Clinical Evaluation of Polyethersulfone High-flux Hemodialysis Membrane Compared to Other Membranes

Bai-Hai Su,[1,2] Yunying Shi,[1] Ping Fu,[1] Ye Tao,[1] Shengqiang Nie,[2] Chang-Sheng Zhao[2]

[1]*Department of Nephrology, West China Hospital, Sichuan University, Chengdu 610041, People's Republic of China*
[2]*College of Polymer Science and Engineering, State Key Laboratory of Polymer Materials Engineering, National Engineering Research Center for Biomaterials, Sichuan University, Chengdu 610065, People's Republic of China*

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ABSTRACT: In this study, the blood compatibility and performance of a new polyethersulfone (PES) high-flux hemodialysis membrane were clinically investigated, and compared with two commercial high-flux membranes, polysulfone (PSF) and polyamide (PA) membranes. The structure of the membranes was observed by scanning electron microscopy, and the membrane structure showed significant difference among the three membranes. However, there was no significant difference (no statistical difference, $P > 0.05$) in the solute clearance and the reduction ratio for small molecules (urea, creatinine, and phosphate) and middle molecule β_2-microglobulin. The changes of total bilirubin (TBIL) and aspartate aminotransferase (AST) for the PES and PSF membranes showed no significant differences, both the TBIL and DBIL levels slightly increased compared to the initial levels. However, for the PA membrane, the TBIL and AST levels decreased obviously. The PES hollow fiber membrane hemodialyzer was effective and safe for the treatment of uremic patients, and the performances of PES, PSF and PA high-flux hemodialysis membranes are comparable. The PES and PSF membranes showed similar blood compatibility and solute clearance, and might be better than the PA membrane.

Key words: polyethersulfone; hollow fiber membrane; hemodialysis; clinical evaluation

INTRODUCTION

Hemodialysis has been widely used as a life-sustaining treatment for end-stage renal disease patients.[1] Cellulose membranes are widely used for hemodialysis because of their hydrogel structure and small thickness which provide a very effective removal of small solutes such as urea and creatinine. However, these membranes provide relatively little clearance for "middle" molecules and cause complement activation upon contacting with blood.[2] Complement activation occurs during the interactions between the blood and various components of the hemodialysis membrane, which was defined as the bad biocompatibility and may adversely affect the patients and even lead to deleterious outcomes.[3] What's more, among the chronic hemodialysis patients these interactions are repetitive and occur three times a week. Therefore, even mild interactions may, on a chronic basis, lead to adverse clinical sequelae.

To improve the clearance for middle molecules and the efficiency of dialysis, high-flux dialysis was developed in recent years. It has succeeded in both improving the quality of dialysis and in shortening the dialysis times.[4] For high-flux dialysis, the membrane should have larger pores for the removal of both small and middle molecular uremic toxins. Recently, evidences have showed that middle molecular uremic toxins may play an important role in causing the uremic symptoms that are both annoying and dangerous to dialysis patients. Such molecules are too big to be removed by conventional dialysis, but they can be removed by high-flux dialyzers. In fact, there are reports about patients with less joints pain when switched from conventional to high-flux dialysis. Thus, the removal of larger molecules is crucial for high-flux dialysis. The larger pore size also allows much faster removal of fluid. Another important characteristic of high-flux dialysis is that the higher blood and dialysate flows are used, and significant improvements in dialysis efficiency can be obtained. Since high-flux dialysis (also called high-efficiency dialysis in some times) is so much more efficient, it can allow significant reduction of dialysis times, often by 25%.[5] Thus, the patient can receive adequate dialysis and meanwhile minimize the discomfort of long dialysis time. Another characteristic of high-flux dialysis is that the membranes used are more biocompatible, and therefore are less likely to stimulate the autoimmune system, which minimizes the allergic symptoms as well as the

Correspondence to: C.-S. Zhao (zhaochsh70@scu.edu.cn or zhaochsh70@163.com).
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TABLE I
Specifications of the Hollow Fiber Membrane Dialyzers

Membrane materials	Polyethersulfone	Polyamide	Polysulfone
Hollow fiber			
Internal diameter (μm)	205	215	200
Wall thickness (μm)	47.5	47.5	47.5
Effective length (mm)	240	258	228
Membrane area (m^2)	1.5	1.4	1.3
Potting material	Polyurethane	Polyurethane	Polyurethane
Sterilized method	γ-ray	ETO	Steam
Ultrafiltration coefficients (mL/h mmHg)	72	40	40

changes in white blood cell counts that were previously caused by less biocompatible membranes.

Polysulfone (PSF) is one of the most important polymeric materials and is widely used. PSF-based membranes show outstanding oxidative, thermal, and hydrolytic stability as well as good mechanical and film-forming properties.[6] The PSF membranes also showed high permeability for low-molecular weight proteins when used for hemodialysis. The commercial product of PSF hollow fiber hemodialyzer was produced by Germany (Fresenius Polysulfones, Fresenius Medical Care, Bad Homburg, Germany), and was widely acknowledged as providing an optimal biocompatibility in terms of good solute removal and low-complement activation.[7]

Polyethersulfone (PES) is a parent material of PSF, with a better chemical resistance, thermal stability, mechanical properties as well as a better hydrophilicity compared to PSF. Samtleben et al.[8] compared the new PES high-flux membrane DIAPES (R) HF800 with conventional high-flux membranes [PSF and polyamide (PA)] during on-line hemodiafiltration (HDF). Combarnous et al.[9,10] investigated the albumin loss in on-line HDF of the DIAPES membrane; Linemen et al.[11] studied the pyrogen retention by the membrane. Locatelli et al.[12] also mentioned the efficiency in hemodialysis with DIAPES membrane.

In our previous study, PES high-flux hemodialysis membrane was evaluated by animal experiments, and the membrane showed good biocompatibility and high clearance for middle molecules.[13] In this study, PES high-flux hemodialysis membrane was investigated by clinical application, and compared with PSF and PA membranes.

MATERIALS AND METHODS

Materials

PES and polyvinylpyrrolidine (PVP, PVP-90K was selected) were obtained from BASF Aktiengesellschaft, and used to prepare PES hollow fiber membranes by the dry–wet spinning method,[13] based on a complex process involving phase inversion or precipitation. *N*,*N*-Dimethyl acetamide (DMAc) was purchased from Chengdu Chemical Reagent, China, and used as the solvent to dissolve the PES and PVP. Micro BCA™ Protein Assay Reagent kits were the product of PIERCE. All the other chemicals (analytical grade) were obtained from the Chemical Reagent Factory of Kelong, China, and were used without further purification.

Hemodialyzers

The PES hollow fiber was spun by ourselves, and the PES hemodialyzer was manufactured in Chengdu OCI Medical Device Co. The specifications of the PES hollow fiber hemodialyzer are shown in Table I. At the same time, PA membrane hemodialyzer (Polyflux 14s, Gambro Dialysatoren GmbH, Germany) and PSF membrane hemodialyzer (*F60s, Fresenius Medical* Care) were also evaluated, and as controls.

Scanning electron microscopy observation

For scanning electron microscopy (SEM) observation, the hollow membrane samples were broken in liquid nitrogen, attached to the sample supports and coated with a gold layer. The SEM images were recorded using an S-2500C microscope (voltage = 20 kV, Hitachi, Tokyo, Japan).

Hemodialysis procedure and patients

Ninety-seven uremic patients were enrolled into the study in our HD centers with the following inclusion criteria: age between 18 and 80 years. Exclusion criteria were serious life-limiting comorbid situations, namely active malignancy, infection, end-stage cardiac, pulmonary, or hepatic disease (Hep B and Hep C negative). Ninety-seven uremic patients were randomly allocated into three groups. Three groups of hemodialysis patients with mature functioning arteriovenous fistula participated in this study. Their mean age was 48 ± 12 year, and they had been receiving dialysis treatments for 35 ± 14 months with an average frequency of three times weekly

(12 h/week). For each patient, Hct was determined at the beginning of the hemodialysis session.

Standard midweek hemodialysis sessions were analyzed, and bicarbonate dialysate was used. The dialysate contained 140 mmol/L sodium, 2 mmol/L potassium, 108 mmol/L chloride, 1.50 mmol/L calcium, 0.5 mmol/L magnesium, and 32 mmol/L bicarbonate. The blood flow was 200 mL/min and the dialysate flow was 500 mL/min. The three kinds of dialyzers (PES, PSF, and PA) were used for the three groups of patients, respectively.

Calculation of solute clearance

The levels of urea, creatinine, phosphate, total proteins, albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were determined using an Auto Biochemistry Analyzer 7170A (Hitachi).

The removal of β_2-microglobulin was established by the changes in plasma level during the treatment at different time intervals (30, 60, 120, 180, and 240 min). Plasma β_2-microglobulin levels were determined using a commercially produced ELISA assay (Cambridge Life Sciences, Cambridge, UK).

Electrolyte levels were determined before and after hemodialysis. The levels of K^+, Na^+, and Cl^- were determined using electrolyte analyzer (NOVA CRT-4, US), and Ca^{2+} was determined using an Auto Biochemistry Analyzer 7170A (Hitachi).

Protein adsorption

Total protein adsorption onto the hollow fiber membranes was measured after the hemodialysis. The membranes were taken out from the housing, and then immersed in a washing solution (2 wt % SDS, 0.05*M* NaOH) at 37°C, and shaken for 2 h to remove the adsorbed protein. The adsorption and desorption time were carefully determined in preliminary experiments. The protein concentration was also determined by using the Micro BCA™ Protein Assay Reagent Kit (PIERCE). The same method had been used in our previous study studies.[6,13] Then the adsorbed protein amounts were calculated.

Evaluation of blood compatibility

In order to investigate the complement and immunoglobin activation, complement C3, C4 and immunoglobin G, A, M, and E were determined by enzyme-linked immunosorbent assays (ELISA).

Blood cells including red blood cell (RBC) and white blood cell (WBC), and blood components including hemoglobin (HGB) and platelet were determined using a blood cell analyzer (BC-3000peus, Shenzhen Mairui Biomedical Device Co., China). Blood gas was determined by a blood gas analyzer (CORNing 238, US).

Statistical analysis

The software of SPSS 13.0 was used for statistical analysis. The deviation between the three groups was calculated by analysis of one-factor variance (ANOVA), and the deviation between samples in one group was calculated by Student–Newman–Keuls (q test). All the data are shown by mean values and standard deviations ($x \pm s$), $P < 0.05$ is considered to have statistical difference.

RESULTS

Morphology of the PES hollow fiber membrane

Figure 1 shows the cross-sections of the hollow fiber membranes used to prepare the dialyzers. As shown in Figure 1, different morphology was observed among the three kinds of membranes. For the PES membrane as shown in Figure 1(a), the wall thickness of the hollow fiber was about 47.5 μm, and the inner diameter was about 205 μm. Skin layers were found on both sides of the membrane wall, under which followed was a finger-like structure and then the porous structure.

For the PSF membrane as shown in Figure 1(b), no finger-like structure and macrovoids were observed; instead a sponge-structure was found. For the PA membrane as shown in Figure 1(c), a skin layer was also found, under which followed were macrovoids. However, the three kinds of hollow fibers had the similar internal diameter and membrane wall thickness, as shown in Table I.

Clinical observations

All the patients participated in the whole study period. The vital signs were stable with no adverse events during the dialysis, and there were no abnormal findings in laboratory security parameters. During the dialysis by PA membrane dialyzer, some clots were found after 175 min in the extracorporeal blood circuit of a male patient who was on a repeated bolus fraxiparine anticoagulation regimen (6000 IU in total), but the patient still finished the treatment. This was the only adverse event during the whole study. All of patients who were treated by PES, PA, or PSF membrane dialyzer were performed without provoking any adverse symptoms, such as headache or hypotension.

Solute clearance

The clearance of small molecular and middle molecular toxins was expressed as the solute reduction

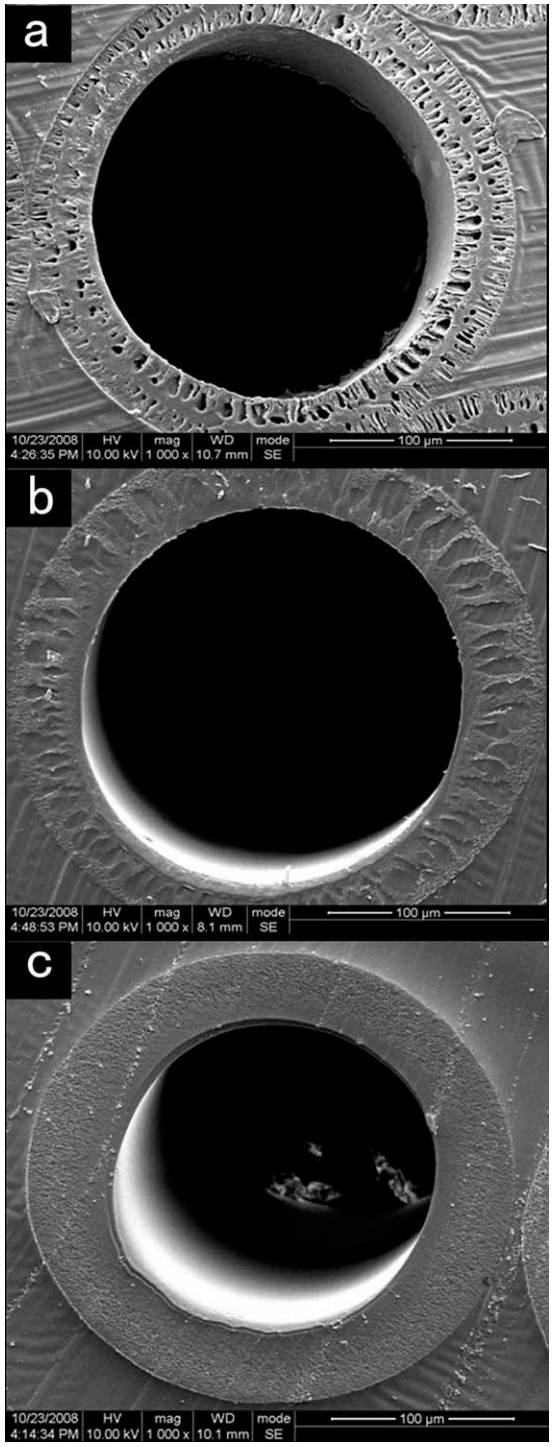

Figure 1 SEM images of the cross-section of the hollow fiber membranes: (a) PES, (b) PA, and (c) PSF (voltage = 20 kV, Hitachi).

ratio (RR) after 4-h hemodialysis, and could be calculated by: RR (%) = [1 − (postsolute concentration/presolute concentration)] × 100%. The blood flow was controlled at 200 mL/min and the dialysate flow was 500 mL/min. Figure 2 shows the RRs of urea, creatinine and β_2-microglobulin for the three kinds of hollow fiber dialyzers. As shown in Figure 2, large amount of the toxins were removed after the hemodialysis. The RRs of urea for PES, PA, and PSF membranes were 61.2%, 63%, and 62.3%, respectively. The RRs of creatinine were 51.3%, 54.5%, and 54.7%, respectively. Meanwhile, the RRs of β_2-microglobulin were 60.8%, 51.3%, and 57.7%, respectively. The RRs of urea and creatinine for the PES membrane were slightly smaller than those for the PA and PSF membranes, but no statistical difference. However, the RR of β_2-microglobulin for the PES membrane was slightly larger than that for the PA and PSF membranes. It has been approved that the PES, PA and PSF hollow fiber hemodialysis membranes could effectively remove waste products including not only small molecular weight solutes such as urea and creatinine but also middle molecular solutes as β_2-microglobulin.

Biocompatibility

Figure 3 shows the WBC changes in the patient bloods during the dialysis for the three kinds of membranes. The blood cell counts have been normalized to pretreatment levels and expressed as a percentage of these values. A small decline was noted at the first 30 min for all the membranes, and returned to the initial levels after about 1 h, and no significant difference was observed among the three membranes. The changes in platelet, complement factor C3, and complement C4 during the hemodialysis process for the three membranes were also investigated, and similar results were obtained as the change in WBC (data not shown).

The concentration of albumin (ALB) and immunoglobin (GLB) slightly increased after 4-h hemodialysis, and no significant difference among the three

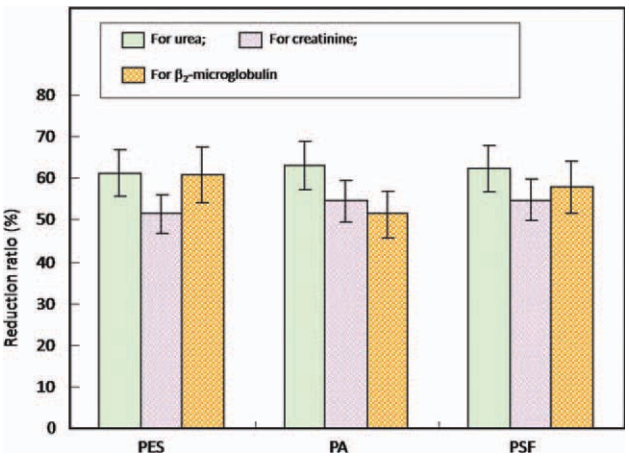

Figure 2 Reduction ratios of small molecules urea and creatinine, as well as middle molecules β_2-microglobulin after 4 h hemodialysis at a blood flow rate of 200 mL/min and dialysate flow rate of 500 mL/min. Data are expressed as the means ± SD, n =3. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

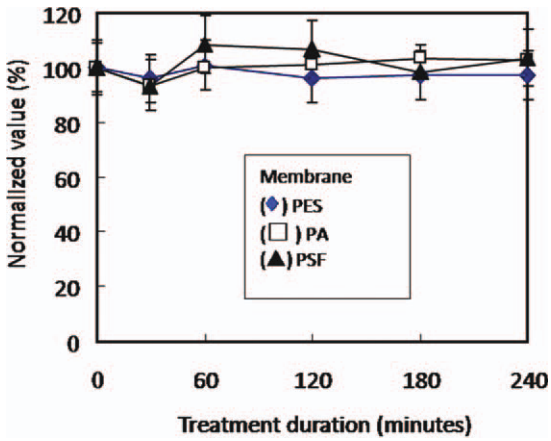

Figure 3 Changes in WBC during the dialysis *in vivo*. Data are expressed as the means ± SD, $n = 3$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

membranes. Total protein adsorption of the membranes was also determined, and the amounts for PES, PA, and PSF membranes were 12.2, 10.2, and 11.9 μg/cm^2, respectively.

Total bilirubin (TBIL), direct bilirubin (DBIL), ALT, and AST levels were measured after 4-h hemodialysis, and compared with the initial levels for the three kinds of membranes, as shown in Figure 4. There are no significant differences in the changes of TBIL, DBIL, ALT, and AST for the PES and PSF membranes, and both the TBIL and DBIL levels increased compared to the initial levels. However, for the PA membrane, the TBIL, and AST levels decreased obviously.

DISCUSSION

In this study, PES high-flux hemodialysis membrane was evaluated *in vivo*, and compared with PA and PSF membranes in membrane morphology, solute clearance and biocompatibility. The results indicated that the PES hollow fiber membrane hemodialyzer was effective and safe in the therapy for uremic patients. The PES hollow fiber hemodialysis membrane could effectively remove water and waste products including not only small molecular weight solutes such as urea and creatinine but also middle molecular solute as β_2-microglobulin, and the PES membrane might be better for the removal of β_2-microglobulin due to the convective and adsorptive removal.[14]

PES membrane

Synthetic hollow fiber membranes are manufactured by blending of normally hydrophobic polymers with hydrophilic materials to make them suitable for use in renal replacement therapy. As we know, hydrophobic polymer membrane surface adsorb much more proteins from plasma when they come into contact with blood, which is so-called "membrane fouling" and can induce flux decrease. The membrane fouling was caused by the adhesion of plasma proteins, and could be induce a severe problem. The blending of hydrophilic polymer materials is one practical approach to modify hydrophobic membrane surface.[15]

Polyvinylpyrrolidone (PVP) is usually used to modify PSF and PES membrane by blending method to increase the hydrophilicity of the resultant membranes. The PSF hollow fiber membrane hemodialyzer used in this study was modified by blending of PVP. Hoenich et al.[4] evaluated the clinical performance of a hemodialysis membrane manufactured from a blend of PA, polyarylethersulfone, and PVP. Qin et al.[16] prepared PES/PVP blended hollow fiber membranes with enhanced flux for humic acid removal. Huang et al.[17] evaluated two high-flux dialyzers, dialyzer A (cellulose triacetate) and dialyzer B (PES), in their study water solution with urea and creatinine were made as "blood," and pure water was used as dialysate. Gerdemann et al.[18] studied the advanced glycation end products (AGEs) removal by high-flux dialysis; they used a DIAPES membrane prepared from PES, which was similar to the PES membrane in our study. The difference was that the ultrafiltration coefficient in this study was 81 mL/mmHg h, while that for the DIAPES membrane was 35 mL/mmHg h. The higher ultrafiltration coefficient indicated that higher water removal rate could be obtained, but the plasma protein level was not significantly decreased as mentioned above. These results could contribute the higher molecular weight of PVP used in this study, which significantly increased the hydrophilicity of the membrane.

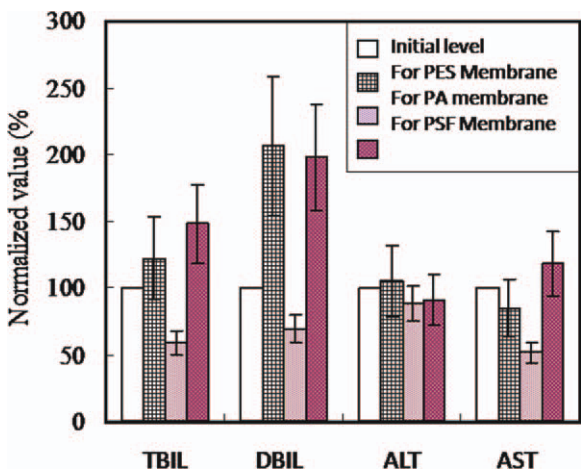

Figure 4 TBIL, DBIL, ALT, and AST level changes after 4-h hemodialysis. Data are expressed as the means ± SD, $n = 3$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The morphology of the PES hollow fiber membrane was different from that for PSF or PA membrane. The PES hollow fiber membrane was prepared using a dry–wet spinning method based on the common phase inversion and precipitation technique, and has an inner skin as shown in Figure 1. For the PES membrane as shown in Figure 1(a), the wall thickness of the hollow fiber was about 47.5 μm, and the inner diameter was about 205 μm. Skin layers were found on both sides of the membrane wall, under which followed was a finger-like structure and then the porous structure. Furthermore, it was clearly observed that the finger-like structure was interdicted in the middle of the membrane. This was caused by the exchange between the solvent NMP and water during the membrane formation. The hollow fiber membrane was spun by the dry–wet spinning method. The exchange occurred rapidly from the internal side of the nascent hollow fiber membrane when the polymer solution was extruded through the spinneret. After the fiber immersing in the coagulation bath, the exchange began from the outside of the membrane. Thus, a porous structure formed in the middle of the hollow fiber membrane.[19] By manipulating the membrane wall thickness and the air gap, or adding larger amounts of hydrophilic polymer, the porous wall could be adjusted.[20]

The difference in the membrane structure might be caused by the different manufacture process, and thus led to different ultrafiltration coefficients. The two skin layers on both sides of the hollow fiber membrane might be good for using as a high-flux hemodialysis membrane. For high-flux hemodialysis membrane, both the water flux and the mean pore size were large; the skin layer could act as the flux and retention barrier, especially the outer skin layer, since sometimes there may be present pyrogen in dialysate. In this study, no penetration of valuable species during the treatment was observed, and these could be proved by the slightly increase of the concentrations of albumin (ALB) and immunoglobin (GLB) after 4-h hemodialysis.

An acceptable structure for low-flux hemodialysis membrane is one skin layer in one side, and the low-flux hemodialysis membranes were usually deliberately hydrophobic to avoid water permeation through the membrane, since the conventional hemodialysis did not need remove excess water from blood. However, for high-flux hemodialysis membrane, it should remove the excess water, and the procedure was applicable.

Solute clearance

To increase the removal of large molecular solutes, the rates of diffusion and convection should be increased, and the membrane pore size and porosity should be increased. However, the manufacturing and clinical considerations led to the limitations of membrane structure for large solute removal. For example, strength limitations lead to a maximum porosity and minimum thickness specific to each type of membrane material. Nevertheless, manufacturers have maximized porosity not only to improve the solute transport but also to improve the clearance of middle-molecular toxins, since fiber cost represents the majority of the cost of manufacturing a dialyzer.

Pore size limitations arise from the concern over potential loss of blood proteins such as albumin. Given that dialysis patients are generally malnourished, and the relative risk of death of dialysis patients increases as the serum albumin concentration decreases, it is desirable to minimize the albumin loss to the dialysate. Furthermore, small albumin losses may be clinically insignificant to the patient, but may lead practical problems in the dialysis clinic, such as the foam formation in the dialysate drains. An ideal dialysis membrane should have a uniform pore size, which was large enough to allow the passage of β_2 microglobulin but small enough to retain albumin (66,000 Da).[21] Unfortunately, methods currently used to produce dialysis membranes resulted in a nonuniform pore size distribution, as shown in Figure 1. The aim of this study is to demonstrate the safety and validity of the PES membranes by clinical evaluation. In this study, there was no significant difference in the solute clearances and the reduction ratios of small molecules (urea, creatinine, and phosphate) among the three high-flux hemodialysis membranes. The solute reduction ratio of β_2-microglobulin for the new PES membrane was larger than that for the other two ones, though there was no statistical difference among the three groups. In clinical practice, the middle molecular toxin of the uremic patients can not be cleaned effectively which might induce the cardiovascular complications. Thus, it needs the dialyzer cleans more middle molecular toxin. In addition, PES membrane shows better chemical resistance, thermal stability, mechanical properties as well as a better hydrophilicity compared to PSF, thus it is benefit for the uremic patients who are treated for a long time.

Many studies focused on the modification of PES membrane and its performance evaluation in vitro, but few clinical evaluations were reported. Wang et al.[22] investigated the hydrophilicity and blood compatibility on PES membrane by adding PVP, the modified membranes showed higher water flux, water adsorption, and lower water contact angle (CA) than the pristine PES membrane. Moreover, adding PVP as an additive could effectively reduce bovine serum albumin adsorption and prolong the blood coagulation time, thereby improving blood

compatibility of PES membrane. However, no solute clearance was reported in the study. Samtleben et al.[23] compared PES high-flux membrane DIAPES(R) HF800 with conventional high-flux membranes (PSF and PA) during on-line hemodiafiltration (HDF). The mean plasma RR of β_2-microglobulin was 77 $\pm$ 1% for DIAPES(R) HF800 and PSF whereas it was 71.1% for PA ($P < 0.05$). The RRs were slightly larger than those obtained in this study, which were 60.8%, 57.7%, and 51.3% for PES, PSF, and PA, respectively. This was caused by the larger blood flow rate (250 mL/min) than that in this study (blood flow rate of 200 mL/min). Kohn et al.[24] studied the solute clearances with short-daily home hemodialysis using slow dialysate flow rate. β_2-microglobulin clearance of the PES dialyzer averaged 53 $\pm$ 14 mL/min, and β_2-microglobulin recovered in the dialysate was 106 $\pm$ 42 mg per treatment; phosphorus removal averaged 694 $\pm$ 343 mg per treatment. The removal was smaller than that in this study due to the slow dialysate flow rate. These results indicated that the performance of the PES high-flux hemodialyzer was comparable with that of the reported PES membranes.

In the phase inversion membrane production process, polymer is dissolved in a solvent and then exposed to a nonsolvent as it is extruded through an annular die. The breadth of the distribution produced by the phase inversion process resulted from the finite rate of molecular diffusion through the viscous polymer solution during the membrane coagulation phase.[20] While previous membrane improvements have resulted from reducing the viscosity of the polymer solution, it is unlikely that the breadth of the pore size distribution can be significantly reduced by further modification of the phase inversion process. Given a fixed breadth of the pore size distribution, the requirement for albumin retention limited not only the maximum pore size but also the mean pore size. As a result, the sieving coefficient of β_2-microglobulin is generally 0.6 or less in order to maintain the albumin sieving coefficient at 0.01 or less. The PES membrane may be adequate to this requirement.[25]

Biocompatibility

Retrospective analyses have shown that hemodialysis with synthetic dialysis membranes is associated with improved patient survival in ESRD.[25] This observation was mainly attributed to membrane biocompatibility. Synthetic membranes are generally regarded as to be highly biocompatible, since they lead to low complement activation and leucopenia, two classical parameters to characterizing biocompatibility in dialysis.[25] However, several other systems become altered during blood–membrane interaction. Among them are the coagulation system and imbalances of the oxidative and antioxidative system.[26,27]

A slightly decrease in outlet leukocyte counts was observed for the three dialyzers, and significant difference was observed among them, as shown in Figure 3. The phenomena had been reported frequently in hemodialysis, hemofiltration, and plasma separation.[27] The decrease of white blood cells was caused by complement activation, thus similar results were obtained in the changes of complement factor C3 and complement C4 during the hemodialysis process. When comparing PES, PA, and PSF membranes, these change showed no significant difference, and this indicated that the blood compatibility might be the same, though different membrane materials were used. These had also been demonstrated by the protein adsorption as mentioned above. In fact, the hydrophilicity of PES and PSF was different, and their water contact angles were about 72° and 89°, respectively, thus the protein adsorption for pure PSF was higher than that for PES. The similar protein adsorption was gained by the modification of the matrix. For the PES membrane, smaller amount of hydrophilic polymer PVP was used compared to that for PSF membrane. Since the smaller amount of PVP, the morphology of the cross-section showed finger-like structure, and no significant change compared to pure PES membrane. Of all the substances evaluated, maybe only D-dimer was detected in the dialysate. However, its levels were lower by several orders compared with its plasma levels. Moreover, the dialysate levels of D-dimer did not differ significantly among the three kinds of dialyzers compared (data not shown).

In Figure 4, slight changes in TBIL, DBIL, ALT, and AST were also observed. The change ratios for all of them ranged 3–10%. There are no significant differences in the changes of TBIL, DBIL, ALT, and AST for the PES and PSF membranes, and both the TBIL and DBIL levels increased compared to the initial levels, which were presumably caused by the dilution of the blood by normal saline solution infused or pachemia after the hemodialysis process. However, for the PA membrane, the TBIL, and AST levels decreased obviously. TBIL, DBIL, ALT, and AST are produced primarily in the liver; all of them are lipophilic and hydrophobic. The dialyzer permits diffusive clearance of nonprotein-bound, water soluble uremic solutes, such as urea and creatinine. The corollary is that the substances are tightly protein-bound and present in small quantities in the aqueous phase, or are lipophilic and removed by HD in negligible amounts, if at all. The results indicated that the PES and PSF membrane had no effect on the liver, and might have possibly higher hydrophilicity than PA membrane.

We speculated that the high-flux dialysis membrane might possibly let some biocompatibility markers enter into dialysis solution so that the plasma levels of these markers could provide biased

information. The plasma levels of biocompatibility markers may have also been influenced by adsorption to the membrane surface.[28,29] The adsorption to the membrane was not determined in our study. However, the protein adsorption capacity was investigated, and no difference was observed. On the basis of our results, we concluded that the design modifications of the new high-flux PES dialyzer resulting in its higher middle molecule clearance efficacy, and have an effect on thrombogenicity as assessed by platelet behavior and fibrinolysis. Although coagulation system judged by one of the evaluated parameters was slightly higher compared with the other dialyzers, it was still within the biocompatible dialyzer range. In terms of complement activation and changes in leukocyte count, the new dialyzer is also comparable with the other biocompatible dialyzers. Besides the thrombogenicity, complement activation, and WBC count changes, other issues must be considered when evaluating bio(in)compatibility.[26]

One further aspect merits considered that the PES membrane dialyzer series exhibits a higher permeability and thus, cytokine-inducing substances, possibly present in the dialysis fluid, might gain access to the blood stream through internal filtration (backfiltration). Therefore, investigations on the pyrogen permeability of PES membranes have been performed to the studies on the inflammatory response of the membrane. In this study, the dialysate compartment was deliberately contaminated with purified lipopolysaccharides (LPS) from *Escherichia coli*, as well as with LPS derived from *Stenotrophomonas* (Sten) *maltophilia*. No significant generation of interleukin 1 (IL-1), IL-6 or tumor necrosis factor (TNF) was found in the blood compartment for the PES dialyzer and *Fresenius* PSF series of dialyzers as compared with sterile controls. However, significant induction of IL-1, IL-6, and TNF was observed for the highly permeable PSF membrane DIAPES, suggesting that not all of the PSF membranes were alike with regard to their pyrogen permeability due to the different modification methods. The PES, PA, and PSF dialyzers offered important safety features with regard to a possible contamination of the dialysis fluid.[30]

CONCLUSION

The PES hollow fiber membrane hemodialyzer was effective and safe in the therapy for uremic patients, and the membrane could effectively remove water and waste products including not only small molecular weight solutes such as urea and creatinine but also middle molecular solute as β_2-microglobulin. Slight neutropenia and platelet adhesion were observed at the initial stage of the hemodialysis and no significant difference was found in electrolyte or blood biochemistry before and after the treatment. Some performances were also compared with some other commercial membranes, and the data indicated that the performance of PES, PSF, and PA hemodialyzers in the clinical setting were comparable and the PES hemodialyzer might be better than the others. The results indicated that PES hollow fiber membrane had a potentially wide application for hemodialysis. Clinical characterization is now undertaken in our university hospital.

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