcidin on conventional dialysis [11].

Historically, the removal of middle molecules during hemodialysis (HD) is in part limited by the properties of the membrane. Recently, a new medium cut-off (MCO) membrane has been developed which expands the capacity of HD to remove large middle molecules (>25 kDa), without significant loss of albumin [12]. This new therapy is termed expanded hemodialysis (HDx), and in clinical trials, clearances of middle molecules during HDx exceeded the clearances provided by high-flux membranes in HD and HDF mode [13]. As studies have previously

1 year follow-up measurement variables in HF-HD and year follow-up measurement variables in HDx	Baseline	1 Month	2 Month	3 Month	4 Month	5 Month	6 Month	7 Month	8 Month	9 Month	10 Month	11 Month	12 Month
Albumin, P, Ca, hsCRP, platelet lymphocyte ratio, HbA_{1c}*	x	x		x			x			x			x
Hb, erithropoietin resistance, Kt/V	x	x	x	x	x	x	x	x	x	x	x	x	x
PTHi, TSAT, ferritin, Fe	x			x			x			x			x
ESA, iron, calcium carbonate, aluminium hydroxide	x			x			x						x
Hospitalization events, days hospitalization and readmission	→												
Withdraw or end of follow-up	→												

Fig. 2. Schedule of visits during the high-flux HD and HDx portions of the study. *Only for diabetic patients. CA, calcium; ESA, erythropoiesis-stimulating agent; Fe, iron; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDx, expanded hemodialysis; HF-HD, high-flux hemodialysis; hsCRP, high-sensitivity C-reactive protein; Kt/V, dialysis dose; P, phosphate; PTHi, parathyroid hormone; TSAT, transferrin saturation.

demonstrated that increased clearance of large middle molecules can improve patient care and outcomes [14], there is now significant interest in the ability of HDx to improve patient outcomes through multiple pathways, such as inflammation [15].

While there are several international studies starting to explore potential patient benefits of HDx in prospective studies, the introduction of HDx to Colombia in 2017 has provided the ability to report real-life comparative data of the effects of HDx on outcomes of interest. In this article, we report the key clinical parameters, hospitalization rates, and medication use before and after transition from high-flux HD to HDx in a stable cohort of chronic dialysis patients.

Materials and Methods

Study Design and Patients

This historical, multicenter, observational cohort study of chronic HD patients was undertaken in 3 Renal Therapy Services clinics in Bogotá, Colombia. Inclusion criteria consisted of the following: 18 years of age or greater, established ESRD treated with chronic HD, patients had to have received high-flux HD for at least 1 year prior to conversion to HDx and then maintained on HDx for at least 1 year.

Dialysis clinic inclusion was based on standardized process and electronic medical record, and only centers where 100% of patients switched from HD to HDx were included. Patients were required to receive both treatments at the same center. Patients were excluded if they discontinued therapy, changed dialysis provider, had a kidney transplant, recovered kidney function, or switched to peritoneal dialysis, another hemodialyzer, or renal clinic (Fig. 1).

All patients provided written informed consent, and the study was conducted in accordance with the principles of the Helsinki Declaration and Good Clinical Practices. The study protocol was approved by the clinical research ethics committee of Renal Therapy Services (RTS), December 11, 2018, Minute, Item No. 025.

Hemodialysis Treatments Administered

Hemodialysis treatments were administered by clinical staff at local RTS centers. Patients who had received high-flux HD (Polyflux 140; Revaclear 300 or 400, Baxter, Deerfield, IL, USA) thrice weekly for 4 h, for at least 12 months, were switched to receive HDx (Theranova; Baxter, Deerfield, IL, USA). The patient's prescriptions (Q_D, Q_B, target Kt/V, duration, and dialysate) were not changed as part of this study. An existing functioning permanent vascular access (AVF, AVG, or permanent HD catheter) was re-

Table 1. Demographics of the study population at time of entry

Patient demographics	$N = 81$
Age, years; mean (SD)	61.1 (12.6)
Male, *n* (%)	52 (64.2)
CKD cause, *n* (%)	
Diabetes mellitus	32 (39.5)
Hypertension	23 (28.4)
Obstructive	5 (6.2)
Glomerular/autoimmune	3 (3.7)
Unknown	13 (16.0)
Others	5 (6.2)
Vintage in RRT; median (IQR)	3.8 (9.4)
Influenza vaccine, *n* (%)	68 (84.0)
Pneumococcal vaccine, *n* (%)	12 (14.8)
Vascular access, *n* (%)	
Vascular catheter	19 (23.5)
Arteriovenous fistula	62 (76.5)
Time per HD session, h; mean (SD)	4 (0)
Dialysate flow rate, mL/min; mean (SD)	500 (0)
Blood flow rate, mL/min; mean (SD)	391.5 (50.2)
Ultrafiltration, L; mean (SD)	2 (0.7)
Dialyzer type in before phase, *n* (%)	
Polyflux 140	5 (6.2)
Revaclear 300	60 (74.1)
Revaclear 400	16 (19.8)
Dialyzer type in after phase, *n* (%)	
Theranova 400	68 (84.0)
Theranova 500	13 (16.0)
Body mass index, kg/m^2; mean (SD)	25 (4)
Systolic blood pressure, mm Hg; mean (SD)	131 (18)
Diastolic blood pressure, mm Hg; mean (SD)	75 (16)

CKD, chronic kidney disease; RRT, renal replacement therapy; HD, hemodialysis; SD, standard deviation; IQR, interquartile range; mm Hg, millimeters of mercury.

quired but the interim use of temporary dialysis catheters was permitted. Dialyzers were not reused. Regarding dialysate composition, all the patients used a standard solution containing the following: bicarbonate, 34 mEq/L; potassium, 2 mEq/L; chloride, 109.5 mEq/L; calcium, 1.75 mEq/L; magnesium, 0.5 mEq/L; and acetic acid, 3.0 mEq/L. Sodium conductivity was adjusted according to medical prescription.

Patient Demographics and Clinical Characteristics

Information on patient demographic characteristics including age, sex, cause of CKD, diabetes status, duration of dialysis, and influenza and pneumococcal vaccination status were collected. Treatment parameters including vascular access, HD session duration, dialysate flow rate, blood flow rate, and dialyzer type were also collected. The following laboratory parameters were collected: hemoglobin, albumin, phosphorus, platelet-lymphocyte ratio, ferritin, transferrin saturation, glycosylated hemoglobin, and single-pool Kt/V (spKt/V). Monthly data on medication prescriptions of ESA and IV iron were also extracted from the medical records.

Outcomes

Outcomes studied were laboratory parameters, annual hospitalization rates, hospitalization rates by causes, annual hospital stay, 30-day readmission rates, adverse events related to hemodialysis procedures, and medication use. All outcomes were assessed during the year on HF-HD and the year after switching to HDx. In instances of missing data, no data imputation was carried out, and for the specific case of albumin, an approach was made by intention to treat and by protocol. Methoxy polyethylene glycol-epoetin beta was converted to international units using the conversion factor of 4 μg every 4 weeks for each weekly dose of 125 IU epoetin-α [16]. The schedule of measurements is shown in Figure 2.

Statistical Analysis

A statistical description was prepared for all the variables, including calculations of the central trend measures and dispersion, quantitative variables, and determinations of absolute frequencies for qualitative variables. The Wilcoxon signed-rank test was used to evaluate any differences before and after switching to HDx to account for the distribution of continuous variables. Rates of hospitalization, hospital days, and hospital readmission were estimated where the numerator was constituted by the number of events and the denominator by the time contributed by each patient within the study. These rates were presented with their respective 95% confidence intervals. The incidence rates pre- and post-HDx were compared using the incidence rate ratio. The hospitalization event was counted if the duration was 1 day or more. A readmission event was counted when the new hospitalization occurred between the fourth and thirtieth day of hospital discharge immediately before. Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX, USA) was used to perform statistical analyses. Two-tailed tests were used, and a p value of <0.05 was considered significant.

Results

Patient Demographics and Treatment Parameters

Of a potential 175 patients receiving HF-HD at the 3 study clinics, a total of 81 patients were included in the analysis (Fig. 1). Twenty three did not meet eligibility criteria, 48 were lost to follow-up during the HF-HD period, and 23 were lost during the HDx study period, leaving 81 patients for analysis. Patient demographics are shown in Table 1. At baseline, the mean age of patients was 61.1 years (standard deviation [SD], 12.6) and 52 (64.2%) were male. The most common cause of ESKD was diabetic kidney disease (32 patients, 39.5%), followed by hypertension (23, 28.4%). Prior to switching to HDx, patients had been receiving HF-HD for a median of 3.8 (interquartile range [IQR] 9.37) years.

The majority of patients had an arteriovenous fistula (76.5%) for vascular access (Table 1). Hemodialysis treatment parameters were a Q_D of 500 mL/min (SD 0) and Q_B of 391.48 mL/min (SD 40.22) using standard high-flux dialyzers.

Table 2. Laboratory results before and after switching to HDx

Parameters	Mean	SD	P_{25}	Median	P_{75}	IQR	*p* value*
Anemia profile							
Hemoglobin, g/dL							
Before	12.10	1.94	10.80	11.90	13.10	2.30	0.397
After	12.09	1.80	10.90	11.80	13.10	2.20	
Erythropoietin resistance							
Before	5.26	5.68	0.00	4.16	8.03	8.03	0.016
After	4.84	5.85	0.00	3.37	7.28	7.28	
Ferritin, ng/mL							
Before	745.96	724.96	194.10	482.70	1,129.00	934.90	0.855
After	727.94	700.82	199.60	530.20	1,025.00	825.40	
TSAT, %							
Before	30.21	14.57	22.33	27.73	36.81	14.28	0.454
After	33.14	15.27	22.43	31.01	38.70	16.27	
CKD-bone mineral disease							
Phosphorus, mg/dL							
Before	4.60	1.39	3.67	4.47	5.40	1.73	0.004
After	4.44	1.36	3.44	4.29	5.31	1.87	
Calcium, mg/dL							
Before	8.84	0.82	8.37	8.80	9.35	0.98	0.188
After	8.88	0.84	8.40	8.88	9.40	1.00	
PTHi, % pg/mL							
Before	458.21	436.44	155.00	314.95	608.50	435.50	0.003
After	461.45	449.41	154.20	318.10	568.20	414.00	
Inflammation							
Albumin, g/dL							
Before	3.99	0.35	3.80	4.01	4.23	0.43	0.082
After	3.96	0.32	3.76	3.99	4.19	0.43	
Platelet-lymphocyte ratio							
Before	134.11	58.98	91.98	122.46	160.87	68.89	0.076
After	132.41	54.40	94.42	121.17	158.00	63.58	
hsCRP,*** mg/dL							
Before	1.45	2.65	0.26	0.58	1.18	0.92	0.122
After	1.08	2.14	0.29	0.43	0.85	0.56	
Others							
spKt/V							
Before	1.70	0.37	1.47	1.67	1.89	0.42	<0.001
After	1.78	0.40	1.52	1.76	2.04	0.52	
Glycosylated hemoglobin, %**							
Before	6.64	1.09	5.79	6.57	7.35	1.56	0.161
After	6.82	1.18	5.91	6.60	7.40	1.49	

CKD, chronic kidney disease; spKt/V, single-pool clearance of urea × dialysis time/volume of distribution of urea; hsCRP, serum high-sensitivity C-reactive protein; IQR, interquartile range; TSAT, transferrin saturation; SD, standard deviation, P_{25}, 25th percentile; P_{75}, 75th percentile. * Wilcoxon signed-rank test. ** Only for diabetic patients. *** Sixty-six measurements in 20 patients.

Laboratory Parameters

Clinical laboratory parameters during HF-HD and the 12 months after switching to HDx are shown in Table 2. Median hemoglobin levels did not change significantly, being 11.90 g/dL (IQR 2.3) in the 12 months of HF-HD and 11.80 g/dL (IQR 2.2) after switching ($p = 0.397$). Median erythropoietin resistance was reduced significantly on HDx 3.37 (IQR 7.28) compared with during HF-HD 4.16 (IQR 8.03), $p = 0.016$. The median ferritin levels decreased and median TSAT% increased during the 12

Table 3. Clinical outcomes before and after switching to HDx

Characteristic	Events	Rate	95% CI		*p* value
Global hospitalization rate (events/patient-year)					
Before	61	0.77	0.60	0.98	0.698
After	57	0.71	0.55	0.92	
Hospitalization rate for cardiovascular causes					
Before	17	0.21	0.13	0.34	0.589
After	14	0.18	0.10	0.30	
Hospitalization rate for causes related with dialysis					
Before	17	0.21	0.12	0.34	0.356
After	12	0.15	0.08	0.26	
Hospitalization rate for infectious causes per patient-year					
Before	8	0.10	0.04	0.20	0.653
After	10	0.13	0.06	0.23	
Hospitalization rates for others causes per patient-year					
Before	19	0.24	0.14	0.37	0.764
After	21	0.26	0.16	0.40	
Hospital days per patient-year					
Before	473	5.94	5.41	6.50	<0.001
After	353	4.41	3.97	4.90	
30-day readmission rates per patient-year					
Before	12	0.15	0.09	0.27	0.259
After	7	0.09	0.04	0.18	

CI, confidence interval; rate is defined as events per person-year. Person-year is the sum of each person's individual time in the population by 1 year at risk to the event hospitalization; Events are defined as hospitalization events with a duration longer than 24 h.

months of HDx compared with the 12 months of HF-HD, but not significantly ($p = 0.855$ and $p = 0.454$, respectively).

Median phosphorous levels decreased significantly from 4.47 mg/dL (IQR 1.73) during HF-HD to 4.29 mg/dL (IQR 1.87) with HDx ($p = 0.004$). Median calcium levels were 8.80 mg/dL (IQR 0.98) during HF-HD and 8.88 mg/dL (IQR 1.00) during HDx ($p = 0.188$). Median parathyroid hormone levels were 314.95 pg/mL (IQR 453.5) during HF-HD and 318.10 pg/mL (IQR 414) during HDx ($p = 0.003$).

The median levels of the studied markers of inflammation did not change significantly. The median albumin level was 4.01 g/dL (IQR 0.43) during HF-HD and 3.99 g/dL (IQR 0.43) during HDx ($p = 0.082$). The median platelet-lymphocyte ratio was 122.46 (IQR 68.89) during HF-HD and 121.17 (IQR 63.58) during HDx ($p = 0.076$). High-sensitivity CRP decreased from a median level of 0.58 mg/dL (IQR 0.92) during HF-HD to 0.43 mg/dL (IQR 0.56) during HDx ($p = 0.122$). The median dialysis dose (spKt/V) was 1.67 (IQR 0.42) with HF-HD and 1.76 (IQR 0.52) with HDx ($p \leq 0.001$). Median glycosylated hemoglobin levels were unchanged, being 6.57% (IQR 1.56) and 6.60% (IQR 1.49) during HF-HD and HDx, respectively ($p = 0.161$).

Hospitalization Rates

Total patient-years at risk of hospitalization were 79.7 during the year of HF-HD and 80.0 in the 12 months after switching to HDx. The rate of hospitalization events per patient-year decreased from 0.77 (95% CI: 0.60–0.98; 61 events) during HF-HD to 0.71 (95% CI: 0.55–0.92; 57 events) with HDx, $p = 0.698$ (Table 3). The hospitalization rate per patient-year due to cardiovascular events or due to events related to dialysis both decreased with HDx compared with HF-HD, while the rate due to infections increased, none of these changes were significant (Table 3). The rate of hospital days per patient-year was 5.94 (95% CI: 5.41–6.50) with HF-HD and significantly decreased to 4.41 (95% CI: 3.97–4.90) with HDx ($p < 0.001$). The 30-days readmission rate per patient-year was not significantly different, being 0.15 and 0.04 with HF-HD and HDx, respectively ($p = 0.259$).

Medication Use

After switching to HDx, the median dose of ESA (SC epoetin-α) significantly decreased from 12,000.00 (IQR 24,000.00) to 10,000.00 (IQR 12,000.00) IU/month ($p = 0.036$), Table 4. Likewise, the mean dose of IV iron was significantly reduced from 73.46 (SD 142.13) mg/month to 66.36 (SD 167.34) mg/month during HF-HD and HDx, respectively ($p = 0.003$). The median dose of calcium carbonate showed variability in the different measurements ($p < 0.001$), but without clinical importance, see Table 4. Finally, the median dose of aluminum hydroxide was not significantly different between the 2 treatment periods ($p = 0.461$).

Adverse Events

We observed a reduction in adverse events related to hemodialysis procedures after switching to HDx, especially we did not find any adverse events related to the dialyzer membrane, see Table 5.

Discussion

The purpose of this study was to evaluate the potential benefits of HDx in a stable chronic HD cohort. We found that transferring patients from HF-HD to HDx resulted in a significant reduction in the number of days in hospital per year but no significant reductions in absolute hos-

Table 4. Medication consumption before and after switching to HDx

Characteristics	Mean	SD	P_{25}	Median	P_{75}	IQR	*p* value*
ESA (epoetin α), IU/month							
Before	15,109.82	15,564.73	0.00	12,000.00	24,000.00	24,000.00	0.036
After	14,010.29	15,864.38	0.00	10,000.00	22,000.00	22,000.00	
IV iron, mg/month							
Before	73.46	142.13	0.00	0.00	100.00	100.00	<0.001
After	66.36	167.34	0.00	0.00	100.00	100.00	
Calcium carbonate, mg/month							
Before	749.28	1,001.60	0.00	600.00	1,200.00	1,200.00	<0.001
After	989.51	167.34	0.00	600.00	1,800.00	1,800.00	
Aluminum hydroxide, mg/month							
Before	410.33	1,056.54	0.00	0.00	0.00	0.00	0.471
After	319.17	788.36	0.00	0.00	0.00	0.00	

ESA, erythropoiesis-stimulating agents; IU, international unit; IV, intravenous; IQR, interquartile range; SD, standard deviation; P_{25}, 25th percentile, P_{75}, 75th percentile. * Wilcoxon signed-rank test.

pitalization rates nor readmission rates. As anticipated, there was a significant reduction in erythropoietin use and erythropoietin resistance.

In the context of an expanding global population with kidney disease [17, 18] and the subsequent growth in the number of patients with ESKD, advances in dialysis technologies and patient care are paramount to improving patient outcomes and reduce the burden of ESKD on healthcare systems worldwide [19]. Expanded hemodialysis offers for the first time the ability to remove large middle molecules in chronic dialysis populations without the need for machine adaptation to enable convection [20]. A recent multicenter prospective study demonstrated a significant reduction in large middle molecules without a significant reduction in serum albumin over a 6-month treatment period with HDx [21]. This study by Krishnasamy et al. [21] was undertaken to address questions of efficacy for removal of the large molecules and the safety of potential albumin loss on a more porous membrane. With these efficacy and safety issues after addressed, further work is required to identify potential clinical benefit of HDx over conventional therapies such as HF-HD.

In designing this study, it was anticipated that potential patient benefit of HDx would come from reduced chronic inflammation, reduced secondary immune deficiency, reduced cardiac events, and reduced erythropoietin resistance. In this context, the data reported here on the impact of switching patients from HF-HD to HDx on laboratory parameters, hospitalization rates, and medication use in a cohort of patients in Colombia provide further insight into the potential benefits of HDx. Over the 24 months of the study, a number of positive outcomes associated with the switch to HDx were observed. During the 12 months of HDx, there was a significant reduction in the rate of hospital days per patient-year as well as a trend toward a reduction in the hospitalization rate compared with the 12 months of HF-HD therapy. However, there was no observed reduction in infection-related events.

During the 12 months of HDx, the doses of ESA and IV iron were both reduced compared with the previous 12 months of HF-HD therapy, while hemoglobin levels remained stable, resulting in a net improvement in erythropoietin resistance. There are a number of mechanisms by which HDx could have improved the erythropoietin resistance including improved clearance of hepcidin, a middle molecule which contributes to increased degrada-

Table 5. Adverse events related to hemodialysis procedure

Adverse events related to hemodialysis procedure	Before phase	After phase
Clotted dialyzer	4	1
Hematoma	3	0
Hypotension	1	1
Infection of vascular access	5	3
Insufficient weight loss > or <1 kg	2	0
Reaction type A	1	0
Bleeding >150 mL	2	0
Total	18	5

tion of ferroportin and subsequent iron deficiency [22]. It has also been reported that increased levels of inflammatory mediators have also been linked with anemia [23], and we observed a nonsignificant decrease in markers of inflammation to support this hypothesis. Interestingly, this study population had relatively low levels of inflammation seen as measured by hsCRP, in comparison to other reports [24]. Furthermore, our findings coincide with a recent randomized clinical trial that showed that compared to HD performed with high-flux dialyzers, HDx was associated with a superior removal of inflammatory cytokines, improving iron metabolism in a manner independent of that related to hepcidin [25].

Other interesting trends were observed during the study. First, the single-pool Kt/V was improved during the 12 months of HDx compared with the 12 months of HF-HD therapy. This may be indicative of improved clearance properties with HDx. In addition to the improved dialysis dose, the level of albumin was unchanged after switching to HDx, suggesting that despite the improved removal properties of the membrane, the removal of albumin should not be greater than with high-flux HD or other modalities. Although not significant, we observed an interesting trend toward a reduction in the level of hsCRP after switching to HDx. Intriguingly, we observed a nonsignificant trend toward a reduction in the rate of hospitalizations related to cardiovascular events with HDx; this aligns with observations from the general population which have shown that a raised hsCRP is associated with cardiac events [26]. While a protective effect of HDx on the heart remains to be proven, it will be interesting to observe if these important trends are replicated in larger controlled studies.

Our study does have some limitations. Most importantly that although this was a multicenter study, when the study was complete, only 81 patients met full study criteria for analysis. While a study population of this size enables the observation of changes in parameters, many of these did not achieve statistically significance because of the population size. Second, a "before and after" design introduces the potential for bias that is secondary to the changes in dialysis care after switching from high-flux HD to HDx. Finally, this was a single-arm observational study. Further work now needs to occur in larger cohorts with control arms to confirm the results observed in this study and explore other potential benefits in multiyear studies. Also, it would be interesting to observe long-term effects on symptoms in patients with chronic hemodialysis such as carpal tunnel syndrome, pruritus, postdialysis asthenia, and restless legs syndrome.

Given the scarcity of outcome data for HDx, this real-world evidence in a substantial number of patients provides the HD community with further insight into the utility of HDx. We followed patients for 24 months, and the reduced medication consumption and rate of hospital days per patient that we observed in the 12 months of HDx represent encouraging improvements in the quality of care received by dialysis patients. Furthermore, they have the potential to help inform wider clinical decisions regarding choice of dialysis treatment modality and may help to reduce the impact of ESKD on patients and healthcare systems.

Conclusion

In this cohort of chronic HD patients, switching to HDx was associated with improvements in the rate of hospital days per patient-year and medications use, including ESA and IV iron. These observations may have important implications for patients and healthcare systems.

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Statement of Ethics

As this was an observational study, where the procedure of HD therapy was not changed in any respect, the study was considered without risk. All patients provided written informed consent, and the study was conducted in accordance with the principles of the Helsinki Declaration and Good Clinical Practices. The study protocol was approved by the clinical research ethics committee of Renal Therapy Services (RTS), December 11, 2018, Minute, Item No. 025.

Conflict of Interest Statement

R.S. and J.A. are employed by Baxter Latin America, Bogotá, D.C., Colombia; J.V. and A.S. are employed by Renal Therapy Services (RTS), Bogotá, Colombia; R.S. has received grant/research support from RTS, Colombia, and served as a statistical consultant for this study. C.H. is from the Department of Medicine, Hawke's Bay District Health Board, Hastings, New Zealand.

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Author Contributions

Mr. Sanabria, Ms. Vesga, Mr. Sanchez, and Ms. Suarez: original research project conception and design, data acquisition, and data interpretation. Mr. Hutchison and Mr. Ariza: original research project conception and design and data interpretation. All authors contributed to the research conception, protocol design, and analysis and interpretation of the data. All authors contributed to the development and critical review of the manuscript and provided final approval for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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