A Comparison of Three Brands of Polysulfone Membranes

Nicholas A. Hoenich, Celia Woffindin, Annmarie Brennan, Penelope J. Cox, John N.S. Matthews, and Monica Goldfinch

ABSTRACT
A prospective clinical crossover study comparing the functional performance and biocompatibility of three brands of polysulfone membranes (Fresenius Polysulfone®, Fresenius AG, Bad Homburg, Germany; Polyphen®, Minntech Corp., Minneapolis, MN; and Biosulfane® (WR Grace Inc., Danvers, MA)) incorporated in ethylene oxide-sterilized dialyzers of comparable surface area (1.3 to 1.35 m²) was undertaken. The clearance of small molecules by each membrane was comparable. Plasma levels of β2 microglobulin fell to 49.9% of pretreatment values by 210 mm when using the Fresenius Polysulfone® membrane, 60.2% with the Polyphen® membrane, and 63.1% with the Biosulfane® membrane. The reduction achieved by using the Fresenius Polysulfone® membrane was superior (P = 0.003). The plasma reductions were associated with the recovery of 195 mg β2 microglobulin from the dialysate for the Fresenius Polysulfone® membrane and 158 mg for the Polyphen® membrane, but no β2 microglobulin was recovered from the dialysate with the Biosulfane® membrane. The dialysate collected with the Fresenius Polysulfone® membrane also contained a mean of 6853 mg of total protein, compared with 5490 mg with the Polyphen® membrane and 8422 mg with the Biosulfane® (P = 0.04) membrane. The neutropenia was slight and independent of mem-

brane brand, as were the changes in C3a des arg and SC5b-9 complement components. The reduction in platelet counts was higher for the Biosulfane® membrane than for the other brands (P = 0.003). This study indicates that whereas the polymer base of the membrane is the same, its production and subsequent handling during dialyzer production induce changes that attain statistical significance, most notably in the way that the membrane removes β2 microglobulin and interacts with proteins. The differences observed are a consequence of the different alloying polymers used during manufacture and, consequently, the membranes cannot be considered equivalent.

Key Words: Hemodialysis, β2 microglobulin removal, polysulfone, biocompatibility, hemodialysis membrane

The most commonly used membranes for the treatment of ESRD are those that are cellulose-based. Membranes based on synthetic polymers were first described in the early 1970s (1). Today they are produced from a variety of polymers by numerous manufacturers. Such membranes are used extensively in treatment strategies designed to exploit their high solute- and water-transport characteristics.

A recently published survey for the United States (2) showed that in the period from 1988 to 1992, the percentage of dialysis centers using high-flux membranes had increased from 23 to 50% and the most commonly used membrane was polysulfone. Over a decade of clinical experience with polysulfone membranes (Fresenius Polysulfone®; Fresenius AG, Bad Homburg, Germany) (3), other polysulfone membranes (Polyphen®, Minntech, Minneapolis, MN; and Biosulfane®, WR Grace, Danvers, MA) have recently become available for clinical use. These membranes use the same polymer, but the manufacturing process differs. To investigate if this difference influences the membranes' functional performance and biocompatibility, we undertook a prospective comparative clinical study using hemodialyzers containing the above membranes.

MATERIALS AND METHODS
Membranes and Hemodialyzers

The production of hollow fibers from synthetic materials involves several distinct steps, including the transformation of the polymer, its extrusion via an annular nozzle or spinnerette, phase inversion of the extruded material, and the removal of residues of the chemicals used in the manufacturing process. Historical detail about the production of polysulfone membranes has been published (4). The details regarding currently used production processes remain carefully shielded. Published scanning electron micrographs show polysulfone membranes to be asymmetrical: the lumen

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or blood side of the membrane is characterized by a thin skin (1 micron or less) beneath which is a porous foam structure whose principal function is to provide support for the inner layer (4). The structure of the membranes manufactured by Fresenius and Minntech are similar, and both use polysulfone-pyridylidone (PVP) as an alloying polymer, whereas the membrane produced by WR Grace (Biosulfane®) uses glycercin to maintain membrane functionality during production. This membrane retains the inner skin but has a substantially different substrate morphology (5).

Ethylene oxide-sterilized dialyzers incorporating the polysulphone membranes were studied. The membranes studied were the F60 (Fresenius AG, Bad Homburg, Germany), with an effective surface area of 1.3 m² and incorporating Fresenius Polysulfone®, the Primus 1350 (Minntech Corporation, Minneapolis, MN), with an effective surface area of 1.35 m² and incorporating Polyphen®, and the National Medical Care BioCare 130 (WR Grace, Danvers, MD), with an effective surface area of 1.3 m² and utilizing Biosulfane®. The dialyzers studied were drawn from current production batches and their preparation before use was in accordance with the manufacturers’ recommendations.

Patients

The study was approved by the Joint Ethics Committee Newcastle and North Tyneside HealthAuthorities and performed on a group of nine patients receiving regular dialysis treatment for chronic renal failure, all of whom had given informed consent to participate in the study. The patients’ mean age was 58.4 yr (range, 35 to 72 yr). Access to the circulation was gained by arteriovenous fistula or dual-lumen subclavian catheter. Bicarbonate-buffered dialysis fluid produced by single-patient proportioning systems incorporating ultrafiltration control systems were used. The bicarbonate dialysis fluid was prepared before dialysis from powdered bicarbonate. Dialysate endotoxin levels were below 5 IU/mL. The average treatment duration was 216 min (180 to 240 min). Before the study, all patients had been receiving treatment with cellulose-containing devices.

Study Design

For each patient, the study lasted 3 consecutive wk, with a different brand of polysulfone membrane being used each week. The order in which the membranes were allocated was determined by a Latin-square design appropriate for a crossover study (a Williams square) (6). The patients were allocated to treatments at random. This type of experimental design permits the differences among patients and among weeks to be eliminated from treatment comparisons and their standard errors.

Measurements

Measurements relating to functional performance were undertaken during the second dialysis with each dialyzer type, whereas those relating to biocompatibility were made during the third week, thereby eliminating any carryover effects. The dialyzers were not reused.

With respect to functional performance, the blood-side clearance of small molecules was measured by sampling the extracorporeal circuit 1 h after treatment began. The blood flow rate during the treatments was in accordance with the patients’ clinical requirements. To provide a consistent base for comparison, the blood flow rate was reduced to 200 mL/min at the time of the clearance measurements and the actual flow rate was determined using a bubble transit technique (7). The fluid removal rate was adjusted to 0.3 kg/h (5 mL/min) for the duration of the clearance measurements.

Before clearance measurements were taken, each membrane’s sieving coefficient for β₂ microglobulin was determined. For these measurements, the dialysate lines were disconnected from the dialyzer, the dialyzer was drained, and the ultrafiltrate was allowed to drain from the dialyzer for a period of 2 min before the samples were taken from the ultrafiltrate and the blood entering and leaving the dialyzer. The changes in plasma levels of β₂ microglobulin during each treatment were established by serial blood sampling (predialysis, and at 60, 180, and 210 min). The transmembrane removal of β₂ microglobulin, albumin, and total protein during the treatment was established by continuous collection and sampling of dialysate fluid during treatment.

Plasma small-molecule metabolite concentrations were determined using a Technicon DAX 72 Analyser (Bayer Diagnostics, Newbury, UK), and plasma and dialysate β₂ microglobulin concentrations were measured by an ELISA assay. Plasma protein concentrations were determined using a Boehringer Hitachi 717 analyzer (Boehringer, Mannheim, Germany), which was also used to measure the plasma albumin levels. Dialysate total protein concentrations were established by using a modification of the Lowry method (8), whereas dialysate albumin concentrations were determined by use of a differential protein analyzer (Technicon DPA 1 System; Bayer Diagnostics).

The sampling for biocompatibility parameters was performed via special sampling ports inserted into the extracorporeal circuit immediately before and after the hemodialyzer at timed intervals during treatment. White blood cell and platelet counts were performed by using a Coulter Counter on samples taken from blood entering the dialyzer, whereas complement activation (C3a and SC5b-9) was assessed on blood leaving the dialyzer. The samples were processed immediately, stored, and batch-analyzed with commercially available assays.

Statistical Analysis

The data collected was analyzed using the GENSTAT 5 statistical package (Numerical Algorithms Group, Oxford, UK). The GENSTAT algorithm assigned values where data was missing. To verify that this procedure did not distort the analysis, the tables of means with and without imputation were compared. Serial measurements were analyzed as a summary measure, and the area under the concentration-time curve (AUC) was divided by the final time at which the reading was taken, so that the AUC was expressed in the same units as the original measurement. Preliminary to each analysis of variance, individual plots for each patient were established by using a modification of the Lowry method (8), whereas dialysate albumin concentrations were determined by use of a differential protein analyzer (Technicon DPA 1 System; Bayer Diagnostics).

The sampling for biocompatibility parameters was performed via special sampling ports inserted into the extracorporeal circuit immediately before and after the hemodialyzer at timed intervals during treatment. White blood cell and platelet counts were performed by using a Coulter Counter on samples taken from blood entering the dialyzer, whereas complement activation (C3a and SC5b-9) was assessed on blood leaving the dialyzer. The samples were processed immediately, stored, and batch-analyzed with commercially available assays.

RESULTS

There were no differences in the dialyzers small-molecule clearance characteristics (Table 1). The mean (SD) predialysis levels of β₂ microglobulin were...
### Table 1. In vivo clearance of small molecules

<table>
<thead>
<tr>
<th>Dialyzer Membrane</th>
<th>Conditions of Study</th>
<th>Clearance (mL/min)</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>F60 Fresenius Polysulfone</td>
<td>Blood flow 200 mL/min</td>
<td>163</td>
<td>142</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysate flow 500 mL/min</td>
<td>(8)</td>
<td>(8)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 0.3 kg/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primus 1350 Polyphen</td>
<td>Blood flow 202 mL/min</td>
<td>158</td>
<td>146</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysate flow 500 mL/min</td>
<td>(8)</td>
<td>(8)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 0.3 kg/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BioCare 130 Biosulfane</td>
<td>Blood flow 200 mL/min</td>
<td>167 ± 5.1</td>
<td>148 ± 7.7</td>
<td>151 ± 8.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dialysate flow 500 mL/min</td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 0.3 kg/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mean (standard error of the difference between two sample means) shown.*

*Figures in parentheses refer to the number of observations.*

35.6 mg/L (6.02) for the Fresenius Polysulfone membrane, 37.6 (6.46) mg/L for the Polyphen membrane, and 36 (6.46) mg/L for the Biosulfane membrane. Because the experimental study was balanced, and there is a period effect in the model, the first time that membranes capable of removing $\beta_2$ microglobulin are used does not bias the treatment comparisons. A reduction in $\beta_2$ microglobulin levels during dialysis was observed with each membrane (Table 2). To analyze these changes, the values at the end of dialysis were expressed as a percentage of predialysis value, after correction for changes in distribution volume (9), and compared. These results demonstrate an overall difference among the membranes ($F_{2,12} = 4.59, P = 0.003$), essentially because of the superior removal of $\beta_2$ microglobulin by the Fresenius Polysulfone membrane compared with the Polyphen and Biosulfane membranes. Analysis of the actual $\beta_2$ microglobulin levels with the baseline used as a covariate gave similar results.

The mechanism of $\beta_2$ microglobulin removal during treatment results from adsorption to the membrane and convective mass transport. To assess the latter process, we measured the membrane's sieving coefficient and established a mean (SD) value for the Fresenius Polysulfone membrane of 0.336 (0.098), compared with 0.236 (0.061) for the Polyphen membrane. We were unable to establish a sieving coefficient for the Biosulfane membrane because of the absence of any $\beta_2$ microglobulin in the filtrate. A clear difference between the Biosulfane membrane and the other membranes exists. Comparison of the Fresenius Polysulfone and Polyphen membrane data failed to differentiate between them ($F_{1.8} = 3.29, P = 0.012$).

The mean $\beta_2$ microglobulin recovered in the dialysate when using the F60 hemodialyzer was 195 mg, compared with 158 mg for the Primus 1350. In agreement with sieving coefficient measurements, no $\beta_2$ microglobulin was present in samples collected during dialysis with the BioCare 130 dialyzers. No formal analysis is required to demonstrate differences between the Fresenius Polysulfone and Polyphen membranes, compared with the Biosulfane membrane.

### Table 2. Changes in $\beta_2$ microglobulin concentration during treatment

<table>
<thead>
<tr>
<th>Dialyzer Membrane</th>
<th>Conditions of Study</th>
<th>$\beta_2$ Microglobulin Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Predialysis</td>
</tr>
<tr>
<td>F60 Fresenius Polysulfone</td>
<td>Blood flow 226 mL/min</td>
<td>35.6 ± 6</td>
</tr>
<tr>
<td></td>
<td>Dialysate flow 500 mL/min</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 0.72 kg/h</td>
<td>(8)</td>
</tr>
<tr>
<td>Primus 1350 Polyphen</td>
<td>Blood flow 230 mL/min</td>
<td>37.6 ± 6.5</td>
</tr>
<tr>
<td></td>
<td>Dialysate flow 500 mL/min</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Ultrafiltration 0.72 kg/h</td>
<td>(8)</td>
</tr>
<tr>
<td>BioCare 130 Biosulfane</td>
<td>Blood flow 250 mL/min</td>
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</tr>
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<tr>
<td></td>
<td>Ultrafiltration 0.72 kg/h</td>
<td>(9)</td>
</tr>
</tbody>
</table>

*Mean (standard deviation) shown.*

*Figures in parentheses refer to the number of observations.*

*Sample taken at the end of dialysis for those patients in whom the treatment duration was less than 210 min.*
brane. The differences between the Fresenius Polysulfone® and Polyphen® membranes were not significant (F_{1,0} = 3.29, P = 0.23).

Dialysate samples contained albumin and total protein. The albumin concentrations were below the limit of detection (5 mg/L), although for each of the membranes, values above this baseline were occasionally noted. In contrast, the total amount of protein recovered in the dialysate expressed as the mean was 8422 mg for the Biosulfane® membrane, 6853 mg for the Fresenius Polysulfone® membrane, and 5490 mg for the Polyphen® membrane. The differences between the Fresenius Polysulfone® and Polyphen® membranes were not significant (F_{1,14} = 2.14, P = 0.17); however, the difference between the Biosulfane® membrane and the Fresenius Polysulfone® and Polyphen® membranes was (F_{1,14} = 4.97, P = 0.04).

The white blood cell and platelet counts observed during dialysis have been normalized and expressed as a percentage of pretreatment values (Figures 1, 2). For the Fresenius Polysulfone® membrane, the white blood cell count had declined to 81.6% of the predialysis level after 15 min, compared with 84.8% for the Polyphen® membrane and 86.1% for the Biosulfane® membrane. These differences were not significant (F_{2,14} = 0.35, P = 0.71). The platelet counts over the same period declined to 95.7% (Fresenius Polysulfone®), 92.6% (Polyphen®), and 86.2% (Biosulfane®) of the predialysis levels. The standard error of difference between any pair was 2.6%. The differences between the Fresenius Polysulfone® and Polyphen® membranes were not significant (F_{2,14} = 1.36, P = 0.26); however, the fall induced by the Biosulfane® membrane, compared with those of the Fresenius Polysulfone® and Polyphen® membranes, was significant (F_{1,14} = 12.7, P = 0.003). This significance remained after 180 min. Analyses using the baseline as a covariant rather than as a normalizing value gave similar results.

The changes in the complement components C3a and SC5b-9 observed during dialysis are shown in Figures 3 and 4. The time-weighted average values obtained were similar: 1516 ng/mL (Fresenius Polysulfone®), 1597 ng/mL (Polyphen®), and 1309 ng/mL (Biosulfane®). The standard error of differences between any pair was 339 ng/mL and the observed differences were not statistically significant (F_{2,14} = 0.39, P = 0.69). For SC5b-9, the time-weighted averages were 240 ng/mL (Fresenius Polysulfone®), 334 ng/mL (Polyphen®), and 162 ng/mL (Biosulfane®), respectively, with the standard error of difference between any pair being 126 ng/mL. As with the C3a values, we were unable to differentiate among the membranes (F_{2,14} = 0.94, P = 0.41).

**DISCUSSION**

Matsuda (10) showed that the modification of polymers used in the manufacture of dialysis membranes leads to a predictable pattern. By blending polymers or chemically modifying an individual polymer, the
membrane functionality and biocompatibility may be altered. The production of membranes by Fresenius and Minntech involves the use of polyvinyl pyrrolidone (PVP) as a blending agent, whereas the membrane produced by WR Grace uses glycerin. PVP is available in a range of molecular weights, and published studies indicate that increasing the concentration of PVP modifies the hydrophilic properties of the material (11). Our study comparing polysulfone membranes from three different producers show that the clearance characteristics for small-molecule compounds are comparable. Plasma \( \beta_2 \) microglobulin levels are reduced with each of the membranes, with the largest reduction noted with Fresenius Polysulfone\textsuperscript{®} membranes. In parallel with the plasma level changes, we noted differences in the membranes' sieving coefficients. The mean sieving coefficient for the Fresenius Polysulfone\textsuperscript{®} membrane was 0.34, whereas it was 0.24 for the Polyphen\textsuperscript{®} membrane. The value established for Fresenius Polysulfone\textsuperscript{®} is substantially below that established by Schaefer et al. (12), but is comparable to values established by Kandus et al. (13). A possible explanation for this variation may be the secondary membrane formation as a result of protein deposition on the membrane surface. We failed to measure a sieving coefficient for the Biosulfane\textsuperscript{®} membrane. Because the clinical use of this membrane is associated with a reduction in plasma \( \beta_2 \)-microglobulin levels, the reduction in plasma levels occurs because of adsorption to the membrane rather than because of transmembrane transport. This has been confirmed by Ronco et al. (14) and suggests that this variant of polysulfone behaves in a manner comparable with that of polymethylmethacrylate (15) and sulfonated polycrylonitrile (16).

The removal of low molecular weight proteins and amino acids is associated with the removal of \( \beta_2 \) microglobulin. It is notable that whereas no \( \beta_2 \) microglobulin was recovered from the dialysate when using Biosulfane\textsuperscript{®}, the dialysate did contain 5490 mg of protein. This suggests that the interaction between the polymer and proteins is very specific. Although the amount of protein recovered in the dialysate is not sufficient to alter the patient's postdialysis total plasma protein level, the repeated loss of 2 to 3% of the total plasma protein pool may require closer monitoring of patients when using such membranes. An important requirement of high-flux hemodialysis is the limitation of albumin loss, which causes catabolism and malnutrition. This requirement is fulfilled by the three membranes studied, because the majority of the dialysate levels were largely at the limit of detection. Occasionally, however, readings above this baseline were noted. The relevance of mild albumin loss may be overestimated, as Naito and Miyazaki showed the beneficial effects on the improvement of anemia when using a membrane with an albumin loss of 6 to 8 g/dialysis (17).

Despite the different manufacturing processes utilized in producing the membranes, neutropenia was similar but changes in platelet count were membrane-dependent. The highest falls in platelet count were noted for the Biosulfane\textsuperscript{®} membrane not only at 15 min after the start of treatment but also at 180 min. It is possible that this observation is related to the membrane's adsorptive behavior.

Membrane complement-activating potential is governed by the membrane's ability to bind regulatory proteins. For all membranes, an increase in plasma levels of C3a des arg occurred; however, the magnitude of the changes were independent of membrane type. Blood-membrane contact leads not only to the generation of C3a but also to the release of C5a, because of the cleavage of C5 into C5a and C5b. The C5b thus formed initiates the formation of SC5b-9, the terminal complement complex (TCC), or membrane attack complex (MAC). No biological dysfunction has been attributed to increased plasma levels of SC5b-9, pathophysiological responses resulting from increased levels of SC5b-9 have been reported during both hemodialysis (18) and cardiopulmonary bypass (19). The linkage or deposition of such complexes with blood cells may be in part responsible for the lysis of erythrocytes, and the stimulation of monocytes and granulocytes to release enzymes or various mediators, including cytokines and eicosanoids, during extracorporeal circulatory procedures. Increases in SC5b-9 levels during dialysis with all brands have been observed; however, we have not been able to distinguish among the membranes despite the suggestion of Delpisch and coworkers (20) that this is a more sensitive parameter for distinguishing among membranes.

The polymer base of the membranes studied in this article is the same, but their production and subsequent handling during the manufacturing process differ and result in differences among the membranes, notably in the way that they they remove \( \beta_2 \) microglobulin and interact with proteins and blood cells: consequently, they cannot be considered equivalent. The reason for these differences is the use of different
alloying polymers during the manufacturing process, which results in the alteration of the membranes’ hydrophilic properties as well as the cationic and anionic domains at the polymer surface.

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