Tolerance of Hemodialysis: A Randomized Prospective Trial of High-Flux Versus Conventional High-Efficiency Hemodialysis

Deirdre M. Collins, Michael B. Lambert, Jerome S. Tannenbaum, Michael Oliverio, and Steve J. Schwab

D.M. Collins, M.B. Lambert, M. Oliverio, S.J. Schwab, Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC
J.S. Tannenbaum, REN Corporation USA Incorporated, Nashville, TN

ABSTRACT
Hemodialysis is frequently complicated by hypotension and associated symptoms. It has been suggested that these symptoms may be related to the biochemical changes caused by cellulosic dialysis membranes. In this study, a prospective randomized crossover trial was conducted comparing the incidence of hypotension and acute symptoms during dialysis with large-surface-area (1.6 m²) cellulosic (cuprophane [CUP]) and noncellulosic (polyacrylonitrile [PAN], AN69) membranes. Dialyzers were used for a single use only. There was no difference in predialysis BUN, predialysis blood pressure, intradialytic weight gain, blood flow, dialysis efficiency (urea reduction), dialysis duration, hematocrit, or erythropoietin dose between the two study phases. When these clinical characteristics were matched, there was no difference in the number of episodes of hypotension (CUP, 19 ± 3; PAN, 22 ± 3; P = not significant [NS]). The incidence of symptomatic hypotension, as reflected by the number of episodes of hypotension requiring more than 100 mL of saline for correction, was also not different between study phases (CUP, 10 ± 1; AN69, 11 ± 2; P = NS). The incidence of intradialytic symptoms, including emesis, cramping, headache, angina, pruritis, and bronchospasm, was similar during the two study phases (CUP, 11 ± 2; AN69, 10 ± 1; P = NS). It was concluded that noncellulosic membranes do not offer any significant advantage over cellulosic membranes in reducing the acute complications of hemodialysis.

Key Words: Hemodialysis, hypotension, dialysis membrane, cuprophane, polyacrylonitrile

Currently, over 100,000 persons in the United States undergo maintenance hemodialysis every year (1). Although a life-saving procedure in these patients, the process of hemodialysis itself may produce adverse clinical effects. For example, hemodialysis is frequently complicated by hypotension and acute hemodialysis-related symptoms (2). Further, recent studies suggest that the hemodialysis process may also play a role in the development of chronic complications of ESRD, such as dialysis-associated arthropathy and increased susceptibility to infections (3,4). It has been suggested that these adverse effects may relate to the type of membrane used during hemodialysis (5).

There are two general classes of dialysis membrane material. Cuprophane (CUP), the membrane material most commonly used in the United States, is derived from cellulose and represents the prototypic cellulosic membrane. Cellulosic dialyzers have undergone several modifications in recent years, including the use of a larger membrane surface area, in order to provide more rapid, or “high-efficiency,” dialysis. Dialysis membranes may also be constructed from more-porous synthetic polymers (noncellulosic membranes). Many of these noncellulosic membranes are called “high-flux” membranes because of their much greater hydraulic permeability and because of their increased permeability to vitamin B12-sized and larger molecules such as β-2 microglobulin.

Cellulosic membranes in general differ from noncellulosic membranes in their ability to activate several potentially adverse biologic processes. For example, CUP stimulates the alternate pathway of complement and induces neutrophil and platelet aggregation, pulmonary leukostasis, and the production of cytokines (6). It has been hypothesized that the activation of these biologic events may produce some of the complications of hemodialysis. Because...
membranes derived from synthetic noncellulosic polymers produce substantially fewer of these laboratory effects, they have been characterized as more "biocompatible" [6]. Whether the use of noncellulosic membranes offers any clinical advantage, however, remains unclear.

In these studies, we used a randomized, prospective crossover study design to examine whether patients dialyzed with one of the most biocompatible synthetic membranes (polyacrylonitrile [PAN or AN69]) had a lower incidence of intradialytic hypotension and acute hemodialysis-related symptoms when compared with those dialyzed with CUP. These studies were accomplished with dialysis membranes of similar surface area, urea clearance capability, blood flow rates, and dialysate composition. We monitored several factors that may affect the incidence of intradialytic symptoms, including predialysis BUN, predialysis blood pressure, and magnitude of intradialytic ultrafiltration. We also monitored variables that may affect patients' sense of well being, including dialysis efficiency and predialysis hematocrit.

METHODS

Forty chronic in-center hemodialysis patients from the REN Durham Dialysis Center in Durham, NC, were the subjects for our study. All patients gave informed consent, and the study was approved by the institutional review board of Duke University Medical Center. Before the initiation of the study, all patients were dialyzed with single-use CUP membranes. Data on intradialytic symptoms were obtained at each dialysis treatment by one of the study coordinators and were entered into the data base. Laboratory data were entered into the data base at the time that they were obtained. Patients were randomized to inclusion in Group A, receiving dialysis with a cellulosic CUP membrane first, and Group B, receiving dialysis with a noncellulosic AN69 membrane first. Of the 40 patients initially randomized, two patients died after hospitalization within the first 4 wk of the study, one patient required removal because of prolonged hospitalization at another facility, one patient converted to peritoneal dialysis, and one patient was transplanted. These five patients were not included in the statistical analysis because insufficient data were obtained for study inclusion. Characteristics of the remaining patients are listed in Table 1.

Patients in Group A received dialysis with a CUP membrane for 3 months, followed by dialysis with an AN69 dialyzer for an additional 3 months. Patients in Group B were dialyzed with AN69 dialyzers for 3 months, followed by CUP membranes for 3 months. CUP membranes used were the Gambro 6N plate; AN69 membranes were the Hospal F16 hollow fiber (both dialyzers, CGH Medical, Lakewood, CO).

Characteristics of dialyzers are listed in Table 2. Urea clearance (C_{urea}) was listed as provided by the membrane manufacturer and as measured during the midpoint of each study phase in all subjects. Membrane C_{urea} (mean of three clearances) was calculated by the formula:

\[ C_{urea} = \frac{\text{arterial BUN} - \text{venous BUN}}{\text{arterial BUN}} \times \text{blood flow (mL/min)} \]

Kidneys were used for a single dialysis only. The convective removal of urea, which is associated with ultrafiltration, is not considered by this formula. Four patients developed frequent, severe adverse effects in one arm of the study, two during dialysis with CUP and two during dialysis with the AN69 dialyzer. For the remainder of the phase of the study in which frequent adverse effects occurred, these patients were dialyzed with CUP dialyzers of a smaller surface area (Gambro 5N plate; surface area = 1.1 m²). For these patients, only data collected during dialysis with the study kidneys were included in the statistical analysis.

All patients were dialyzed with volumetrically controlled machines (Fresenius 2008D; Fresenius USA Inc., Concord, CA). The composition of the dialysate was sodium, 138 mEq/L; bicarbonate, 35 mEq/L; potassium, 2 mEq/L; calcium, 3.5 mEq/L; magnesium, 1 mEq/L; and acetate, 3 mEq/L; the rate of

<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics by group</th>
<th>CUP (A)</th>
<th>PAN (B)</th>
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<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>White</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Black</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Mean Age (yr)</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Diabetic</td>
<td>9</td>
<td>8</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>TABLE 2. Membrane characteristics</th>
<th>CUP</th>
<th>PAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface Area (m²)</td>
<td>1.6</td>
<td>1.55</td>
</tr>
<tr>
<td>C_{urea} (ml/min) (published)*</td>
<td>272</td>
<td>269</td>
</tr>
<tr>
<td>C_{urea} (ml/min) (measured)</td>
<td>262 ± 10</td>
<td>269 ± 18</td>
</tr>
<tr>
<td>Ultrafiltration Coefficient (ml/mm Hg per h)</td>
<td>8</td>
<td>44</td>
</tr>
</tbody>
</table>

* C_{urea} at blood flows of 400 ml/min; Dialysis flow, 500 ml/min.
dialysate flow was 500 mL/min. Dialysate sodium could be varied by the use of a number of calculated "sodium programs." Available sodium programs allowed an increase in dialysate sodium concentration by up to 14% above the basal level in either a linear or stepped fashion. The sodium program used varied between patients but was kept constant for each patient throughout both phases of the study. All dialysis was performed at blood flow rates between 300 and 400 mL/min, although an effort was made to keep blood flow rates constant at 400 mL/min throughout both arms of the study. In five patients, blood flow was reduced during the second phase of the study because of recurrent symptoms. Two of these patients were in Group A, and three were in Group B. Heparin was used as the only anticoagulant during hemodialysis, in doses that varied between patients but, for the most part, remained constant throughout the study.

Blood pressure was measured at 15-min intervals throughout dialysis with an automated blood pressure cuff integrated into the hemodialysis machine. Blood pressure was also determined upon the occurrence of symptoms. Hypotension was defined as a systolic blood pressure of 100 mm Hg or less, or a reduction in systolic blood pressure by 40% of the predialysis value. If a patient was hypotensive at four or more blood pressure determinations during a single dialysis session, only four episodes of hypotension were recorded. This adjustment was made to allow for patients who were persistently hypotensive throughout a single treatment (<1% of treatments). Saline was administered only during episodes of symptomatic hypotension or cramping, and the amount of saline administered was recorded. Episodes of emesis, cramping, pruritis, and bronchospasm were recorded, and the occurrence of headache or anginal symptoms was also monitored. All hospital admissions, episodes of infection, and incidents of graft thrombosis were recorded.

Each patient had monthly determinations of predialysis BUN. Urea reduction (7) was performed at the midpoint and end of each phase of the study. The purpose of measuring urea reduction in this study was to assure that equivalent hemodialysis was delivered in both treatment groups.

White blood cell (WBC) count, platelet count, C3a, C5a, and P02 were measured before dialysis and at 15 min after the onset of dialysis; these observations were made at the midpoint of each phase of the study. Complement levels were measured as described previously (8).

For the purposes of statistical analysis, data from patients in Groups A and B were pooled and analyzed as a function of dialyzer membrane. For all comparisons, a paired t test was used. When statistical significance was indicated by this test, Bonferroni's method was applied to correct for multiple comparisons, as indicated in Results.

**RESULTS**

Predialysis variables and characteristics of dialysis are listed by membrane in Table 3. Except when specifically mentioned, significance values refer to comparisons between membrane treatment arms (CUP versus AN69). Mean predialysis BUN, predialysis blood pressure, and intradialytic weight gain were not statistically different. Blood flow was similar in the two experimental phases. Dialysis adequacy, as reflected by urea reduction, was similar in the two groups. Predialysis hematocrit was similar, and mean erythropoietin dose was not different in all patients between phases of the study. Mean dialysis duration was not different between the study groups (CUP, 3.3 h; PAN, 3.25 h). All patients received treatments three times per week.

Adverse clinical effects per treatment arm are recorded in Table 4. The mean number of hypotensive episodes per 3-month study phase was 19 ± 3 when

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**TABLE 3. Clinical characteristics**

<table>
<thead>
<tr>
<th></th>
<th>CUP</th>
<th>PAN</th>
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</thead>
<tbody>
<tr>
<td>Predialysis BUN</td>
<td>67 ± 2</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>Predialysis Systolic Blood Pressure (mm)</td>
<td>154 ± 6</td>
<td>156 ± 3</td>
</tr>
<tr>
<td>Predialysis Diastolic Blood Pressure (mm)</td>
<td>84 ± 2</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>Intradialytic Weight Gain (kg)</td>
<td>2.9 ± 0.1</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>Blood Flow (mL/min)</td>
<td>379 ± 6</td>
<td>377 ± 7</td>
</tr>
<tr>
<td>Urea Reduction (%)</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>29 ± 1</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>Erythropoietin Dose (U)</td>
<td>2,854 ± 185</td>
<td>2,692 ± 180</td>
</tr>
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**TABLE 4. Frequency of symptoms per study phase**

<table>
<thead>
<tr>
<th></th>
<th>CUP</th>
<th>PAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotensive Events (per Patient)</td>
<td>19 ± 3</td>
<td>22 ± 3</td>
</tr>
<tr>
<td>Saline Administration &gt;100 mL per Patient</td>
<td>10 ± 1</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>Mean Saline per Treatment</td>
<td>69 ± 13</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>Emesis</td>
<td>6 ± 2°</td>
<td>4 ± 1°</td>
</tr>
<tr>
<td>Cramping</td>
<td>3 ± 4°</td>
<td>6 ± 2°</td>
</tr>
<tr>
<td>Symptom Index</td>
<td>11 ± 2</td>
<td>10 ± 1</td>
</tr>
</tbody>
</table>

* P < 0.05 (P = not significant by Bonferroni).

* P < 0.05.
patients were dialyzed with CUP and 22 ± 3 when patients were dialyzed with AN69 dialyzers. This difference was not statistically significant. Blood pressure variations occur frequently during hemodialysis. In this study, saline was administered only for episodes of symptomatic cramping or hypotension. Thus, the use of saline reflects the clinical significance of the episodes observed. There was no difference in the number of times more than 100 mL of saline was administered to correct symptoms in all patients (CUP, 10 ± 1; AN69, 11 ± 2). The mean amount of saline administered per dialysis treatment was not different between phases in all patients (CUP, 69 ± 13 mL; AN69, 71 ± 12 mL).

The most frequently occurring symptoms were emesis and cramping. There was a mean of 6 ± 2 episodes of emesis in patients dialyzing with CUP and 4 ± 1 episodes in patients dialyzing with AN69. This difference was not statistically significant when Bonferroni's correction was applied (P < 0.05, t test). In contrast, cramping occurred significantly more frequently when patients were dialyzed with AN69 dialyzers, 3 ± 1 episodes during CUP dialysis and 6 ± 2 episodes during the use of AN69 dialyzers. Severe cramping was treated with saline and was recorded as part of the total saline administered. Other symptoms occurred much less frequently. There were 30 episodes of headache on CUP dialysis and 24 episodes of headache when patients were dialyzed with AN59. Angina occurred on 14 occasions during dialysis with CUP and on 10 occasions during AN69 dialysis. There were 10 episodes of pruritis during CUP dialysis and 14 episodes of pruritis when AN69 dialyzers were used. Bronchospasm occurred once during dialysis with CUP and on four occasions during dialysis with AN69; two of these were associated with AN69 and angiotensin-converting enzyme inhibitors. There were no statistical differences in the frequency of headache, angina, pruritis, or bronchospasm between experimental phases of the study. When the intradialytic symptoms of emesis, cramping, headache, angina, pruritis, and bronchospasm were pooled to create a symptom index, there was no significant difference in occurrence between study phases (CUP, 11 ± 2; AN69, 10 ± 1; P = not significant).

This prospective, controlled, crossover study was designed to detect clinically significant differences in hypotension and other intradialytic events between the two study groups. For those observations where a statistical difference was not found, more than 236 patients would have been needed for the study to achieve sufficient statistical power to eliminate any chance for a Type II statistical error. Thus, although possible, it is unlikely that a clinically significant difference in intradialytic symptoms was missed.

Changes in complement levels, peripheral white blood cell count, Po2, and platelet count are illustrated in Figure 1. As depicted in Panel A, C3a levels rose significantly during dialysis with CUP but remained unchanged during the use of AN69 dialyzers. C3a levels remained elevated at the end of CUP dialysis and remained unchanged at the end of AN69 dialysis. As depicted in Panel B, the predialysis WBC count did not differ between experimental phases. The WBC count fell during dialysis with CUP but not during dialysis with AN69. The fall in WBC count coincided temporally with the rise in C3a levels. As shown in Panel C, Po2 did not fall significantly during dialysis in either experimental phase. Similarly, Po2 did not change after 15 min of dialysis (predialysis: CUP, 37 ± 1; AN69, 38 ± 1; postdialysis: CUP, 37 ± 1; AN69, 39 ± 1; P = not significant). As illustrated in Panel D, predialysis platelet counts were not significantly different between phases of the study nor between patient groups. There was a small but significant fall in platelet count at 15 min after the onset of dialysis in patients during the use of CUP but not AN69.

Subacute outcomes were also tallied. Hospital admissions, infections, and graft thromboses were monitored. Infection included those related to vascular access, peripheral ischemia, and urinary tract infections. There were no significant differences in the occurrence of any of these complications. However, the limited time frame of the study prevents any conclusions related to subacute outcomes.

DISCUSSION

Noncellulosic membranes are considerably more costly than traditional CUP membranes. It is therefore crucial to determine whether the use of noncellulosic membranes provides any significant clinical advantage.

Data from the Bergamo Collaborative Dialysis Study Group suggest that noncellulosic dialyzers produce acute intradialytic symptomatology as frequently as CUP (9). This large European trial compared patients dialyzed with relatively small-surface-area dialyzers (1.0 m2) composed of either CUP or polysulfone. These authors used matched patients in a multicenter protocol. They were unable to find significant differences in acute dialytic symptoms between the two membrane types.

The study presented here, a randomized crossover comparison conducted in the United States, used large-surface-area (1.6 m2) dialyzers composed of PAN (AN69) and CUP without reuse. Thus, one of the most antigenic membranes (CUP) was compared with one of the least antigenic membranes (AN69). In addition, membranes of large surface area were compared in a rapid dialysis format. The study design allowed us to match variables that may be important
Figure 1. Changes in C3a, WBC count, PO2, and platelet count during dialysis with CUP or PAN membranes. During dialysis with CUP, C3a levels rose and WBC and platelet counts fell significantly 10 min after the initiation of hemodialysis. No changes were noted during dialysis with PAN. Arterial oxygen tension did not change with either membrane.

in the production of intradialytic hypotension, including dialysate osmolarity, potassium concentration, ultrafiltration rate, predialysis blood urea, female sex, age, and diabetes mellitus. In addition, predialysis blood pressure and intradialytic blood flow rates did not differ between periods of membrane use. When these variables were matched, no difference in the incidence of hypotension occurred between experimental periods. Further, the incidence of symptomatic hypotension, as indicated by the number of episodes requiring more than 100 mL of saline for correction, or the average quantity of saline administered per dialysis session was not different between membranes.

The development of symptoms may be related to the acute physiologic changes that occur during dialysis. However, the development of intradialytic symptoms occurs against a background of variable interdialytic well being, which may be influenced by the adequacy of dialysis, as well as by the level of hematocrit. In this study, we demonstrated that subjective symptoms occur as frequently during dialysis with AN69 as with CUP. These findings occurred not only during matching of predialytic and intradialytic variables, but also during conditions of similar dialysis adequacy, as indicated by urea reduction.

PAN membranes were associated with reduced emesis, and CUP membranes were associated with reduced cramping. However, when emesis, cramping, headache, pruritis, bronchospasm, and angina were pooled to create a symptom index, there were no differences between the two study groups. Further, both hematocrit and erythropoietin doses were similar during both phases of the study. This latter finding suggests that the patients' interdialytic sense of well being, as affected by the hematocrit, was not different between experimental phases. The similarity in erythropoietin doses is noteworthy for a second reason. It has been postulated that the clearance of putative inhibitors of red blood cell production by more permeable noncellulosic membranes may improve hematocrit and allow lower erythropoietin doses (10). In this study, however, we were unable to demonstrate any such erythropoietin-sparing effect when comparing these two membrane types.

It has now been clearly established that CUP membranes activate the complement pathway to a greater extent than do synthetic membranes (5,9,11,12). Al-
though the anaphylotoxins C3a and C5a may be produced at a greater rate during dialysis with synthetic membranes (13), these membranes bind complement more effectively than CUP (14), resulting in lower circulating levels of complement. As described previously (5,9,15), C3a levels increased significantly after the initiation of dialysis with CUP and remained elevated at the conclusion of the dialysis session. In contrast, no change was noted in C3a levels during dialysis with AN69.

The clinical significance of intradialytic complement activation is not yet clear. CUP-induced complement activation appears to be linked to a number of adverse biologic processes, including neutrophil aggregation (15,16). Neutrophil aggregation may lead to pulmonary sequestration of neutrophils (17), with attendant development of pulmonary hypertension and hypoxemia (18). Intradialytic hypoxemia has not been a consistent finding during CUP dialysis, however (19), and was not observed in the study presented here. In vitro, alternate pathway complement components stimulate monocyte production of cytokines, including interleukin-1 (20,21); a similar effect occurs in vivo during dialysis with CUP membranes (22). Because interleukin-1 causes systemic vasodilation, it has been postulated that the complement-induced production of interleukin-1 accounts for the hypotension that occurs commonly during dialysis with CUP (23). This hypothesis, however, is not supported by this study.

The chronic effects of dialysis with less “biocompatible” membranes remain largely unknown. Hornberger and associates recently reported improvements in patient mortality but no change in hospital admission rates in patients being dialyzed with noncellulosic polysulfone dialyzers (24). Those investigators concluded that noncellulosic membranes provided an advantage in reducing hemodialysis mortality. It has also been suggested that dialysis with less biocompatible membranes may exacerbate the immunosuppression observed in dialysis patients (3). A recent report suggests that these alterations in immune cells are significant and result in a higher incidence of infection in patients dialyzed with noncellulosic polycarbonate dialyzers (25). In contrast, the lowest mortality currently reported occurs in patients dialyzed with conventional CUP membranes (25). Despite these conflicts, the results of this study and the Bergamo Collaborative Study (9) confirm that morbidity and mortality differences between membranes, if present, are not related to acute intradialytic symptoms. It has been proposed, and we believe, that the reasons for morbidity and mortality differences are related to the amount of hemodialysis delivered and not to the membrane used (25).

This study does not address the issue of reuse of artificial kidneys. When individual cellulosic kidneys are reused during multiple dialysis treatments, the degree of complement activation and neutropenia associated with cellulosic membranes is reduced and is similar to that produced by noncellulosic membranes (26).

We conclude that the use of synthetic noncellulosic membranes does not provide any advantage over the use of CUP dialyzers in reducing the acute complications of hemodialysis. Prospective randomized trials are needed to evaluate the effects of membrane type and amount of dialysis delivered on chronic complications and morbidity and mortality in hemodialysis patients.

ACKNOWLEDGMENTS

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REFERENCES


