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A Retrospective Study on Erythropoiesis Stimulating Agent Dose Reducing Potential of an Anti-Platelet Activation Membrane Dialyzer in Hemodialysis Patients

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Abstract: Our previous small-scale trial demonstrated an erythropoiesis stimulating agent (ESA)-sparing potential of the TORAYLIGHT NV (NV) dialyzer in hemodialysis patients with high interleukin-6 levels. We now retrospectively explored this ESA-sparing potential of the NV dialyzer in 122 and 129 prevalent dialysis patients who were on the NV and conventional polysulfone (PS) dialyzers, respectively, for 12 months. ESA resistance index (ERI) increased with the PS dialyzers whereas neither ERI nor ESA dose changed with the NV dialyzer. Analyses of baseline ERI or ESA dose-based subgroups revealed a decrease in ERI and ESA dose with the NV dialyzer in patients with a baseline ERI ≥12 IU·dL/week·kg·g Hb ($P < 0.05$) and in those with a baseline ESA dose >6000 IU/week ($P < 0.001$), respectively. Neither ERI nor ESA dose improved in the corresponding subgroups on the PS dialyzers. These findings suggest that NV dialyzer can improve ESA responsiveness in hemodialysis patients with advanced ESA resistance. **Key Words:** Anti-platelet activation membrane, Erythropoiesis stimulating agent resistance, NV dialyzer, Polysulfone membrane, Renal anemia.

Renal anemia develops in a number of hemodialysis patients. Mainstay treatment is administration of erythropoiesis stimulating agents (ESAs). Some hemodialysis patients become poorly responsive to ESAs and require a higher dose of ESAs than usual to achieve target hemoglobin levels, a condition called ESA resistance. Previous studies indicate that ESA resistance is associated with unfavorable outcomes including cardiovascular disease, early advancement to end-stage renal disease, and death (1–5).

The TORAYLIGHT NV dialyzer (NV dialyzer) is equipped with a polysulfone membrane that is modified to enhance the mobility of water adjacent to the membrane (6,7). The modifications include local application of a new hydrophilic polymer onto the inner surface of a hollow-fiber membrane composed of polysulfone (6,7). This modification reduces dialysis-associated platelet activation that occurs when blood contacts the dialysis membrane (6,7). Dialysis with the NV dialyzer appears to improve vascular endothelial function in hemodialysis patients (8). Recently, it was reported that NV dialyzer has a lower platelet-activating property than that of conventional high-flux dialyzers (9).

Our previous small-scale randomized controlled trial showed that ESA resistance was improved within 1 year after hemodialysis patients were switched from conventional polysulfone membrane dialyzers onto the NV dialyzer while ESA resistance worsened in those who stayed on conventional polysulfone membrane dialyzers (10). The trial raised a question whether the observed effect of the NV dialyzer on ESA resistance can be seen in prevalent hemodialysis patients because the trial enrolled 20 patients who were selected for their relatively high serum interleukin-6 levels from 72 eligible patients (10).

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The present study retrospectively analyzed the effect of the NV dialyzer on ESA requirement in a total of 251 prevalent hemodialysis patients.

PATIENTS AND METHODS

Patients and data collection

The study subjects were hemodialysis patients who were treated with polysulfone-type membrane dialyzers for at least 15 consecutive months at 13 participating institutions from October 1, 2012 through March 31, 2015. All participating institutions were private clinics. The patients who were treated for at least 15 consecutive months with conventional polysulfone-type dialyzers (PS dialyzers) alone were grouped in the PS group. Those who were initially treated with PS dialyzers for at least 3 consecutive months and switched onto the NV dialyzer (TORAYLIGHT NV dialyzer, Toray Medical Co., Ltd., Tokyo, Japan), and continued dialysis for at least 12 consecutive months were grouped in the NV group. We set the baseline of data collection at the third month after starting dialysis for the PS group and 1 month before the switch from PS dialyzers to the NV dialyzer for the NV group. The study period was 12 months.

We enrolled those patients who met the inclusion criteria at baseline and did not meet any of the exclusion criteria during the study period. The inclusion criteria were age ≥20 years, at least three sessions of 4 h or longer dialysis session per week, ≥3 months of dialysis vintage with polysulfone membrane dialyzers other than the NV dialyzer, and receiving ESA treatment. The exclusion criteria were treatments for renal failure other than hemodialysis, including peritoneal dialysis, hemodiafiltration, and Lixelle, ESA treatment with epoetin beta pegal, blood infusion, ≥2 weeks of hospitalization, hematological disorders other than renal anemia, being pregnant or having given a birth during the study period, treatments for malignancy in 3 months prior to the baseline or during the study period, or being judged inadequate for the study by principal investigator or participating investigators. Target hemoglobin concentration was 10≤ and <12 g/dL at the first dialysis of the week as recommended in the Japanese Society for Dialysis Therapy guidelines (11).

Effectiveness of hemodialysis was examined using Kt/V. Dialysate quality was inspected once a month at all participating facilities according to the guidelines of the Japanese Society for Dialysis Therapy (12). No endotoxin or microorganisms were detected in the dialysates at any time point during the study period.

The following baseline data were collected from the clinical records: age, gender, the date hemodialysis was started, original disease, height, predialysis blood pressure, shunt, and history of cardiovascular disease, bone fracture, malignancy, gastrointestinal bleeding, hepatic disease, or hematological disorder. The following data were collected for every month of the study period: dry weight, predialysis body weight, used dialyzer type, the length of hemodialysis session, Kt/V, membrane surface area, blood flow rate, red blood cell, white blood cell and platelet counts, hemoglobin, albumin, creatinine, calcium, phosphorus, intact parathyroid hormone, iron, transferrin saturation (TSAT), total iron binding capacity (TIBC), ferritin, CRP, ESA type and dose per week, and iron supplementation. Data of ESA type and dose per week were also collected for the 2 months before the baseline month as well as for every month of the study period.

ESA dose and resistance index

The total of ESA dose prescribed in 1 month was averaged for a week, and the resulting mean in IU/week was used as the ESA dose of the month. Darbepoetin alfa dose was converted to ESA dose (IU/week) by multiplying darbepoetin alfa dose prescribed in 1 week (μg) with 200. ESA resistance index (ERI) was derived by dividing the mean weekly ESA dose (IU/week) with dry weight (kg) and hemoglobin concentration (g/dL) and expressed in IU·dL/week·kg·g Hb (13,14).

Statistical analysis

Results were expressed as mean ± SD. ERI and ESA dose were analyzed only in the patients who continued ESA treatment in the 2 months before the baseline month and throughout the study period. For post hoc analyses, ERI and ESA dose of the baseline month and the 2 months before the baseline month were averaged, and the resulting means were used to further divide the patients into three ERI-based or ESA dose-based subgroups: low-ERI <6 IU·dL/week·kg·g Hb, middle-ERI 6≤ and <12 IU·dL/week·kg·g Hb, and high-ERI ≥12 IU·dL/week·kg·g Hb, or low-ESA dose ≤3000 IU/week, middle-ESA dose 3000< and ≤6000 IU/week, and high-ESA dose >6000 IU/week. These cut-off points were set at the first and third quartile values of baseline ERI and ESA dose of the NV group. The resulting subgroups included the following fractions of the subjects of the NV

group: ERI, low-ERI 23.0%, middle-ERI 56.6%, and high-ERI 20.5%; ESA dose, low-ESA dose 17.2%, middle-ESA dose 54.96%, and high-ESA dose 26.25%. Data were compared within or between groups and within or between corresponding subgroups at baseline, months 6 and 12. The difference in data distribution was tested by *F*-test, and either unpaired *t*-test or Welch's test was used as appropriate. Qualitative variables of the patient characteristics and the frequency of iron supplementation were tested by Welch's test regardless of the results of *F*-test. *P*-values <0.05 were considered significant. Categorical variables were tested by the chi-square test.

Ethical considerations

This study conforms to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Tokai University Hachioji Hospital and the Toyu Clinical Study Review Board of the Showa Kai, an association of dialysis clinics of which the participating dialysis clinics are members.

Clinical trials registry

This study is registered with the Clinical Trials Registry of the University Hospital Medical Information Network (registration ID, UMIN 000018431).

RESULTS

Baseline patient characteristics

The NV and PS groups were comparable with the exception of higher age and less frequent history of cardiovascular disease in the NV than in the PS group (Table 1).

Baseline laboratory data were not significantly different between the groups except hemoglobin concentrations were lower and TIBC was higher in the NV than in the PS group (Table 2). As for the conditions of dialysis, Kt/V was not different between the groups. The mean Kt/V was higher than 1.2 in both groups. The membrane area, dialysis time, and blood flow rate were lower in the NV than in the PS group (Table 2). Baseline ESA dose and ERI were higher in the NV than in the PS group. Iron supplementations were more frequent in the NV than in the PS group (Table 2).

TABLE 1. *Baseline patient characteristics*

	NV group		PS group		*P*
Patients	122		129		
Male/female	79/43		86/43		
Age (years)	63 ± 12 (24, 88)	122	60 ± 12 (32, 83)	129	0.044
Dialysis vintage (months)	99 ± 83 (4, 327)	122	106 ± 80 (5, 357)	129	0.520
Height (cm)	161 ± 9 (138, 181)	114	161 ± 9 (137, 182)	126	0.968
Dry weight (kg)	55.9 ± 11.5 (33.0, 88.8)	122	58.2 ± 14.3 (32.0, 112.5)	129	0.168
SBP (mmHg)	151 ± 24 (103, 210)	122	152 ± 21 (109, 220)	129	0.807
DBP (mmHg)	76 ± 14 (44, 121)	122	78 ± 14 (42, 120)	129	0.294
Original disease					
Chronic glomerular nephritis	30		31		0.982
Diabetic nephropathy	36		41		
Chronic pyelonephritis	0		0		
Polycystic kidney	5		5		
Nephrosclerosis	8		4		
Other	31		33		
Unknown	12		15		
Disease history (Y/N)					
Cardiovascular disease	14/108	122	33/96	129	0.007
Bone fracture	8/114	122	14/115	129	0.327
Malignant tumor	3/119	122	5/124	129	0.780
Gastrointestinal hemorrhage	7/115	122	8/121	129	0.911
Liver disease	2/120	122	2/127	129	0.654
Hematologic disease	0/122	122	1/128	129	0.978
Vascular access					
Arteriovenous fistula	118		125		1.000
Arteriovenous graft	3		4		
Subcutaneously fixed superficial artery	1		0		
Catheter	0		0		
Others	0		0		

Results are presented as mean ± SD. Shown in parentheses is the range. The numbers shown on the right side of the range and Y/N values are the numbers of patients whose data were available for analysis. DBP, diastolic blood pressure; NV, the NV dialyzer; PS, conventional polysulfone membrane dialyzers; SBP, systolic blood pressure; Y/N, yes/no.

TABLE 2. *Baseline laboratory data*

	NV group		PS group		*P*
Number of patients	122		129		
Laboratory data					
RBC (cells/μL)	332 ± 30 (273, 415)	122	336 ± 35 (163, 437)	129	0.422
WBC (cells/μL)	5640 ± 1493 (2780, 10 200)	122	5820 ± 1530 (2700, 10 100)	129	0.348
PLT ($\times 10^4$/μL)	18.1 ± 6.1 (6.0, 45.6)	122	18.5 ± 5.1 (8.5, 36.3)	128	0.661
Hemoglobin (g/dL)	10.2 ± 0.9 (8.0, 12.5)	122	10.5 ± 0.9 (4.7, 12.5)	129	0.013
Serum albumin (g/dL)	3.8 ± 0.3 (3.1, 4.5)	122	3.8 ± 0.3 (2.6, 4.5)	128	0.169
CRP (mg/dL)	0.26 ± 0.65 (0.01, 6.00)	122	0.32 ± 1.03 (0.01, 7.97)	65	0.624
UN (mg/dL)	67.0 ± 16.7 (33.1, 123.2)	122	71.0 ± 16.0 (33.6, 120.6)	129	0.052
Cr (mg/dL)	12.3 ± 2.5 (5.9, 19.8)	122	12.1 ± 2.7 (5.0, 18.0)	129	0.623
Ca (mg/dL)	8.9 ± 0.6 (7.2, 10.6)	122	9.0 ± 0.6 (7.8, 10.6)	129	0.326
iP (mg/dL)	5.5 ± 1.3 (2.9, 9.1)	122	5.2 ± 1.2 (1.4, 9.5)	129	0.053
Fe (μg/dL)	59.9 ± 27.1 (19.0, 183.0)	96	61.5 ± 22.9 (14.0, 149.0)	127	0.631
TIBC (μg/dL)	269 ± 60 (164, 429)	74	248 ± 40 (152, 363)	73	0.014
Ferritin (ng/mL)	194 ± 229 (9, 1016)	58	235 ± 307 (13, 2198)	95	0.385
TSAT (%)	22.9 ± 13.1 (5.1, 76.6)	74	25.3 ± 8.5 (7.9, 54.6)	73	0.187
inPTH (pg/mL)	163 ± 126 (4, 777)	55	182 ± 132 (1, 625)	70	0.415
Dialysis prescription					
Kt/V	1.4 ± 0.2 (0.7, 2.0)	122	1.4 ± 0.3 (0.6, 2.2)	127	0.067
Surface area (m^2)	1.9 ± 0.3 (1.3, 2.1)	122	2.0 ± 0.2 (1.5, 2.1)	129	0.001
Dialysis time (h)	4.0 ± 0.2 (4.0, 5.0)	122	4.1 ± 0.3 (4.0, 5.0)	129	0.003
Blood flow rate (mL/min)	189 ± 25 (100, 250)	122	199 ± 26 (120, 300)	129	0.003
Prescribed drugs					
ESA (U/week)	4725 ± 2623 (375, 15 000)	122	3789 ± 2067 (760, 10 125)	129	0.002
ERI	8.8 ± 5.7 (0.4, 28.2)	122	6.8 ± 4.6 (1.1, 26.8)	129	0.002
Iron drug (Y/N)	38/84	122	25/104	129	0.045

Results are presented as mean ± SD. Shown in parentheses is the range. The numbers shown on the right side of the range and Y/N values are the numbers of patients whose data were available for analysis. Ca, calcium; Cr, creatinine; CRP, C-reactive protein; ESA, erythropoiesis stimulating agent; ERI, ESA resistance index, Fe, iron; inPTH, intact parathyroid hormone; iP, inorganic phosphate; NV, the NV dialyzer; PLT, platelet; PS, conventional polysulfone membrane dialyzers; RBC, red blood cell; TIBC, total iron binding capacity; TSAT, transferrin saturation; UN, urea nitrogen; WBC: white blood cell; Y/N, yes/no.

ESA resistance index

ERI was higher in the NV than in PS group at baseline (9.48 ± 5.17 vs. 6.49 ± 3.76 IU·dL/week·kg·g Hb; $P < 0.001$) and month 6 (8.68 ± 6.51 vs. 7.12 ± 5.68 IU·dL/week·kg·g Hb; $P < 0.05$), but was not different between the groups at month 12 (8.71 ± 6.05 vs. 7.84 ± 6.59 IU·dL/week·kg·g Hb; *NS*) (Fig. 1A). ERI did not change from the baseline in the NV group throughout the 12-month study period whereas it was significantly higher than the baseline in the PS group at month 12 ($P < 0.05$; Fig. 1A).

In order to further characterize the changes in ERI, post hoc analyses were performed after dividing the patients of each group into low-ERI (<6 IU·dL/week·kg·g Hb), middle-ERI (6≤ and <12 IU·dL/week·kg·g Hb) and high-ERI (≥12 IU·dL/week·kg·g Hb) subgroups according to the baseline ERI.

There were 28 and 68 low-ERI patients in the NV and PS groups, respectively (Fig. 1B). ERI were significantly higher in the low-ERI patients of the NV than in those of the PS group at baseline (4.45 ± 1.09 vs. 3.79 ± 1.24 IU·dL/week·kg·g Hb; $P < 0.05$), but was not different between the groups at month 6 (5.36 ± 3.27 vs. 4.86 ± 4.19 IU·dL/week·kg·g Hb) and month 12 (5.71 ± 3.81 vs. 4.75 ± 3.83 IU·dL/week·kg·g Hb). ERI did not change from the baseline in the NV group whereas it was higher than the baseline at month 6 in the PS group (3.79 ± 1.24 vs. 4.86 ± 4.19 IU·dL/week·kg·g Hb).

There were 69 and 50 middle-ERI patients in the NV and PS groups, respectively (Fig. 1C). ERI was not different between the middle-ERI patients of the NV and PS groups at baseline (8.52 ± 1.74 vs. 8.24 ± 1.79 IU·dL/week·kg·g Hb; *NS*), but was significantly lower at month 12 in the NV group than the PS group (8.24 ± 5.15 vs. 10.69 ± 6.68 IU·dL/week·kg·g Hb; $P < 0.05$). ERI did not change from the baseline in the NV group throughout the study period, but was significantly higher than the baseline at month 12 in the PS group (8.24 ± 1.79 vs. 10.69 ± 6.68 IU·dL/week·kg·g Hb; $P < 0.05$; Fig. 1C).

There were 25 and 11 high-ERI patients in the NV and PS groups, respectively (Fig. 1D). ERI was not different between the high-ERI patients of the NV and PS groups at baseline (17.75 ± 4.60 vs. 15.17 ± 2.66 IU·dL/week·kg·g Hb), month 6 (15.13 ± 8.47 vs. 11.26 ± 6.02 IU·dL/week·kg·g Hb) and month 12 (13.36 ± 7.52 vs. 13.9 ± 9.6 IU·dL/week·kg·g Hb) (Fig. 1D). However, ERI was significantly lower than the baseline in the NV group at month

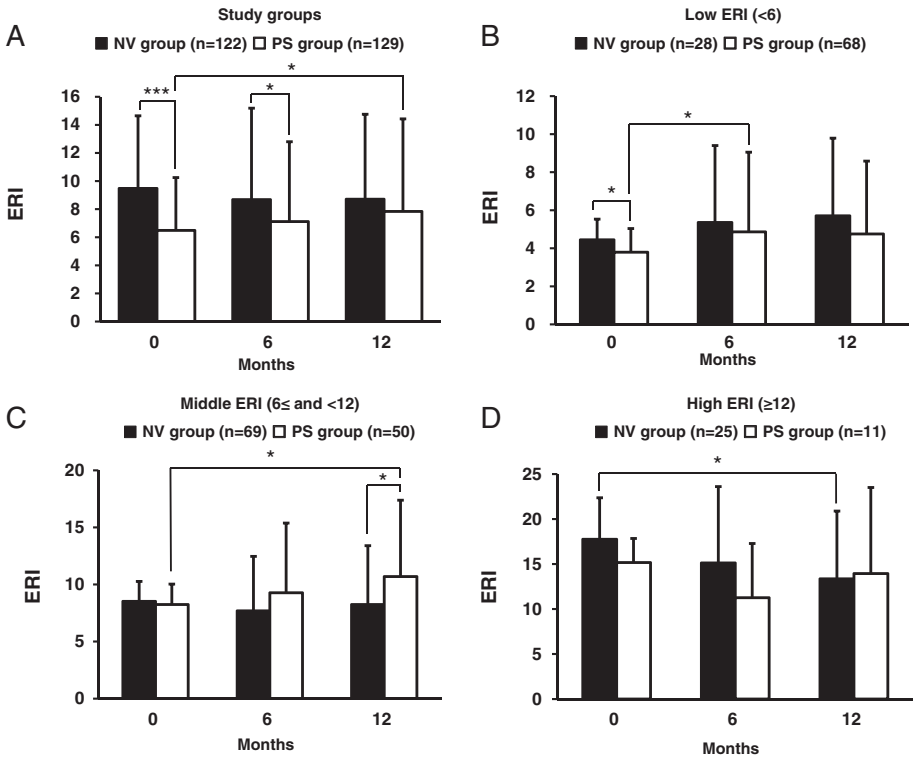

FIG. 1. Erythropoiesis stimulating agent resistance index during the study period. Erythropoiesis stimulating agent resistance indices (ERI) at baseline, months 6 and 12 are shown. (A) ERI was compared within and between patients dialyzed for 12 months with the TORAYLIGHT NV dialyzer (NV group) and those dialyzed with the conventional polysulfone type membrane dialyzers (PS group). (B-D) ERI was compared within and between the subgroups of patients formed in the NV and PS groups according to the ranges of the baseline ERI indicated in the figure. The number of patients available for analysis is shown in the parentheses for each group or sub-group. Values are means ± SD. *$P < 0.05$; ***$P < 0.001$.

12 (17.75 ± 4.60 vs. 13.36 ± 7.52 IU·dL/week·kg·g Hb; $P < 0.05$). ERI did not change significantly in the PS group.

The overall changes that occurred in ERI during the 12-month study period (ΔERI) are shown in Figure 2. At the study population level, the overall changes were −0.77 ± 5.93 IU·dL/week·kg·g Hb in the NV group and 1.35 ± 5.71 IU·dL/week·kg·g Hb in the PS group (Fig. 2A). The difference between the groups was significant ($P < 0.05$). Post hoc analysis of the patient subgroups revealed a significant difference in the overall change in the middle-ERI patients of the NS and PS groups (−0.28 ± 5.34 vs. 2.45 ± 6.39 IU·dL/week·kg·g Hb; $P < 0.05$) (Fig. 2C). The overall changes were not different between the NS and PS groups in the low-ERI patients (1.26 ± 3.80 vs. 0.96 ± 3.66 IU·dL/week·kg·g Hb; *NS*) (Fig. 2A) or the high-ERI patients (−4.39 ± 7.81 vs. −1.23 ± 10.66 IU·dL/week·kg·g Hb; *NS*) (Fig. 2D).

ESA dose

ESA dose was higher in the NV than in the PS group at baseline (5052 ± 2239 vs. 3657 ± 1720 U/week; $P < 0.001$) and month 6 (4557 ± 2921 vs. 3882 ± 2407 U/week; $P < 0.05$) (Fig. 3A). However, ESA dose was not different between the NV and PS groups at month 12 (4594 ± 279 vs. 4213 ± 2924 U/week). ESA dose did not change significantly in either the NV or PS group during the study period.

In order to further characterize the changes in ESA dose, post hoc analyses were performed after dividing the patients of each group into low-ESA dose (≤3000 IU/week), middle-ESA dose (3000< and ≤6000 IU/week) or high-ESA dose (>6000 IU/week) subgroups according to the baseline ESA dose.

There were 21 and 61 low-ESA patients in the NV and the PS groups, respectively (Fig. 3B). ESA dose was not significantly different between the low-ESA patients of the NV and PS groups throughout the study period. ESA dose did not change significantly from the baseline in the NV group during the study period (baseline, 2393 ± 462 IU/week; month 6, 3196 ± 2224 IU/week; and month 12, 2900 ± 2051 IU/week). In contrast, ESA dose was higher than the baseline in the PS group at month 6 (2292 ± 622 vs. 3080 ± 2102 IU/week; $P < 0.01$) and month 12 (3151 ± 2370 IU/week; $P < 0.01$).

There were 67 and 54 middle-ESA patients in the NV and the PS groups, respectively (Fig. 3C). ESA dose did not change significantly from the baseline in the middle-ERI patients of the NV group (baseline, 4349 ± 755 IU/week; month 6, 4092 ± 2388 IU/week; and month 12, 4647 ± 2421 IU/week) or in those of the PS group (baseline, 4296 ± 799 IU/

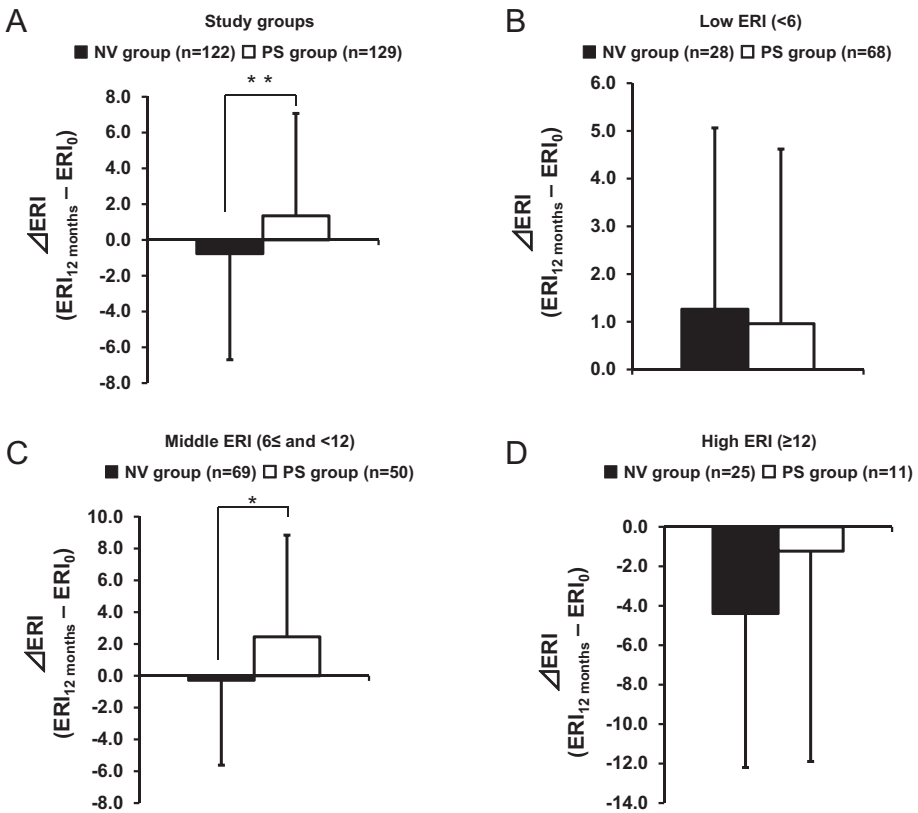

FIG. 2. Overall changes in ERI during the study period. The overall changes that occurred in ERI during the 12-month study period (ΔERI) are shown. (A) ΔERI was compared between patients dialyzed for 12 months with the TORAYLIGHT NV dialyzer (NV group) and those dialyzed with the conventional polysulfone type membrane dialyzers (PS group). (B-D) ΔERI was compared between the subgroups of patients formed in the NV and PS groups according to the ranges of the baseline ERI indicated in the figure. The number of patients available for analysis is shown in the parentheses for each group or subgroup. Values are means ± SD. *$P < 0.05$; **$P < 0.01$.

week; month 6, 4056 ± 1976 IU/week; and month 12 4630 ± 2662 IU/week).

There were 34 and 14 high-ESA patients in the NV and the PS groups, respectively (Fig. 3D). ESA dose was higher in the high-ERI patients of the NV group than in those of the PS group at baseline (8082 ± 1468 vs. 7140 ± 1108 IU/week; $P < 0.01$). However, ESA dose was not different between the NV and PS groups at month 6 (6316 ± 3476 vs. 6152 ± 3475 IU/week) and month 12 (5538 ± 3410 vs. 7231 ± 3679 IU/week). ESA dose was significantly lower than the baseline (8082 ± 1468 IU/week) in the NV group at month 6 (6316 ± 3476 IU/week; $P < 0.01$) and month 12 (5538 ± 3410 IU/week; $P < 0.001$). ESA dose did not change significantly from the baseline in the PS group during the study period.

The overall changes that occurred in ESA dose during the 12-month study period (ΔESA dose) are shown in Figure 4. At the study population level, the overall changes were −458 ± 3058 IU/week in the NV group and 556 ± 2564 IU/week in the PS group (Fig. 4A). The difference between the groups was significant ($P < 0.01$). Post hoc analysis of the patient subgroups revealed a significant difference between the high-ESA dose patients of the NV and PS groups (−2543 ± 3724 vs. 91 ± 3680 IU/week; $P < 0.05$) (Fig. 4D). No significant differences were found between the NV and PS groups in the low-ESA dose patients (507 ± 1948 vs. 859 ± 2252 IU/week) (Fig. 4B) or the middle-ESA dose patients (298 ± 2437 vs. 334 ± 2570 IU/week) (Fig. 4C).

Hemoglobin

Hemoglobin concentrations were lower in the NV than in the PS group at baseline ($P < 0.001$), but were not different between the groups at month 12. Hemoglobin concentrations did not change from the baseline in the NV group throughout the study period, but were lower than the baseline in the PS group at month 6 ($P < 0.05$) and 12 ($P < 0.05$).

For the low-ERI patients, hemoglobin concentrations were lower in the NV than in the PS group at baseline ($P < 0.01$), but were not different between the groups at months 6 or 12. Hemoglobin concentrations did not change from the baseline in the NV group throughout the study period, but were lower than the baseline in the PS group at months 6 ($P < 0.01$) and 12 ($P < 0.01$). For the middle-ERI patients, hemoglobin concentrations were lower in the NV than in the PS group at baseline ($P < 0.05$), but were not different between the groups at months 6 or 12. For the high-ERI patients,

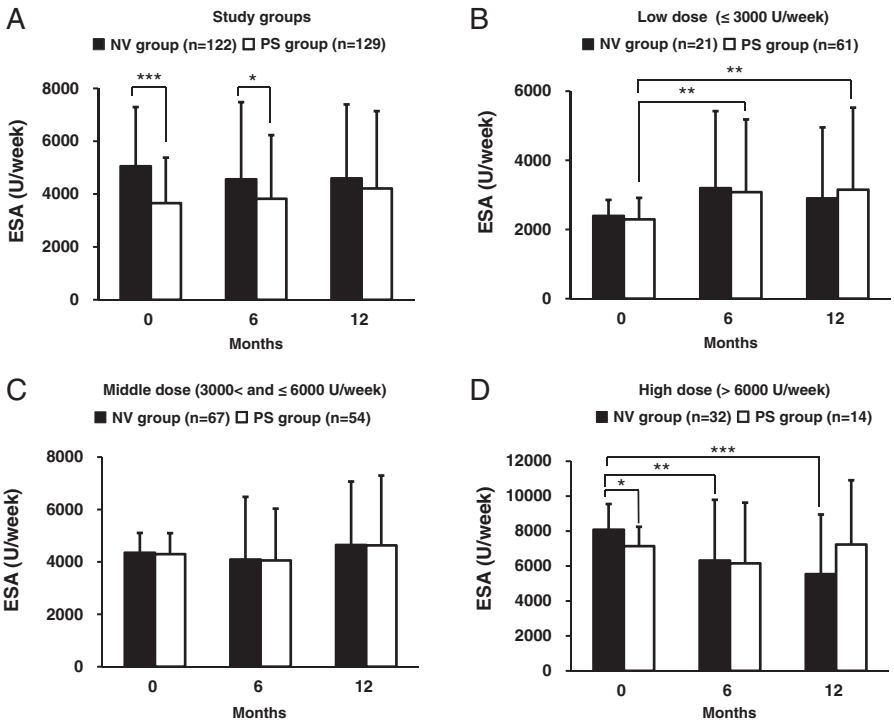

FIG. 3. Erythropoiesis stimulating agent dose during the study period. Erythropoiesis stimulating agent (ESA) doses at baseline, months 6 and 12 are shown. (A) ESA dose was compared within and between patients dialyzed for 12 months with the TORAYLIGHT NV dialyzer (NV group) and those dialyzed with the conventional polysulfone-type membrane dialyzers (PS group). (B-D) ESA dose was compared within and between the subgroups of patients formed in the NV and PS groups according to the ranges of the baseline ESA dose indicated in the figure. The number of patients available for analysis is shown in the parentheses for each group or subgroup. Values are means ± SD. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

hemoglobin concentrations neither were different between the groups nor changed in either group.

C-reactive protein

CRP was not different between the NV and PS groups or between the corresponding ERI-based subgroups throughout the study period, and did not change significantly in either the NV or PS group, or in any of the subgroups.

Iron utilization

TSAT was lower in the NV group than in the PS group at baseline ($P < 0.01$) and month 6 ($P < 0.01$), but was not different between the groups at month 12 (Table 3). TSAT did not change in either group throughout the study period. For the low-ERI patients, TSAT did not change in the NV group but was lower than the baseline in the PS group at month 12 ($P < 0.05$). For the middle-ERI patients, TSAT neither was different between the groups nor showed significant changes from the baseline in either group. For the high-ERI patients, TSAT was not different at baseline between the groups but was lower in the NV group than in the PS group at month 12 ($P < 0.05$). TSAT did not change significantly from the baseline in either group.

The frequency of iron supplementations was significantly higher in the NV than in the PS group at baseline and month 6 (Table 3). Prescribed iron supplementations were all intravenous.

Laboratory data

White blood cell and platelet counts were not different at baseline between the NV and PS groups or between corresponding ERI-based subgroups, and did not change significantly in either group or any subgroup throughout the study period (Table 3).

Serum albumin was not different between the NV and PS groups or between the corresponding ERI-based subgroups throughout the study period, and did not change significantly in either the NV or PS group, or in any of the subgroups (Table 3).

DISCUSSION

ERI and ESA dose were higher in the NV than in PS group at baseline and month 6, but were not different between the groups at month 12. The overall changes in ERI and ESA dose were both reductions in the NV group compared to those in the PS group. Subgroup analyses revealed a significant decrease in ERI and ESA dose in the high-ERI and high-ESA patients, respectively, of the NV group. In contrast, ERI increased in the low- and middle-ERI patients, and ESA dose increased in the low-

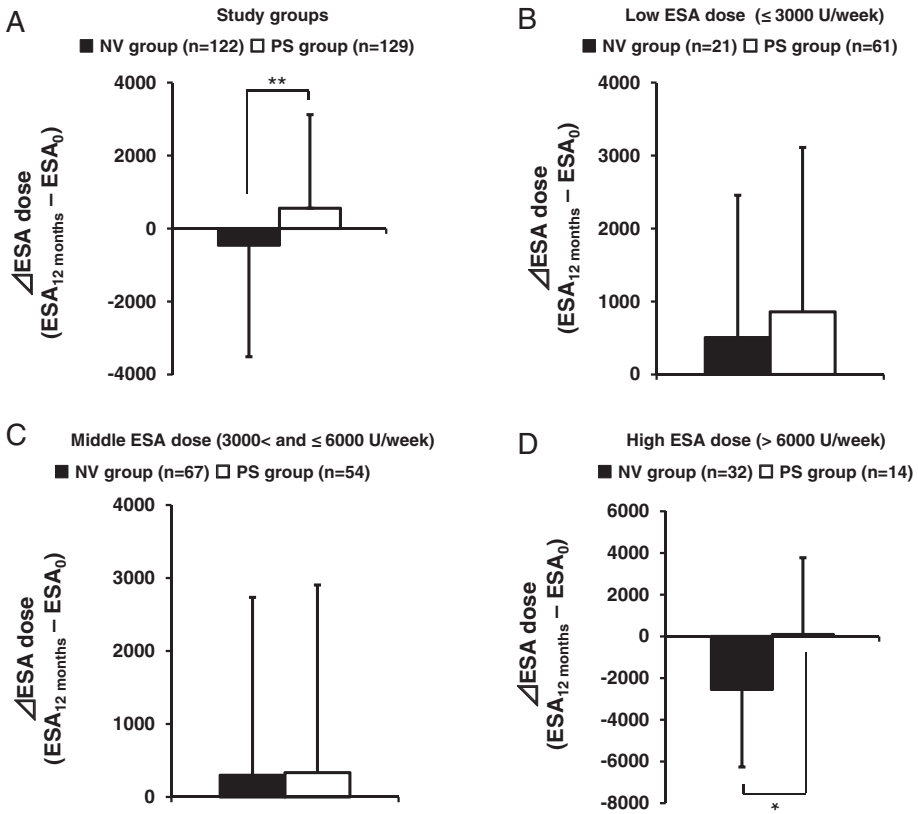

FIG. 4. Overall changes in ESA dose during the study period The overall changes that occurred in Erythropoiesis stimulating agent (ESA) dose during the 12-month study period (ΔESA dose) are shown. (A) ΔESA dose was compared between patients dialyzed for 12 months with the TORAYLIGHT NV dialyzer (NV group) and those dialyzed with the conventional polysulfone type membrane dialyzers (PS group). (B-D) ΔESA dose was compared between the subgroups of patients formed in the NV and PS groups according to the ranges of the baseline ESA dose indicated in the figure. The number of patients available for analysis is shown in the parentheses for each group or subgroup. Values are means ± SD. $*P < 0.05$; $**P < 0.01$.

ESA patients of the PS group. Thus, ESA responsiveness improved in the highly ESA-resistant patients of the NV group. ESA resistance either remained unchanged or worsened in the subgroups of the PS group.

Hemoglobin did not change in the NV group or in any of its ERI-based subgroups whereas a significant decrease occurred in the PS group and its low-ERI patients. TSAT did not change in either the NV or PS group or in their ERI-based subgroups except it decreased in the low-ERI patients of the PS group. CRP and serum albumin did not change significantly in either the NV or PS group, or in any of the subgroups throughout the study period. Taken together, ESA resistance was improved in the high-ERI patients of the NV group with no changes in hemoglobin, TSAT, CRP, or albumin. In contrast, ESA resistance worsened in the low-ERI patients of the PS group in association with decreases in hemoglobin and TSAT and no changes in CRP or albumin.

Our previous small-scale randomized controlled trial showed that ESA dose and ERI decreased in hemodialysis patients within 1 year after the patients were switched from conventional PS dialyzers onto the NV dialyzer (10). The mean baseline ESA dose of the subjects was 3050 ± 2147 IU/week, which would place these patients in the low- or middle-ESA dose subgroup of the present study. These patients have similarities and differences with the present high-ERI patients. The inclusion and exclusion criteria were essentially identical between the two studies except baseline dialysis vintage was ≥7 years as opposed to ≥15 months in the present study, resulting in the baseline vintage of 18.0 ± 6.9 years in the previous patients and 8.7 ± 7.2 years in the present high-ERI patients. Importantly, the previous patients were enrolled for their relatively high baseline serum interleukin-6 (IL-6) levels (mean ± SD 5.4 ± 2.1 pg/mL; range 3.2–8.5 pg/mL) in the initial population of 72 eligible patients. This selection was done because the primary objective of the trial was to compare dialysis-associated IL-6 removal and induction between the NV and conventional PS dialyzers (10). The baseline CRP was 1.48 ± 1.52 (range 0.26–5.25) μg/mL as opposed to 0.38 ± 1.19 (range 0.01–6.00) mg/dL in the present high-ERI patients. Other baseline values of the previous patients and present high-ERI patients, respectively, are hemoglobin 11.1 ± 1.1 vs. 9.8 ± 0.7 g/dL and age 57 ± 11 vs. 67 ± 10 years. Given that the present study was powered for analyses at

TABLE 3. *Laboratory data during the study period*

	Months					
	Baseline		6		12	
WBC (cells/μL)						
ERI (total)						
NV group	5736 ± 1647	(2563, 15 833) (*n* = 122)	5775 ± 1587	(2730, 11 840) (*n* = 122)	5658 ± 1455	(2600, 9980) (*n* = 122)
PS group	5835 ± 1423	(3023, 10 647) (*n* = 129)	5994 ± 1616	(2770, 12 630) (*n* = 129)	5997 ± 1743	(2300, 13 450) (*n* = 129)
Low ERI (<6)						
NV group	6419 ± 2255	(3607, 15 833) (*n* = 28)	6469 ± 1996	(3800, 11 840) (*n* = 28)	6056 ± 1512	(3600, 8800) (*n* = 28)
PS group	6003 ± 1474	(3263, 10 647) (*n* = 68)	6201 ± 1698	(3360, 12 630) (*n* = 68)	6216 ± 1599	(2960, 10 970) (*n* = 68)
Middle ERI (6 ≤ and < 12)						
NV group	5716 ± 1372	(2563, 9423) (*n* = 69)	5617 ± 1380	(2820, 8870) (*n* = 69)	5723 ± 1435	(2600, 9980) (*n* = 69)
PS group	5764 ± 1326	(3517, 9700) (*n* = 50)	5858 ± 1512	(3000, 10 310) (*n* = 50)	5882 ± 1926	(2300, 13 450) (*n* = 50)
High ERI (≥12)						
NV group	5024 ± 1245	(2660, 7633) (*n* = 25)	5433 ± 1435	(2730, 8200) (*n* = 25)	5032 ± 1290	(3000, 8000) (*n* = 25)
PS group	5123 ± 1397	(3023, 7003) (*n* = 11)	5328 ± 1450	(2770, 8420) (*n* = 11)	5165 ± 1564	(2970, 8820) (*n* = 11)
PLT (x10^{4}cells/μL)						
ERI (total)						
NV group	18.2 ± 5.6	(5.7, 41.6) (*n* = 122)	19.5 ± 7.1	(7.9, 52.5) (*n* = 121)	18.4 ± 5.4	(7.0, 41.1) (*n* = 122)
PS group	18.6 ± 4.6	(8.8, 36.8) (*n* = 129)	19.0 ± 4.8	(8.7, 33.9) (*n* = 129)	18.9 ± 4.6	(7.7, 32.0) (*n* = 129)
Low ERI (<6)						
NV group	18.8 ± 4.8	(12.4, 30.6) (*n* = 28)	19.6 ± 5.4	(12.2, 29.9) (*n* = 28)	19.0 ± 4.8	(12.7, 30.3 (*n* = 28)
PS group	18.9 ± 4.3	(9.2, 30.0) (*n* = 68)	19.7 ± 5.1	(9.0, 33.9) (*n* = 68)	19.6 ± 4.6	(10.2, 30.6) (*n* = 68)
Middle ERI (6 ≤ and < 12)						
NV group	18.2 ± 5.1	(9.7, 33.1) (*n* = 69)	19.4 ± 6.4	(10.6, 43.8) (*n* = 69)	18.1 ± 4.6	(8.9, 29.3) (*n* = 69)
PS group	18.3 ± 5.0	(9.0, 36.8) (*n* = 50)	18.3 ± 4.3	(8.8, 31.3) (*n* = 50)	18.3 ± 4.7	(7.7, 32.0) (*n* = 50)
High ERI (≥12)						
NV group	17.7 ± 7.6	(5.7, 41.6) (*n* = 25)	19.9 ± 10.1	(7.9, 52.5) (*n* = 25)	18.4 ± 7.8	(7.0, 41.1) (*n* = 25)
PS group	17.5 ± 4.5	(8.8, 24.2) (*n* = 11)	17.3 ± 5.4	(8.7, 24.9) (*n* = 11)	17.4 ± 4.5	(8.0, 24.2) (*n* = 11)
TSAT (%)						
ERI (total)						
NV group	21.7 ± 9.4$^{\#\#}$	(3.8, 48.0) (*n* = 100)	20.6 ± 10.4$^{\#\#}$	(4.5, 54.5) (*n* = 74)	22.9 ± 9.9	(6.3, 53.6) (*n* = 96)
PS group	25.6 ± 7.1	(10.8, 47.2) (*n* = 74)	26.0 ± 10.1	(11.5, 62.1) (*n* = 75)	23.8 ± 7.5	(8.2, 47.4) (*n* = 75)
Low ERI (<6)						
NV group	25.4 ± 9.6	(6.2, 44.1) (*n* = 23)	21.3 ± 10.3	(8.7, 43.5) (*n* = 17)	22.0 ± 5.3	(12.9, 31.4) (*n* = 20)
PS group	27.0 ± 6.9	5.5, 47.2) (*n* = 45)	27.1 ± 10.9	(13.4, 62.1) (*n* = 45)	23.2 ± 7.0$^{\$}$	(11.9, 42.0) (*n* = 45)
Middle ERI (6 ≤ and < 12)						
NV group	22.2 ± 9.2	(3.8, 48.0) (*n* = 56)	22.9 ± 10.5 (40)	(6.5, 54.5) (*n* = 40)	25.0 ± 10.7 (55)	(6.3, 53.6) (*n* = 55)
PS group	24.3 ± 6.8	(15.9, 44.7) (*n* = 23)	25.0 ± 8.5 (24)	(11.5, 45.9) (*n* = 24)	24.4 ± 9.2 (24)	(8.2, 47.4) (*n* = 24)
High ERI (≥12)						
NV group	16.5 ± 7.8	(9.3, 44.7) (*n* = 21)	14.3 ± 8.4	(4.5, 42.0) (*n* = 17)	18.6 ± 10.0$^{\#}$	(7.0, 46.2) (*n* = 21)
PS group	20.5 ± 8.2	(10.8, 33.4) (*n* = 6)	21.8 ± 10.4	(12.0, 39.4) (*n* = 6)	25.2 ± 3.6	(19.9, 28.6) (*n* = 6)
Alb (mg/dL)						
ERI (total)						
NV group	3.8 ± 0.3	(3.2, 4.6) (*n* = 122)	3.8 ± 0.3	(3.0, 4.6) (*n* = 122)	3.7 ± 0.3	(3.0, 4.5) (*n* = 122)
PS group	3.8 ± 0.3	(2.7, 4.5) (*n* = 129)	3.8 ± 0.3	(2.9, 4.5) (*n* = 129)	3.8 ± 0.3	(2.5, 4.5) (*n* = 129)
Low ERI (<6)						
NV group	3.8 ± 0.2	(3.4, 4.2) (*n* = 28)	3.8 ± 0.2	(3.3, 4.2) (*n* = 28)	3.7 ± 0.2	(3.3, 4.2) (*n* = 28)
PS group	3.8 ± 0.3	(2.9, 4.5) (*n* = 68)	3.8 ± 0.3	(3.0, 4.3) (*n* = 68)	3.8 ± 0.3	(3.2, 4.4) (*n* = 68)

(Continues)

TABLE 3. *Continued*

	Months					
	Baseline		6		12	
Middle ERI (6 ≤ and < 12)						
NV group	3.8 ± 0.3	(3.2, 4.6) (*n* = 69)	3.8 ± 0.3	(3.0, 4.6) (*n* = 69)	3.7 ± 0.3	(3.2, 4.5) (*n* = 69)
PS group	3.8 ± 0.3	(3.1, 4.5) (*n* = 50)	3.9 ± 0.3	(3.2, 4.5) (*n* = 50)	3.8 ± 0.3	(3.1, 4.5) (*n* = 50)
High ERI (≥12)						
NV group	3.8 ± 0.2	(3.4, 4.2) (*n* = 25)	3.8 ± 0.3	(3.3, 4.4) (*n* = 25)	3.8 ± 0.3	(3.0, 4.2) (*n* = 25)
PS group	3.7 ± 0.4	(2.7, 4.1) (*n* = 11)	3.7 ± 0.4	(2.9, 4.4) (*n* = 11)	3.6 ± 0.6	(2.5, 4.1) (*n* = 11)
Iron supplementation (Y/N)						
ERI (total)						
NV group	43/79[#]	(35.2% / 64.8%) (*n* = 122)	49/73[##]	(40.2% / 59.8%) (*n* = 122)	23/99	(18.9% / 81.1%) (*n* = 122)
PS group	27/102	(20.9% / 79.1%) (*n* = 129)	29/101	(21.7% / 78.3%) (*n* = 129)	14/115	(10.9% / 89.1%) (*n* = 129)
Low ERI (<6)						
NV group	7/21	(25.0% / 75.0%) (*n* = 28)	10/18	(35.7% / 64.3%) (*n* = 28)	6/22	(21.4% / 78.6%) (*n* = 28)
PS group	10/58	(14.7% / 85.3%) (*n* = 68)	12/56	(17.6% / 82.4%) (*n* = 68)	7/61	(10.3% / 89.7%) (*n* = 68)
Middle ERI (6 ≤ and < 12)						
NV group	27/42	(39.1% / 60.9%) (*n* = 69)	28/41	(40.6% / 59.4%) (*n* = 69)	14/55	(20.3% / 79.7%) (*n* = 69)
PS group	14/36	(28.0% / 72.0%) (*n* = 50)	15/35	(30.0% / 70.0%) (*n* = 50)	6/44	(12.0% / 88.0%) (*n* = 50)
High ERI (≥12)						
NV group	9/16	(36.0% / 64.0%) (*n* = 25)	11/14[#]	(44.0% 56.0%) (*n* = 25)	3/22	(12.0% / 88.0%) (*n* = 25)
PS group	3/8	(27.3% / 72.7%) (*n* = 11)	1/10	(9.1% / 90.9%) (*n* = 11)	1/10	(9.1% / 90.9%) (*n* = 11)

[#]$P < 0.05$, [##]$P < 0.01$, and [###]$P < 0.001$ for the NV group vs. the PS group. [$]$P < 0.05$, [$$]$P < 0.01$, and [$$$]$P < 0.001$ for baseline vs. each month within each group or subgroup. Results are presented as mean ± SD. Shown in the parentheses is the range. Alb, serum albumin; ERI, erythropoiesis stimulating agent resistance index; Hb, hemoglobin; NV, the NV dialyzer; PLT, platelets; PS, conventional polysulfone membrane dialyzers; TSAT, transferrin saturation; WBC, white blood cell.

the study population level, the post hoc analyses may have been insufficiently powered to detect potential effects of the NV dialyzer on mild ESA resistance.

Chronic inflammation is implicated in ESA resistance in hemodialysis patients (15–18). However, the NV dialyzer reduced ERI with no significant changes in inflammation markers in both the present and our previous studies (10). A similar ESA-sparing effect has been identified in a large-scale randomized controlled trial on vitamin-E-coated PS membranes (14). Analyses at the study population level found no beneficial effects of the vitamin-E-coated membranes on ERI or CRP. However, when the patients were stratified into tertiles of baseline ERI, a significant decrease in ERI was revealed in the highest tertile of ERI while no changes occurred in CRP. ERI increased in the lowest tertile of ERI who were either on the vitamin-E-coated or on noncoated control membrane, with no changes in CRP (14). The authors noted that Panichi et al. (13) found no significant correlations between the reductions in ERI and inflammation markers although these parameters were reduced after 6 months of dialysis with vitamin-E-coated membranes. The authors further pointed out that the baseline ERI levels were higher in the studies describing ESA-sparing effects of vitamin-E-coated membranes than in those showing no such effects (14). This notion holds true for a recent multicenter trial of a vitamin-E-coated membrane that reports an ESA-sparing effect of the membrane in hemodialysis patients with median ERI of 12.8 (19). It appears that the ESA-sparing potentials of the vitamin-E-coated membrane and the NV dialyzer are independent of their effects on systemic inflammation.

We have previously suggested that the ESA-sparing effect of the NV dialyzer can be attributed to its reduced dialysis-associated acute IL-6 induction as compared with conventional PS dialyzers (10). Our hypothesis is that dialysis-associated acute IL-6 induction causes a transient increase in circulating IL-6 levels, which affects the erythropoietic system at each dialysis session, aggravating ESA resistance over time. Likewise, vitamin-E-coated membranes suppress dialysis-associated acute IL-6 induction. A prospective crossover trial showed that vitamin-E-coated cuprophane membranes caused less dialysis-associated acute IL-6 production than noncoated polyamide membranes (20). Vitamin-E-coated membranes bring benefits primarily by quenching oxidative substances that are generated when blood cells contact the dialysis membrane (21,22). The NV dialyzer reduces dialysis-associated platelet activation by enhancing the water mobility adjacent to the membrane (6–9), resulting in reduced dialysis-associated acute IL-6 production (10). Common to these two types of dialysis membrane are an ESA-sparing potential independent of effects on systemic inflammation and reduced dialysis-associated acute production of pro-inflammatory substances.

The present study did not address the mechanisms for the ESA-sparing potential of the NV dialyzer. Of the inflammation markers associated with ESA resistance (15–18,23), IL-6 may be causally related with ESA resistance because IL-6 induces the production of hepcidin from hepatocytes (24). Hepcidin is an acute phase protein that downregulates iron absorption and recycling, thereby suppressing erythropoiesis (25). Hence, this IL-6-hepcidin pathway is a likely mediator of anemia of inflammation (24,25). Hemodialysis unavoidably brings about contact of dialysis membranes with platelets and other blood cells, causing a transient increase in pro-inflammatory cytokines and oxidative stress upon each dialysis session. Resulting IL-6 upregulates hepcidin production, which suppresses erythropoiesis, leading to ESA resistance over time. We speculate that activation of the IL-6-hepcidin pathway underlies dialysis-associated ESA hyporesponsiveness. The NV dialyzer and vitamin-E-coated membranes reduce the impact of dialysis-associated activation of IL-6-hepcidin pathway and decelerates the aggravation of ESA resistance or improves ESA requirement.

Limitations

First, some data of CRP and TSAT were unavailable. These tests were not among routine laboratory tests at some of the participating institutions. Second, we had to resort to post hoc analysis to explore the ESA-sparing potential of the NV dialyzer, which may have reduced the power of analysis. Third, we could not adjust for potential confounding factors such as inflammation markers, iron utilization/status markers, parathyroid hormone levels, and angiotensin II receptor blockers (ARBs) use because some of these data were not available for some patients.

CONCLUSIONS

Given the limitations of the present study, we limit our conclusions to suggesting that the TORAYLIGHT NV (NV) dialyzer decelerates

aggravation of erythropoiesis stimulating agent (ESA) resistance in prevalent dialysis patients and can improve ESA responsiveness at least in highly ESA-resistant hemodialysis patients. Further investigation is warranted for potential benefits of the NV dialyzer on ESA resistance in hemodialysis patients.

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