Benefits of the Nephros Dual Stage Ultrafilter in Chronic Hemodialysis Patients: Evidence for Improved ESA Responsiveness

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Key Words

Erythropoiesis-stimulating agent · ESA · Dual Stage Ultrafilter · Hemodialysis

Abstract

Installation of the Nephros Dual Stage Ultrafilter (DSU) added to a conventional hemodialysis unit to achieve ultrapure dialysate was tested in a group of 23 stable outpatients on chronic hemodialysis. Comparing the 6-month period prior to the installation of the filters (as baseline) to the 6-month period after the installation of the filters, we found a significant 40% reduction in the darbepoetin dose needed to maintain a stable hemoglobin level ($p < 0.001$). In addition, surrogate inflammatory markers, WBC count and serum albumin level, showed small but statistically significant improvements ($p = 0.008$ and $p = 0.042$, respectively). In conclusion, the use of the Nephros DSU to further reduce endotoxin exposure in chronic hemodialysis patients can result in improved erythropoiesis-stimulating agent (ESA) responsiveness and a lower ESA dose.

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Introduction

Current CMS (Centers for Medicare and Medicaid Services) guidelines based on previous AAMI (Association for the Advancement of Medical Instrumentation) recommendations mandate that water used in the preparation of dialysate for the treatment of end-stage renal disease patients on chronic hemodialysis must have bacterial cell counts <200 CFU/ml and

Limulus amebocyte lysate (LAL) endotoxin levels <2 EU/ml. Ultrapure dialysate is defined as fluid with bacterial cell counts <100 CFU/l (0.1 CFU/ml) and LAL endotoxin levels <0.03 EU/ml. In Europe and Japan, ultrapure dialysate is required for dialysate and replacement fluid used in convective forms of dialysis, such as hemodiafiltration.

Chronic exposure to low levels of bacteria and bacteria by-products, such as lipopolysaccharide or endotoxin, has been associated with chronic inflammation in hemodialysis patients. Ultrapure dialysate has been shown to reduce inflammatory markers and improve nutritional and anemia parameters in patients on chronic maintenance hemodialysis [1–6].

The Nephros Dual Stage Ultrafilter (DSU; Nephros Inc., River Edge, N.J., USA) contains a hydrophobic polysulfone hollow fiber membrane that is configured to provide a 2-stage (redundant) filtering system. The 2nd stage is designed to act as a failsafe backup to the 1st-stage filtration process. The membrane has a 15-kDa molecular weight cutoff. It has been shown to reduce bacterial counts and endotoxin levels by at least a 5-log order of magnitude with endotoxin levels not to exceed 0.03 EU/ml (bacterial retention >11-log order and endotoxin retention >5-log order magnitude).

We performed an observational trial of this filter in a hospital-based acute dialysis facility in the USA.

Methods

Conventional thrice-weekly hemodialysis was performed using a central reverse osmosis (RO) water treatment unit that produced water meeting current CMS guidelines. Prior to the introduction of the Nephros DSU, dialysis was performed on a standard thrice-weekly regimen using Fresenius 2008T dialysis machines with Fresenius DiaSafe® filters installed on each machine. Conventional hemodialysis was performed thrice weekly using Baxter® Exeltra 190 dialyzers [1.9 m² cellulose triacetate high-flux membrane with a KoA urea (dialyzer mass transfer coefficient) of 1,214 ml/min] at prescribed blood flows of 400 ml/min and dialysate flows of 600 ml/min for 3.5–4 h to attain a single-pooled Kt/V (spKt/V) of ≥1.2 (for patients who failed to attain an adequate spKt/V on 4 h, a Baxter® 210+, a 2.1 m² cellulose triacetate high-flux dialyzer with a KoA urea of 1,714 ml/min was used instead). All dialyzers were used only once. The central RO system used for the processing of the water needed for the preparation of the dialysate solution consisted of a booster pump and temperature blending valve to obtain water at the desired pressure and temperature for the RO system, a sediment filter, a water softener, 2 carbon tanks (a ‘worker’ tank and a second ‘polisher’ tank for the removal of chlorine and chloramine) and the RO filter. The processed water was delivered to the dialysis machines via an indirect feed system. The disinfection routine consisted of nightly heat disinfection of the dialysis machines with monthly chemical disinfection of the RO system and the distribution loop. Dialysate was prepared from standard acid and bicarbonate concentrates at each machine station and purified by the DiaSafe® filter prior to introduction into the dialyzer. Though dialysate was not monitored to the ultrapure standard, bacterial and endotoxin levels were routinely well below the AAMI standard on account of the RO system and the DiaSafe® filters. The Nephros DSU was then installed at each of all 10 dialysis stations in-line between the incoming RO water and the dialysis machines. This provided an additional level of ultrafiltration of the water which was upstream of the DiaSafe® filter. Routine monthly laboratory work was obtained for each patient per standard protocol along with quarterly testing of the dialysate fluid at each machine station for bacterial colony counts and LAL endotoxin testing. Identification of micro-

organisms on positive cultures was not performed or available. Dialysate prescriptions were adjusted to maintain a $\text{spKt/V} \geq 1.2$ per patient.

Anemia management (intravenous darbepoetin and intravenous iron sucrose dosing) was chosen by the individual treating nephrologist(s) as there was no standardized protocol for the dialysis facility. Prescription of darbepoetin was done by unit vial dosing (25, 40, 60 or 100 μg per dose). In general, the target hemoglobin level was 10–11 g/dl. The treating nephrologists were not aware of the installation of the Nephros DSU.

Statistical comparisons between the 2 time periods (6 months before versus 6 months after the introduction of the DSU) was performed using nonparametric exact statistical methods with the Wilcoxon signed-rank test for paired data in SPSS, version 17 (SPSS®, Chicago, Ill., USA). Statistical significance was assumed at $p < 0.05$.

Results

There were 23 stable outpatients on chronic hemodialysis treated during the 6 months after the installation of the Nephros filters. The mean age was 51 years (range 12–91), 61% were male, predominantly Hispanic (70% Hispanic, 17% African-American, 9% Caucasian and 4% Asian) and 30% diabetic. Comparing data from the 6-month period after the installation of the filters to the preceding 6 months, there was an increase in the mean hemoglobin level of 0.5 g/dl (table 1; $p = 0.010$), with a reduction in the mean weekly darbepoetin dose of 14.6 μg (table 1; $p < 0.001$) translating to a reduction in the erythropoiesis-stimulating agent (ESA) resistance index (weekly ESA dose/hemoglobin level) of 1.52 (table 1; $p < 0.001$). Because there was active dose titration of darbepoetin in response to changing hemoglobin levels, the weekly hemoglobin trends do not show a clear unidirectional change. Given the longer half-life of darbepoetin, we also looked at the average hemoglobin level and darbepoetin dose over the first 3 months after the DSU installation, and then the subsequent 3 months. From prior to filter installation compared to the first 3-month period after the installation of the filter, the average weekly hemoglobin level increased from a mean of 10.48 to 10.63 g/dl ($p = 0.088$), with an additional increase to 10.71 g/dl over the second 3-month period after filter installation ($p = 0.43$ compared to the prior 3-month period after filter installation, but $p = 0.017$ compared to the period prior to filter installation; table 2). Over these same intervals, the mean weekly darbepoetin dose decreased from 32.3 to 21.6 μg ($p = 0.04$) over the first 3 months after filter installation and then further to 17.1 μg over the subsequent 3-month period after filter installation ($p = 0.049$ compared to the prior 3-month period after filter installation and $p = 0.017$ compared to the period prior to filter installation; table 2).

During this time period, indirect inflammatory markers showed a reduction in the mean WBC count of $0.46 \times 10^9/\text{l}$ ($p = 0.008$), an increase in serum albumin of 0.08 g/dl ($p = 0.024$), an increase in transferrin saturation of 1.0% ($p = 0.34$, n.s.) and an increase in the serum ferritin level of 85 ng/ml ($p = 0.06$; table 3). The total intravenous Venofer® (iron sucrose) dose administered during each 6-month period did increase from a mean 764 mg (before filter installation) to 1,087 mg (after filter installation) or 325 mg, but was not statistically significant ($p = 0.07$; table 3). The mean spKt/V was unchanged during the 2 time periods (before installation 1.609 vs. after installation 1.607; $p = 0.30$; table 1).

In dialysate water testing for bacterial colony counts and LAL endotoxin assays, the limit of detection and reporting for the assay used by an outside water testing facility was a bacterial colony count <2 CFU/ml and for the LAL endotoxin assays <0.01 EU/ml. As such, given the limits of the assay for bacterial colony counts, no difference could be measured after the

installation of the Nephros DSUs, with an average bacterial colony count <2 CFU/ml both before and after the introduction of the DSUs (table 4). There was a reduction in the LAL endotoxin levels after the introduction of the DSUs from an average of 0.033 to 0.015 EU/ml, but this did not reach statistical significance ($p = 0.67$; table 4).

Limitations of our study include a small sample size and the use of a standard water testing laboratory whose limit of detection could not allow confirmation of enhancement to the purity of the water used in dialysate preparation. In addition, the trend toward more intravenous Venofer being used and a higher serum ferritin level after the introduction of the DSUs leaves open the question as to what extent better/higher iron stores may have contributed to the enhanced ESA responsiveness seen after the introduction of the DSUs, though there was no significant increase in the transferrin saturation. A randomized trial with a larger sample size would help to clarify these issues.

Conclusion

In conclusion, the use of the Nephros DSU to further reduce bacterial and endotoxin exposure in chronic hemodialysis patients can result in improved ESA responsiveness, a lower ESA dose and, possibly, reduced systemic inflammation.

Statement of Ethics

This study did not require informed consent nor review/approval by the Institutional Review Board of the Columbia University Medical Center, New York, N.Y., USA.

Disclosure Statement

The authors report no conflicts of interest or financial relationships with the Nephros company or other companies in the conduct of this study.

References

- 1 Ward RA: Ultrapure dialysate. *Semin Dial* 2004;17:489–497.
- 2 Ledeo I: Ultrapure dialysis fluid – direct and indirect benefits in dialysis therapy. *Blood Purif* 2004;22(suppl 2):20–25.
- 3 Bommer J, Jaber BL: Ultrapure dialysate: facts and myths. *Semin Dial* 2006;19:115–119.
- 4 Cappelli G, Ricardi M, Bonucchi D, De Amicis S: Quality of water, dialysate and infusate. *Contrib Nephrol* 2007;158:80–86.
- 5 Glorieux G, Neirynck N, Veys N, Vanholder R: Dialysis water and fluid purity: more than endotoxins. *Nephrol Dial Transplant* 2012;27:4010–4021.
- 6 Susantitaphong P, Riella C, Jaber B: Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. *Nephrol Dial Transplant* 2013;28:438–446.

Table 1. Trend in hemoglobin, ESA dose, ESA sensitivity index and spKt/V

	Hemoglobin, g/l	Darbepoetin, µg/week	ESA sensitivity index (ESA dose/hemoglobin)	spKt/V
Before filter installation				
Mean	10.27	36.3	3.54	1.61
Interquartile range	8.28–11.29	20.8–40.0	2.04–4.83	1.41–1.86
After filter installation				
Mean	10.77	21.7	2.03	1.61
Interquartile range	10.44–11.15	15.6–26.2	1.45–2.40	1.39–1.73
Mean difference	0.50 (+4.9%)	–14.6 (–40%)	–1.52 (–43%)	0.00
p value	0.01	<0.001	<0.001	0.30

Table 2. Quarterly trends in hemoglobin and ESA dosing

	6 months before filter installation	First 3 months after filter in- stallation	Second 3 months after filter installa- tion
Hemoglobin level, g/dl			
Mean	10.48	10.63	10.71
Interquartile range	10.27–10.71	10.48–10.78	10.47–10.96
Before vs. after filter installation		0.088	0.017
First vs. second 3 months after filter installation			0.43
ESA dose, µg			
Mean	32.3	21.6	17.1
Interquartile range	12.9–37.7	13.9–26.5	9.8–20.7
Before vs. after filter installation		0.04	0.017
First vs. second 3 months after filter installation			0.049

Table 3. Trend in inflammatory markers (WBC, serum albumin), iron studies (TSAT and serum ferritin) and intravenous iron dose

	WBC count, cells/l × 10 ⁹	Serum albumin, g/dl	TSAT, %	Serum ferritin, ng/l	Iron sucrose dose (i.v.), mg
Before filter installation					
Mean	7.02	3.59	27.4	575	764
Interquartile range	5.13–8.62	3.30–3.93	20.4–32.8	324–821	300–1,000
After filter installation					
Mean	6.55	3.67	28.4	660	1,087
Interquartile range	5.19–7.89	3.42–3.90	22.8–32.9	423–1,000	500–1,500
Mean difference	–0.46	0.08	1.0	85	325
p value	0.008	0.042	0.34	0.06	0.07

Table 4. Trend in bacterial colony count and LAL

	Bacterial colony count, CFU/ml	LAL, EU/ml
Before filter installation		
Mean	<2	0.03
Interquartile range	<2–<2	<0.01–0.05
After filter installation		
Mean	<2	0.015
Interquartile range	<2–<2	<0.01–0.018
Mean difference	0.0	–0.018
p value	1.00	0.67