A Prospective Multicenter Randomized Controlled Study on Interleukin-6 Removal and Induction by a new Hemodialyzer With Improved Biocompatibility in Hemodialysis Patients: A Pilot Study

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Abstract: We compared interleukin-6 (IL-6) removal and induction between conventional polysulfone (Con) and TORAYLIGHT NV (NV) dialyzers in hemodialysis patients. Twenty patients on Con with high IL-6 concentrations (2.7–8.5 pg/mL) were randomized to Con or NV group. Dialyzer performance was determined in NV group while patients were on Con and after being switched onto NV. Erythropoiesis-stimulating agent (ESA) response index (ERI) was assessed every 4 months for one year. IL-6 clearance was comparable between Con and NV. IL-6 removal rates were comparable for the first 1 h, but were higher with NV for the entire session (P = 0.03). Before-to-during-dialysis IL-6 concentration ratios were lower with NV on the venous side after the session (P = 0.03). During the one-year study, hemoglobin was lower in Con group than in NV group at month 8 (P = 0.046). ERI decreased in NV and increased in Con group, with a significant difference between the groups (P = 0.002). NV and Con are comparable in removing IL-6 and both induce IL-6. However, the data suggest that NV induces less IL-6, which may reduce the risk of ESA hyporesponsiveness. Key Words: Biocompatibility, Erythropoiesis stimulating agent, Hemodialysis, Inflammatory cytokine.

Hemodialysis is a common renal replacement modality. Hemodialysis patients often suffer cardiovascular disease and nutritional disorders. Available evidence has linked these cardiovascular and nutritional risks to chronic inflammatory states of dialysis patients characterized by elevated levels of circulating pro-inflammatory cytokines (1). Particularly, high interleukin-6 (IL-6) levels are a powerful predictor of cardiovascular and all-cause mortality in hemodialysis patients (2,3). Chronic inflammation is implicated in reduced response to erythropoiesis-stimulating agents (ESA) in hemodialysis patients. Elevated C-reactive protein (CRP) or IL-6 levels correlate with higher ESA requirements (4–7). IL-6 gene polymorphisms associated with high IL-6 secretion correlate with higher ESA doses (8). Since ESA hyporesponsiveness predicts mortality in hemodialysis patients (9) or increased risk of adverse outcomes in chronic kidney disease patients (10), measures against inflammation and high pro-inflammatory cytokine levels are of critical importance.
Potential causes of elevated cytokine levels in hemodialysis patients include the loss of renal function, uremia and associated toxic substances, and dialysis-related factors (11). Dialysis-related factors are poor cytokine clearance and its induction. Multifold evidence indicates that hemodialysis induces cytokine production. Peripheral blood mononuclear cells from hemodialysis patients produce more pro-inflammatory cytokines in vitro than those from healthy subjects (12). Dialysis with poorly biocompatible membranes activates mononuclear cells more strongly than more biocompatible membranes (13). Blood IL-6 levels increase both during and after the dialysis session (14).

Biocompatibility of synthetic polymers as biomaterial is in part determined by the mobility of water adjacent to synthetic polymers (15–17). The TORAYLIGHT NV dialyzer is a newly developed dialyzer with its polysulfone membrane surface modified to enhance the mobility of water adjacent to the membrane and exhibits reduced platelet activation and adhesion to the membrane than conventional polysulfone dialyzers (18). A recent study showed that 3 months of dialysis with the TORAYLIGHT NV dialyzer reduced the blood levels of platelet-derived microparticles released from activated platelets and improved flow-mediated arterial dilatation (19).

This study assessed IL-6 removal performance of the TORAYLIGHT NV dialyzer against conventional polysulfone dialyzers and its long-term impact on erythropoiesis and nutritional status in hemodialysis patients.

**PATIENTS AND METHODS**

**Subjects**

Seventy-two patients undergoing dialysis with conventional high-flux polysulfone type dialyzers (Con-DL) including polyethersulfone at seven participating facilities were found eligible for the study (Fig. 1). Inclusion criteria were age $\geq 20$ and $< 80$ years, dialysis vintage $\geq 7$ years, at least three 4-h dialysis sessions per week, and no history of dialysis with the TORAYLIGHT NV dialyzer (NV-DL; Toray Industries, Inc., Tokyo, Japan). Exclusion criteria were renal replacement therapy other than hemodialysis, enrollment in other ongoing clinical studies, within 3 years after radical cancer therapy, cardiovascular events in 6 months, peripheral arterial diseases $\geq$ Fontaine class II, uncontrollable diabetes or HbA1c $> 8\%$, acute inflammation (CRP $\geq 2$ mg/dL), uncontrollable anemia (hemoglobin $< 8.5$ g/dL), being pregnant or intending to be pregnant within 1 year, or being judged inadequate by a participating physician.

**Study design**

Our review of past studies (20,21) concluded that a sample size of 10 patients per dialyzer type would be sufficient to detect differences in cytokine removal performance and clinical effects of dialyzers.

In order to establish two groups of 10 patients each, the above 72 patients were screened for serum IL-6 concentrations before the first dialysis of the week. At this point, 18 patients declined further participation, and two changed the renal replacement modality to hemodiafiltration (Fig. 1). The remaining 52 patients consented to participate in the next phase of the study. From those, 20 patients with the highest IL-6 concentrations were enrolled with no cut-off for IL-6 concentrations and randomly allocated to dialysis with Con-DL (Con group) or NV-DL (NV group) using block randomization as follows: the 20 patients were listed in order of serum IL-6 concentration and separated into five groups of four patients each. The five groups were numbered from 1 to 5 in descending order of IL-6 concentration. Six $1 \times 4$ blocks, each representing one of the six possible permutations of two Cons and two NVs, were prepared and randomly numbered from 1 to 6. The numbers of the patient groups were matched to the numbers of the blocks, allocating the enrolled patients to Con or NV group. Random numbering of the blocks and matching of the block and patient group numbers were repeated until no statistically significant differences were found in patient characteristics of the two groups.

Removal performance for IL-6 and $\beta_2$-microglobulin ($\beta_2$-MG) was determined in the NV group during the first month after the randomization while the patients were on Con-DL and after they were switched onto NV-DL. After switched onto NV-DL, NV group patients stayed on NV-DL for one year for long-term evaluation described blow.

For long-term clinical evaluation, serum IL-6 concentrations, erythropoiesis-stimulating agent (ESA) dose, laboratory parameters and nutritional indices were determined in the Con and NV groups every 4 months for one year using blood and clinical data collected at the first dialysis session of the week. No patient withdrew after randomization.

Effectiveness of hemodialysis was examined using Kt/V. Vascular access was gained via arteriovenous fistula in all patients. Dialysate quality was periodically inspected once a month at all participating facilities according to “Standard on Microbiological Management of Fluids for Hemodialysis and Related
Therapies by the Japanese Society for Dialysis Therapy 2008” (22). No endotoxin or microorganisms were detected in the dialysates at any time point during the study period.

**Serum IL-6 and β2-microglobulin concentrations**

Serum IL-6 and β2-MG concentrations were determined using a chemiluminescence enzyme immunoassay (Human IL-6 CLEIA Fujirebio, FUJIREBIO Inc., Tokyo, Japan) and a latex photometric immunoassay (LZ Test Eiken β2-M, Eiken Chemical Co., Ltd, Tokyo, Japan), respectively.

**Evaluation of removal performance**

Blood was sampled from the arterial side before and after the dialysis session, and from the arterial and venous sides 1 and 4 h after the start of dialysis. Clearance, removal rates and before-to-during-dialysis concentration ratios were determined using the following formulae described in the guidelines from the Japanese Society for Dialysis Therapy:

\[
\text{Clearance} = \left( \frac{Q_{P, A, Xhr} \times C_{A, Xhr}}{Q_{P, V, Xhr} \times C_{V, Xhr}} \right) / C_{A, Xhr}
\]

where

\[
Q_{P, A, Xhr} = \text{Plasma flow on the arterial side after X h}
\]

\[
Q_{P, V, Xhr} = \text{Plasma flow on the venous side after X h}
\]

\[
C_{A, Xhr} = \text{Solute concentration on the arterial side after X h}
\]

\[
C_{V, Xhr} = \text{Solute concentration on the venous side after X h}
\]
\[ Q_{P,V,Xhr} = \text{Plasma flow rate on the venous side after X h} \]
\[ Q_{P,V} = Q_{P,A} \times \text{[surface area (m²)]} \times 10 \text{ (mL)} \]
\[ \text{Hct}_{A,Xhr} = \text{Hematocrit on the arterial side after X h} \]

**Removal rate**

\[
\text{RR} \% = 100 \times \left\{ \frac{C_{P,pre} - C_{P,Xhr} \times \left( \frac{\text{Hct}_{pre}}{\text{Hct}_{Xhr}} \right)}{C_{P,pre}} \right\}
\]

**Concentration ratio**

\[
C_{\text{Ratio},Xhr} = \frac{C_{P,Xhr}}{C_{P,pre}}
\]

**Erythropoiesis-stimulating agent dose and response index**

Darbepoetin alfa and epoetin beta pegol doses were converted to ESA dose (U/week) using darbepoetin alfa dose in one week \( \times 200 \), and epoetin beta pegol dose in one week \( \times 200 \) administration interval (weeks). ESA response index (ERI) was derived by dividing ESA dose with hemoglobin concentration (g/dL) (23).

**Nutritional indices**

Malnutrition-inflammation score (MIS) and geriatric nutritional risk index (GNRI) were determined as described (24,25).

**Statistical analysis**

Results were expressed as mean ± SD. For analysis of removal performance, the difference in the variance of each data set was tested by F-test, and either paired \( t \)-test or Welch’s test was used as appropriate. Qualitative variables of the patient characteristics and the clinical and laboratory variables were tested by Welch’s test regardless of the results of F-test. \( P \)-values < 0.05 were considered significant.

**Ethical considerations**

This study conforms to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Tokai University School of Medicine. Informed consent was obtained from all participating patients before the eligibility determination and the study entry.

**Clinical trials registry**

This study is registered with the Clinical Trials Registry of the University Hospital Medical Information Network (registration ID, UMIN000010357).

**RESULTS**

**Subject characteristics**

The characteristics of the 72 dialysis patients we found eligible for the study were (in means) age 57.3 ± 10.5 years, dialysis vintage 16.0 ± 7.0 years, serum IL-6 concentration 4.0 ± 2.6 pg/mL, CRP concentration 1673 ± 2970 ng/mL, MIS 5.5 ± 1.7, GNRI 95.4 ± 4.3, and serum albumin concentration 3.8 ± 0.2 g/dL. Serum IL-6 concentrations in the 20 enrolled patients ranged 2.7 – 8.5 pg/mL (Table 1). The Con and NV groups had no statistically significant difference in age, dialysis vintage, Kt/V, serum IL-6 or CRP concentrations, or the conditions of dialysis including membrane surface area, dialysis time and blood and dialysate flow rates (\( P > 0.05 \), Table 1). The Kt/V values indicated effective hemodialysis in all patients. Serum IL-6 concentrations were stable in these 20 patients on two consecutive measurements between the eligibility assessment and the study entry (5.4 ± 2.1 and 4.6 ± 2.1 pg/mL in the Con and NV groups, respectively; \( P = 0.12 \)).

**IL-6 and \( \beta_2 \)-MG clearance and removal rates**

Clearance was not different between Con-DL and NV-DL either 1 or 4 h after the start of dialysis for IL-6 (Fig. 2A) or \( \beta_2 \)-MG (Fig. 2B). IL-6 removal rates were indistinguishable between Con-DL and NV-DL for the first 1 h of dialysis (Fig. 3A). However, the removal rates for the entire 4-h session were higher with NV-DL than with Con-DL (8.9 ± 40.1% vs. –11.0 ± 49.6%; \( P = 0.03 \)). \( \beta_2 \)-MG removal rates were not different between the two dialyzer types for either time period (Fig. 3B).
The concentration ratios of IL-6 decreased until 1 h and then increased on both sides with Con-DL or NV-DL (Fig. 4A). The IL-6 concentration ratios were not different between Con-DL and NV-DL at 1 h on either side. However, the ratios were lower with NV-DL at 4 h on the venous side (0.91 ± 0.44 vs. 1.08 ± 0.47 in Con-DL; \(P = 0.03\)). The ratios on the arterial side appeared lower with NV-DL, but the difference was not significant (0.98 ± 0.42 vs. 1.17 ± 0.52 in Con-DL; \(P = 0.05\)). β2-MG concentration ratios continued to decline throughout the session with Con-DL or NV-DL and were not different between the two dialyzer types at either time point (Fig. 4B).

Serum IL-6 concentration during the one-year study

Throughout the one-year study, serum IL-6 concentrations were neither significantly different between the groups nor did they show significant changes in either group (Table 2).

Hemoglobin concentration and hematocrit during the one-year study

Hemoglobin concentrations showed no significant changes in either group throughout the study (Table 2). However, they were significantly lower in the Con group than in the NV group at month 8 (10.3 ± 1.1 vs. 11.2 ± 0.9 g/dL; \(P = 0.046\)). Hematocrit showed no significant changes in either group.

### TABLE 1. Patient characteristics

|                         | NV group | Con group | \(P\)-value |
|-------------------------|----------|-----------|-------------|
| Number                  | 10       | 10        |             |
| Male                    | 7        | 9         |             |
| Female                  | 3        | 1         |             |
| Age (years)             | 57 ± 11  | (40.5, 72.3) | 58 ± 11 | (36.3, 77.7) | 0.82 |
| Dialysis vintage (years)| 18.0 ± 6.9 | (9.8, 32.0) | 18.8 ± 6.6 | (9.4, 31.8) | 0.80 |
| \(K\)/V                 | 1.5 ± 0.2 | (1.1, 1.8)  | 1.5 ± 0.3  | (1.1, 1.9) | 0.90 |
| CRP (ng/mL)             | 5.4 ± 2.1 | (3.2, 8.5)  | 5.4 ± 2.2  | (2.7, 8.5) | 1.00 |
| Surface area (m²)       | 1.480 ± 1.517 | (261, 5250) | 1.508 ± 1.463 | (260, 4650) | 0.97 |
| Dialysis time (h)       | 4.1 ± 0.2 | (4.0, 4.5)  | 4.2 ± 0.4  | (4.0, 5.0) | 0.31 |
| Blood flow rate (mL/min)| 200 ± 21 | (160, 220)  | 199 ± 12  | (180, 220) | 0.91 |
| Dialysate flow rate (mL/min) | 488 ± 23 | (450, 500) | 480 ± 26 | (450, 500) | 0.53 |

Shown are means ± SD (range). Con, conventional polysulfone dialyzer; CRP, C-reactive protein; IL-6, interleukin-6; NV, the TORAYLIGHT NV dialyzer.
throughout the study (Table 2). At month 8, hematocrit was lower in the Con group than in the NV group; but the difference was not statistically significant (vs. 34.8 ± 2.5% in the NV group; \(P = 0.055\)).

Erythropoiesis-stimulating agent dose during the one-year study

ESA doses decreased in the NV group at month 8 and increased in the Con group at month 12 (Table 2). ESA doses did not differ between the two groups at any time point. The overall change from the baseline was \(-1400 ± 2045\) and \(2283 ± 2371\) U/week in the NV and Con groups, respectively. The difference was significant (\(P = 0.002\)).

ERI showed changes similar to those in ESA doses (Fig. 5A). ERI decreased from the baseline in the NV group at month 8 and increased from the baseline in the Con group at month 12. ERI did not differ...
Significantly between the two groups at any time point. However, the overall change from the baseline was –134.1 ± 206.9 and 217.9 ± 220.4 U/week/Hb in the NV and Con groups, respectively (Fig. 5B). The difference was significant (P = 0.002). ERI/body weight produced similar results (data not shown).

Iron metabolism-related factors during the one-year study

Serum iron concentrations and transferrin saturation showed no significant changes in either group throughout the study (Table 2). In the NV group, total iron binding capacity decreased from baseline at month 8 and 12, and ferritin concentrations increased from the baseline at month 8. None of the parameters showed any changes in the Con group. The two groups had no statistically significant difference in any of iron metabolism-related factors at any time point.

**Table 2. Clinical and laboratory variables during the study**

| Items                                             | Group       | Study period (months) |
|---------------------------------------------------|-------------|-----------------------|
|                                                   |             | 0         | 4         | 8         | 12        |
| Number of patients                                 | NV          | Con       |           |           |           |
|                                                   | 10          | 10        |           |           |           |
| Dry weight (kg)                                    | NV          | Con       |           |           |           |
|                                                   | 54.8±8.1    | 54.3±8.2  | 54.0±8.9  | 54.0±8.5  |           |
|                                                   | Con         |           | 56.8±7.6  | 57.2±7.8  | 56.9±7.7  |           |
| ESA (U/week)                                      | NV          | Con       |           |           |           |
|                                                   | 30502±2147  | 23502±2742| 1300±1423 | 1650±1853 |           |
|                                                   | Con         |           | 1575±1179 | 3875±4162 | 2625±2547 | 3858±3119 |
| ΔESA (U/week)                                     | NV          | Con       |           |           |           |
|                                                   | -700±2941   | -1750±2242| -1400±2045|           |           |
|                                                   | Con         |           | 2300±3789 | 1050±2111 | 3858±2371 |
| Number of patients treated with intravenous iron drug| NV          | Con       |           |           |           |
|                                                   | 3           | 6         | 6         | 2         |           |
|                                                   | Con         |           | 5         | 5         | 3         | 4         |
| Number of patients prescribed with ARB             | NV          | Con       |           |           |           |
|                                                   | 4           |           |           |           |           |
| Laboratory tests                                   |             |           |           |           |           |
| IL-6 (ng/mL)                                      | NV          | Con       |           |           |           |
|                                                   | 5.4±2.1     | 4.3±2.4   | 4.9±3.0   | 5.1±3.1   |           |
|                                                   | Con         |           | 5.4±2.2   | 6.3±8.2   | 5.2±3.5   | 6.0±4.1   |
| CRP (ng/mL)                                       | NV          | Con       |           |           |           |
|                                                   | 1480±1517   | 1473±1571 | 1228±1074 | 2088±2500 |           |
|                                                   | Con         |           | 1508±1463 | 1797±2018 | 1446±1339 | 4295±7657 |
| WBC (/μL)                                         | NV          | Con       |           |           |           |
|                                                   | 5669±1520   | 5240±1101 | 5204±1264 | 5819±1397 |           |
|                                                   | Con         |           | 5860±1588 | 5450±1345 | 4980±1127 | 5470±1125 |
| RBC (×10^6/μL)                                    | NV          | Con       |           |           |           |
|                                                   | 369±45      | 368±37    | 365±48    | 359±31    |           |
|                                                   | Con         |           | 352±34    | 348±30    | 340±44    | 351±28    |
| Hb (g/dL)                                         | NV          | Con       |           |           |           |
|                                                   | 11.1±1.1    | 11.1±1.1  | 11.2±0.9  | 11.2±1.0  |           |
|                                                   | Con         |           | 10.9±0.8  | 10.6±0.8  | 10.3±1.1  | 10.7±0.8  |
| Hct (%)                                           | NV          | Con       |           |           |           |
|                                                   | 35.0±2.9    | 34.8±2.7  | 34.8±2.5  | 34.3±2.8  |           |
|                                                   | Con         |           | 33.7±2.5  | 32.9±2.1  | 31.7±3.9  | 32.6±2.1  |
| PLT (×10^3/μL)                                    | NV          | Con       |           |           |           |
|                                                   | 17.6±3.9    | 17.8±3.8  | 16.3±4.5  | 17.9±3.8  |           |
|                                                   | Con         |           | 16.1±4.6  | 15.3±4.6  | 15.1±4.9  | 15.2±3.6  |
| TIBC (μg/dL)                                      | NV          | Con       |           |           |           |
|                                                   | 284±61      | 255±31    | 241±40    | 250±32    |           |
|                                                   | Con         |           | 277±38    | 271±48    | 270±47    | 276±56    |
| Serum Fe (μg/dL)                                  | NV          | Con       |           |           |           |
|                                                   | 65.7±31.9   | 65.3±29.1 | 75.7±30.2 | 75.6±42.4 |           |
|                                                   | Con         |           | 64.5±22.9 | 60.6±19.5 | 68.9±29.2 | 70.3±28.6 |
| TSAT (%)                                          | NV          | Con       |           |           |           |
|                                                   | 25.0±13.3   | 26.4±12.6 | 31.8±13.3 | 31.4±18.3 |           |
|                                                   | Con         |           | 23.5±8.7  | 22.8±7.7  | 26.0±11.3 | 25.9±9.1  |
| Ferritin (ng/mL)                                  | NV          | Con       |           |           |           |
|                                                   | 65.7±64.6   | 79.5±64.7 | 101.2±76.1| 87.6±80.5 |           |
|                                                   | Con         |           | 115.9±107.1| 149.3±107.2| 134.6±151.9| 98.4±72.9 |
| Nutrition                                         |             |           |           |           |           |
| BMI (kg/m2)                                       | NV          | Con       |           |           |           |
|                                                   | 20.4±2.1    | 20.6±2.4  | 20.1±2.3  | 20.0±2.2  |           |
|                                                   | Con         |           | 20.8±2.2  | 21.2±2.3  | 20.8±2.5  | 20.7±2.7  |
| Albumin (g/dL)                                    | NV          | Con       |           |           |           |
|                                                   | 3.9±0.3     | 3.9±0.3   | 3.8±0.3   | 3.7±0.3   |           |
|                                                   | Con         |           | 3.9±0.3   | 3.8±0.4   | 3.8±0.4   | 3.8±0.4   |
| MIS                                               | NV          | Con       |           |           |           |
|                                                   | 5.7±2.1     | 6.2±2.5   | 7.2±3.2   | 6.9±2.1   |           |
|                                                   | Con         |           | 5.7±2.4   | 5.6±2.3   | 6.6±3.4   | 6.0±3.5   |
| GNRI                                              | NV          | Con       |           |           |           |
|                                                   | 95.6±4.7    | 95.4±4.8  | 94.1±4.9  | 92.7±5.1  |           |
|                                                   | Con         |           | 96.3±5.6  | 95.8±7.2  | 95.2±8.0  | 95.1±7.8  |

#P < 0.05 vs. Con.  ARB, angiotensin II receptor blockers; BMI, body mass index; Con, conventional polysulfone dialyzers; CRP, C-reactive protein; ESA, erythropoiesis stimulating agents; GNRI, geriatric nutritional risk index; Hb, hemoglobin; Hct, hematocrit; MIS, malnutrition-inflammation score; NV, TORAYLIGHT NV dialyzer; PLT, platelets; RBC, red blood cells; TIBC, total iron binding capacity; TSAT, transferrin saturation; WBC, white blood cells.

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group, MIS increased at months 8 and 12, and BMI decreased at month 12. GNRI increased from the baseline in the Con group at month 12. No differences were found between the two groups at any time point.

Other clinical parameters and prescriptions during the one-year study

Dry weight and white blood cell count decreased in the NV group at month 12 and 8, respectively (Table 2). No differences were found between the groups at any time point.

During the one-year study, angiotensin II receptor blockers were prescribed to five and four patients in Con and NV groups, respectively (Table 2). The difference between the groups was not statistically significant. No patients were prescribed with angiotensin converting enzyme inhibitors or HMG-CoA inhibitors. No patients had infection or were hospitalized.

DISCUSSION

We used three indices to IL-6 and β2-MG removal performance of the NV and conventional dialyzers. Of these, clearance is determined primarily by the input and output quantities of the target substance at a given time during the dialysis session. Thus, clearance represents the intrinsic removal efficiency at a given time during the session and is not affected by dialysis-associated changes in the target substance concentration. Our data demonstrate that the NV dialyzer is as efficient as the conventional dialyzers in removing IL-6 throughout the 4-h session.

The other two indices are a function of the target substance concentrations before and at a given time during the session. These indices reflect dialysis-associated changes in the target substance concentration. When dialysis-associated target substance synthesis is negligible, the removal rate and concentration ratio will continue to increase and decrease, respectively, because the target substance concentration continues to decrease as a result of removal. This pattern was seen with β2-MG. When dialysis-associated target substance synthesis exceeds its removal, the removal rate will turn towards a decrease and the concentration ratio towards an increase later during the session. This pattern was seen with IL-6, indicating a significant dialysis-associated IL-6 production on both dialyzer types. This dialysis-associated IL-6 production, however, was lower with the NV dialyzer than with the conventional dialyzers because the removal rate was higher and the concentration ratio was lower with the NV dialyzer at 4 h.

The membrane biocompatibility plays a significant role in dialysis-associated IL-6 induction. Cuprophan membranes activate mononuclear cells more strongly than polymethylmethacrylate membranes, as evidenced by a greater secretion of soluble IL-6 receptors (13). Blood IL-6 levels increase modestly during the session and profoundly after the session, causing almost a 70% increase in IL-6 concentration (14). Our findings provide additional evidence for dialysis-associated IL-6 induction and demonstrate that dialysis-associated IL-6 production is lower with the NV dialyzer than with the conventional dialyzers. The consequence of this difference can be seen in IL-6 concentration ratios at 4 h on the venous side, which suggests that the conventional dialyzers are more likely than the NV dialyzer to expose patients to a higher-than-baseline IL-6 “surge” at the end of each session.

Despite the above differences in dialysis-associated IL-6 induction, the every-4-month IL-6 values neither were different between the groups nor showed any changes in either group over the one-year study. These findings indicate that
transient impact on circulating IL-6 levels because the every-4-month IL-6 determinations were made 2 or 3 days after the previous session. Yet, however transient its impact may be on the long-term IL-6 or 3 days after the previous session. Yet, however transient impact on circulating IL-6 levels because the dialysis-associated IL-6 production only had transient impact because the dialysis-associated IL-6 surge of such a magnitude would have certain effects on hemodialysis patients, and the NV dialyzer would spare patients from these effects.

Hemoglobin concentrations were lower once in the Con group than in the NV group. Total iron binding capacity and ferritin showed no changes in the Con group. Red blood cell count, transferrin saturation and serum iron concentrations were neither different between the groups nor showed any changes in either group. Furthermore, neither ESA dose nor ERI differed between the groups throughout the study. However, their overall changes from the baseline were significant increases in the Con group and decreases in the NV group. ESA dose and ERI decreased once in the NV group from the baseline at month 8 when total iron binding capacity decreased and ferritin levels increased, indicating that the NV group was able to regulate iron utilization to optimize ESA responsiveness. In contrast, the Con group was ESA hyporesponsive because they were unable to mobilize iron when needed.

Accumulating evidence implicates inflammation and elevated IL-6 levels in ESA hyporesponsiveness of hemodialysis patients. Elevated CRP levels predict ESA resistance in hemodialysis patients (4,5). A study on dialysate purity and ESA responsiveness demonstrated that increased CRP and IL-6 levels resulting from bacterial dialysate contamination correlated with higher ESA requirements, and high IL-6 levels were a strong predictor of ESA resistance (6). An analysis of a cohort of hemodialysis patients showed that CRP and IL-6 levels are strong and independent predictors of ESA resistance (7). IL-6 gene polymorphisms that determine high IL-6 secretion are associated with higher ESA doses in hemodialysis patients (8). The association between ESA resistance and high IL-6 or CRP levels, however, does not account for the differences we found in overall changes in ESA requirement, because neither IL-6 nor CRP levels were different between the two dialyzer types. These dialyzers only differed in the magnitude of “dialysis-associated IL-6 surge”. As discussed above, dialysis-induced IL-6 does not reflect itself in the subsequent measurement a few days later. Therefore, these cited studies based their analyses on IL-6 values that did not show dialysis-associated short-lived increments. Since such IL-6 values are associated with ESA resistance, acute dialysis-associated IL-6 elevation would have as much or stronger impact on ESA responsiveness.

A new light has been shed on inflammation-associated decreased hematopoiesis. Hepcidin is a protein produced by hepatic cells and suppresses iron absorption and recycling, thereby down-regulating erythropoiesis (26). Hepcidin is a type II acute-phase protein because its production is stimulated by IL-6 but not by IL-1 (27). The present patients on the conventional dialyzers were exposed to a greater “dialysis-associated IL-6 surge” than that with the NV dialyzer and were incapable of mobilizing iron when needed. We speculate that “dialysis-associated IL-6 surge” stimulates hepcidin production and downregulates iron utilization and ESA responsiveness. This cascade of reactions is triggered upon each dialysis session and affects ESA responsiveness in patients on the conventional dialyzers more strongly than those on the NV dialyzer, leading in a long run to an increased ESA requirement.

As for nutritional status, neither albumin level, BMI, MIS nor GNRI was different between the two dialyzer types. The changes within the group were of such a magnitude that they are unlikely to have affected erythropoiesis.

LIMITATIONS

First, the present sample size was small. We may have failed to detect full significance of the data. Second, no specific measures were taken against selection bias in selecting the 20 patients. We enrolled patients with high serum IL-6 concentrations to facilitate evaluation of IL-6 removal performance. However, the enrolled patients may represent a subpopulation of hemodialysis patients with certain unidentified traits.

CONCLUSION

The NV dialyzer is comparable to the conventional dialyzers in removing interleukin-6. Both dialyzer types induce interleukin-6 production. However, the current data appear to suggest that the NV dialyzer induces less interleukin-6 than the conventional dialyzers, which would reduce the risk of erythropoiesis-stimulating agent hyporesponsiveness. Further investigation is warranted focusing on the relationships between dialysis-associated interleukin-6 induction and hepcidin regulation.

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