J Am Soc Nephrol 11: 2344–2350, 2000

A Comparison of On-Line Hemodiafiltration and High-Flux Hemodialysis: A Prospective Clinical Study

RICHARD A. WARD,* BÄRBEL SCHMIDT,† JEANNINE HULLIN,† GÜNTHER F. HILLEBRAND,†‡ and WALTER SAMTLEBEN†‡

**Department of Medicine, University of Louisville, Louisville, Kentucky; †Department of Medicine I, Klinikum Grosshadern, University of Munich, Munich, and ‡Kuratorium fuer Dialyse und Nierentransplantation, Neuried, Germany.*

Abstract. Some of the morbidity associated with chronic hemodialysis is thought to result from retention of large molecular weight solutes that are poorly removed by diffusion in conventional hemodialysis. Hemodiafiltration combines convective and diffusive solute removal in a single therapy. The hypothesis that hemodiafiltration provides better solute removal than high-flux hemodialysis was tested in a prospective, randomized clinical trial. Patients were randomized to either on-line postdilution hemodiafiltration or high-flux hemodialysis. The groups did not differ in body size, treatment time, blood flow rate, or net fluid removal. The filtration volume in hemodiafiltration was 21 ± 1 L. Therapy prescriptions were unchanged for a 12-mo study period. Removal of both small (urea and creatinine) and large (β_2-microglobulin and complement factor D) solutes was significantly greater for hemodiafiltration than for high-flux hemodialysis. The increased urea and creatinine removal did not result in lower pretreatment serum concentrations in the hemodiafiltration group. Pretreatment plasma β_2-microglobulin concentrations decreased with time ($P < 0$ 0.001); however, the decrease was similar for both therapies ($P = 0.317$). Pretreatment plasma complement factor D concentrations also decreased with time ($P < 0.001$), and the decrease was significantly greater with hemodiafiltration than with high-flux hemodialysis ($P = 0.010$). The conclusion is that on-line hemodiafiltration provides superior solute removal to high-flux hemodialysis over a wide molecular weight range. The improved removal may not result in lower pretreatment plasma concentrations, however, possibly because of limitations in mass transfer rates within the body.

Identification of β_2-microglobulin as the precursor of amyloid deposits in long-term hemodialysis patients (1) has focused attention on the need for renal replacement therapies that remove solutes with molecular weights in excess of 10 kD. Solutes of this size are not removed by conventional hemodialysis, and their removal by diffusion through high-flux hemodialysis membranes is also limited. In 1975, Henderson and colleagues (2) demonstrated greatly enhanced removal of high-molecular-weight solutes by convection through highly permeable membranes. This process, which became known as hemofiltration, involved infusion of a large volume of fluid into the blood entering the filter and its subsequent removal by ultrafiltration. Although hemofiltration provided good removal of high-molecular-weight solutes, it was less efficient than hemodialysis in removing small solutes, such as urea. This limitation led to the development of hemodiafiltration, a hybrid therapy that combined the convective clearance of hemofiltration with the diffusive clearance of hemodialysis (3). Initially, the ability to perform hemodiafiltration under routine clinical conditions was severely limited by the need for large volumes of sterile substitution solution. The development of systems that use sequential ultrafiltration to prepare sterile substitution solution on-line from water and concentrate (4) has removed the technical constraints to clinical implementation of hemodiafiltration. However, there have been few reports of controlled clinical trials that examine the putative therapeutic advantages of this therapy. Therefore, we compared hemodiafiltration with high-flux hemodialysis in a prospective clinical trial.

Materials and Methods

Study Design

This study was a single-center, prospective, randomized comparison of postdilution hemodiafiltration and high-flux hemodialysis. Patients who had been treated previously by conventional or high-flux hemodialysis at the Neuried KfH dialysis center were paired on the basis of body size, existing treatment time and blood flow rate, and predialysis serum β_2-microglobulin concentration. Patients from each pair were randomized to either hemodiafiltration or high-flux hemodialysis and followed for 12 mo as described below. During the first 6 mo, additional patients were recruited to replace any patients who withdrew from the study.

Patients

Patients who had been stable on thrice weekly hemodialysis for at least 2 mo and who had a permanent blood access capable of delivering a blood flow rate of at least 250 ml/min were eligible for inclusion in the study. The study received ethics committee approval,

Received September 29, 1999. Accepted April 20, 2000.
Correspondence to Dr. Richard A. Ward, Kidney Disease Program, University of Louisville, 615 South Preston Street, Louisville, KY 40202. Phone: 502-852-5757; Fax: 502-852-7643; E-mail: richard.ward@louisville.edu
1046-6673/1112-2344
Journal of the American Society of Nephrology

and informed consent was obtained from all patients before their enrollment in the study.

Hemodiafiltration and High-Flux Hemodialysis

Postdilution hemodiafiltration was performed using a specifically designed system incorporating on-line preparation of substitution solution (AK 100 ULTRA, Gambro, Lund, Sweden) as described previously (4). Briefly, blood is passed through a high-flux filter, where it is subjected to dialysis with ultrafiltration at a rate in excess of that required to achieve the patient's dry weight. Fluid balance is maintained by infusing sterile, nonpyrogenic substitution solution into the venous blood line. The substitution solution is derived from ultrapure dialysate by passing it through a single-use ultrafilter immediately before its infusion into the venous blood line. The dialysate is prepared by proportioning ultrafiltered water, liquid acid concentrate, and liquid bicarbonate concentrate made on-line from a dry powder cartridge. This dialysate is then rendered ultrapure by passage through a second ultrafilter. The water supplied to the AK 100 ULTRA for preparation of dialysate and substitution solution met the German microbiologic standard of less than 100 CFU/ml and less than 0.25 EU/ml of endotoxin. The dialysate contained 138 mmol/L sodium, 1 to 4 mmol/L potassium, 1.75 mmol/L calcium, 0.5 mmol/L magnesium, 32 mmol/L bicarbonate, 3 mmol/L acetate, and 1 g/L glucose.

The present study used filters containing 1.7 m^2 of polyamide membrane (Polyflux 17/17S, Gambro). During the first 6 mo of the study, filters were sterilized with ethylene oxide (Polyflux 17); thereafter, they were steam-sterilized (Polyflux 17S). At entry to the study, the ultrafiltration rate for each patient was set at 25% of the patient's blood flow rate. The ultrafiltration rate was then increased until the rate that provided a stable transmembrane pressure of 200 mmHg was found. That ultrafiltration rate was used in all subsequent treatments, unless monitored transmembrane pressures indicated that a change was needed to keep the transmembrane pressure from exceeding 200 mmHg. The AK 100 ULTRA was set to prepare 500 ml/min of dialysate. Actual dialysate flow rates were reduced below 500 ml/min by the flow rate of substitution solution. Typical substitution solution flow rates ranged from 65 to 85 ml/min, so that actual dialysate flow rates during hemodiafiltration ranged from 415 to 435 ml/min.

High-flux hemodialysis was performed using a dialyzer containing 1.4 m^2 of steam-sterilized polyamide membrane (Polyflux 14S, Gambro) and a dialysate flow rate of 500 ml/min.

Other aspects of the patients' therapy prescription did not differ between the two groups. Treatment times and blood flow rates, which were individualized for each patient, were unchanged from those in use before entry into the study and remained unchanged throughout the 12 mo of the study. Anticoagulation was achieved using a loading dose and constant infusion of heparin. Net fluid removal was set on an individual basis according to the patient's clinical need.

Data Collection and Analysis

Electrolytes, Urea, and Creatinine. Predialysis concentrations of sodium, potassium, calcium, phosphate, bicarbonate, urea, and creatinine were measured at 6-wk intervals. Single-pool Kt/V_{urea} and eKt/V were calculated from pre- and posttreatment urea concentrations according to Daugirdas (5) and Daugirdas and Schneditz (6), respectively. Creatinine removal was estimated as the reduction in serum creatinine concentration from pre- to posttreatment. Pretreatment blood samples were drawn immediately after access needle insertion. Posttreatment samples were drawn from the arterial blood line 20 s after decreasing the blood flow rate to 80 ml/min. Concentrations of electrolytes, urea, and creatinine were determined by routine clinical laboratory methods.

β_2-Microglobulin and Complement Factor D. Removal of β_2-microglobulin was determined at 6-wk intervals. The pre- to posttreatment reduction in plasma β_2-microglobulin concentration was calculated using a posttreatment concentration corrected for hemoconcentration according to Bergström and Wehle (7). The clearance of β_2-microglobulin was calculated using the method of Leypoldt *et al.* (8). Pretreatment plasma concentrations of complement factor D were determined at entry to the study and after 26, 39, and 52 wk of hemodiafiltration or high-flux hemodialysis using an enzyme-linked immunosorbent assay (9). Pre- to posttreatment reductions in plasma complement factor D concentration were also determined after correcting the posttreatment concentration for hemoconcentration using the method of Bergström and Wehle (7). However, care must be taken in interpreting these results because residual heparin interferes with the assay for complement factor D in the posttreatment sample (R. Deppisch and W. Beck, Hechingen, Germany, personal communication, April 3, 2000), possibly because of binding of heparin to factor D (10).

Anemia Control. Hemoglobin and hematocrit were determined at 6-wk intervals using routine clinical laboratory methods. All patients received recombinant human erythropoietin. Erythropoietin doses were changed as required to maintain a hematocrit in the range of 30 to 36%.

Quality of Life. The patients' assessment of their quality of life was determined after 26 and 52 wk of the study using the Kidney Disease Questionnaire (11). (The questionnaire was not administered before entry into the study because a German language version of the instrument was unavailable then.) The Kidney Disease Questionnaire determines quality of life in five dimensions: physical symptoms, fatigue, depression, relationships with others, and frustration. A single interviewer administered the questionnaire to all patients.

Statistical Analyses

Changes in measured variables with time were assessed by repeated measures ANOVA, with the mode of treatment (hemodiafiltration or high-flux hemodialysis) as a between-subjects factor. All statistical testing was performed using the SPSS statistical package (version 8.0 for Windows, SPSS Inc, Chicago, IL). The multivariate statistic used was the Pillai's Trace. Data are presented as mean ± SEM for n observations.

Results

Forty-four patients were randomized to hemodiafiltration or high-flux hemodialysis at the start of the study. Six additional patients were subsequently recruited to replace patients who withdrew from the study during the first 6 mo. Eleven of the 50 patients did not complete 12 mo of study. Three patients withdrew from the study because of worsening hypertension and a marked increase in BP from pre- to posttreatment after the initiation of hemodiafiltration. In these three patients, the average pretreatment BP increased from 156/86 mmHg before entry into the study to 173/93 mmHg in the month before their withdrawal from the study; postdialysis BP as high as 240/120 mmHg were observed. The worsening of hypertension was, however, limited to these three patients. Excluding these three patients, there was a slight but nonsignificant decrease in predialysis mean BP over the course of the study ($P = 0.103$), which was independent of the mode of therapy ($P = 0.937$)

(data not shown). Again excluding the three patients with worsening hypertension, the change in mean BP from pre- to posttreatment was also small, did not differ between the two groups ($P = 0.969$), and did not change over the course of the study ($P = 0.404$) (data not shown). The other eight patients who withdrew from the study did so for reasons unrelated to the mode of therapy. These patients withdrew because of transfer to another facility (three patients), death (two patients), renal transplantation (one patient), apparent hypersensitivity to the polyamide membrane (one patient), and prolonged access problems that prevented compliance with the study protocol (one patient). Five of the 11 patients who withdrew from the study (4 from the hemodiafiltration group, including the 3 patients who withdrew because of worsening hypertension, and 1 from the high-flux hemodialysis group) did so within 10 wk of entering the study. These five patients are not included in the following analysis and presentation of data, which is based on 24 patients in the hemodiafiltration group and 21 patients in the high-flux hemodialysis group.

Details of the two patient groups and their therapy prescriptions are presented in Table 1. Before entering the study, the patients had been treated by either high-flux (18 hemodiafiltration and 16 high-flux hemodialysis patients) or low-flux (6 hemodiafiltration and 5 high-flux hemodialysis patients) hemodialysis. The two groups did not differ with regard to gender, age, duration of previous dialysis therapy, weight, body mass index, treatment time, or blood flow rate. Five patients in the hemodiafiltration group and three patients in the high-flux hemodialysis group were diabetic. Four patients, two in each group, had some residual renal function (average creatinine clearance, 3.1 ml/min [range, 2.7 to 3.6 ml/min]) at entry to the study. The remaining patients had urine outputs less than 150 ml/d and were considered to have negligible residual renal function.

Actual treatment times did not differ from those prescribed and were unchanged throughout the study. Actual blood flow rates were slightly greater than those prescribed in the hemodiafiltration group (286 ± 5 ml/min *versus* 281 ± 4 ml/min) and slightly less than those prescribed in the high-flux hemodialysis group (269 ± 5 ml/min *versus* 274 ± 6 ml/min). Actual blood flow rates did not change with time, but the difference between groups was significant ($P = 0.022$). Weight and body mass index did not differ between the groups, and neither changed over the course of the study. Net fluid removal averaged 2.7 ± 0.2 kg in the hemodiafiltration group and 2.9 ± 0.2 kg in the high-flux hemodialysis group and did not change over the course of the study or differ between the two groups.

Electrolytes, Urea, and Creatinine

Average pretreatment concentrations of electrolytes for the two groups are presented in Table 2. Pretreatment serum concentrations of sodium, potassium, inorganic phosphorus, and calcium did not differ between the groups. There were statistically significant changes in the pretreatment serum concentrations of sodium, potassium, and calcium over the duration of the study; however, the magnitudes of these changes were very small and of no clinical significance (data not shown). Pretreatment serum bicarbonate concentrations were significantly higher in the hemodiafiltration group than in the high-flux hemodialysis group ($P < 0.001$); however, the magnitude of this difference was independent of the duration of the study ($P = 0.275$).

Single-pool Kt/V_{urea} for the hemodiafiltration group was significantly higher than for the high-flux hemodialysis group (1.58 ± 0.09 *versus* 1.39 ± 0.09, $P = 0.020$). Results for eKt/V were similar (1.37 ± 0.08 *versus* 1.21 ± 0.07, $P = 0.023$). At entry to the study, pretreatment serum urea concentrations were significantly higher in the high-flux hemodialysis group than in the hemodiafiltration group ($P = 0.017$). The magnitude of this difference did not change during the study ($P = 0.372$).

Pre- to posttreatment reduction in serum creatinine concentration was significantly higher with hemodiafiltration than

Table 1. Patient demographics and treatment prescriptions[a]

	Hemodiafiltration ($n = 24$)	High-Flux Hemodialysis ($n = 21$)
Gender (M:F)	15:9	14:7
Age (yr)	61 ± 3	52 ± 3
Cause of ESRD	GN (6), HTN (4), DNS (3), IgA nephropathy (3), PCKD (2), amyloidosis (1), urolithiasis (1), pyelonephritis (1), unknown (3)	GN (9), PCKD (5), DNS (3), Balkan nephritis (1), reflux (1), unknown (2)
Duration of dialysis (mo)	47 ± 9	68 ± 16
Weight (kg)	66.7 ± 2.9	66.6 ± 2.8
Body mass index (kg/m^2)	22.9 ± 0.8	22.7 ± 0.7
Treatment time (min)	247 ± 3	251 ± 6
Blood flow rate (ml/min)	281 ± 4	274 ± 4
Ultrafiltration volume (L)[b]	21 ± 1	2.9 ± 0.2

[a] DNS, diabetes; GN, glomerulonephritis; HTN, hypertension; PCKD, polycystic kidney disease.
[b] Prescribed filtration volume after maximization based on transmembrane pressure (see text).

Table 2. Average predialysis serum electrolyte, urea, and creatinine concentrations over the 12-mo study period

	Hemodiafiltration ($n = 24$)	High-flux hemodialysis ($n = 21$)	P[a]
Sodium (mmol/L)	139 ± 1	139 ± 1	0.238
Potassium (mmol/L)	5.8 ± 0.1	5.8 ± 0.1	0.740
Calcium (mmol/L)	2.30 ± 0.02	2.28 ± 0.03	0.616
Inorganic phosphorus (mg/dl)	4.8 ± 0.2	4.9 ± 0.3	0.767
Bicarbonate (mmol/L)	21.3 ± 0.3	19.6 ± 0.3	<0.001
Urea (mg/dl)	143 ± 5	162 ± 5	<0.001
Creatinine (mg/dl)	9.7 ± 0.4	11.5 ± 0.4	0.005

[a] P values indicate the significance of the difference between hemodiafiltration and high-flux hemodialysis.

with high-flux hemodialysis (64 ± 1 *versus* 60 ± 1%, $P = 0.007$). Pretreatment serum creatinine concentrations, which were higher in the high-flux hemodialysis group than in the hemodiafiltration group at entry to the study ($P = 0.005$), decreased significantly during the study ($P < 0.001$); however, the decrease was similar in both groups ($P = 0.565$).

β_2-Microglobulin and Complement Factor D

Hemodiafiltration effected a greater removal of β_2-microglobulin than did high-flux hemodialysis as indicated by a significantly higher pre- to posttreatment change in plasma concentration (73 ± 1% *versus* 58 ± 1%, $P < 0.001$) and clearance (61 ± 1 *versus* 38 ± 1 ml/min, $P < 0.001$). Pretreatment serum β_2-microglobulin concentrations decreased during the study ($P < 0.001$) and were slightly but significantly lower in the hemodiafiltration group than in the high-flux hemodialysis group ($P = 0.045$; Figure 1). However, the decrease in pretreatment plasma β_2-microglobulin concentrations with time did not differ between the two therapies ($P = 0.317$), despite the apparent difference in removal of β_2-microglobulin.

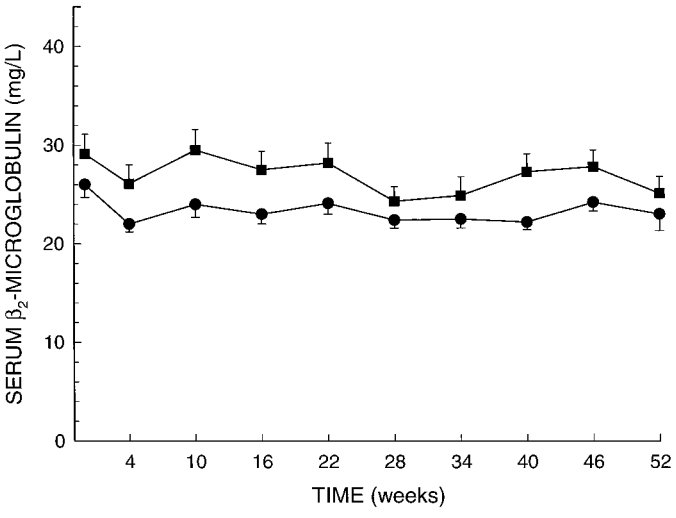

Figure 1. Pretreatment serum concentration of β_2-microglobulin in patients who were treated with hemodiafiltration (●) and high-flux hemodialysis (■). Pretreatment serum concentrations decreased significantly during the study ($P < 0.001$); however, this decrease did not depend on the choice of therapy ($P = 0.317$).

Pretreatment plasma complement factor D concentrations decreased significantly during the study ($P < 0.001$; Table 3). The magnitude of the change depended significantly on the mode of therapy ($P = 0.010$); hemodiafiltration was associated with a 21% decrease in concentration after 12 mo compared with a 13% decrease with high-flux hemodialysis. Hemodiafiltration was associated with a significantly greater pre- to posttreatment decrease in plasma concentration of complement factor D than was high-flux hemodialysis (33 ± 6% *versus* −2 ± 8%, $P < 0.001$). However, as indicated earlier, these latter data must be interpreted with caution because of uncertainties in determining the posttreatment concentration.

Anemia Control

Neither hematocrit (30 ± 1% for both groups) nor hemoglobin (10.3 ± 0.2 g/dl *versus* 10.4 ± 0.2 g/dl for hemodiafiltration and high-flux hemodialysis, respectively) differed between the two groups at entry to the study. Moreover, there was no change in hematocrit or hemoglobin over the course of the study ($P = 0.307$ for hematocrit and $P = 0.360$ for hemoglobin). Because dosing patterns of erythropoietin varied from patient to patient, changes in erythropoietin dose were assessed on the basis of the total weekly dose of erythropoietin received by each patient, regardless of the route or frequency of administration. Overall, the average weekly dose of erythropoietin

Table 3. Predialysis plasma complement factor D concentrations[a]

Time (wk)	Hemodiafiltration ($n = 24$)	High-Flux Hemodialysis ($n = 21$)
0	10.4 ± 0.5	9.5 ± 0.6
28	9.2 ± 0.5	8.6 ± 0.5
46	7.1 ± 0.4	9.1 ± 0.7
52	8.0 ± 0.6	8.2 ± 0.6

[a] Pretreatment concentrations decreased significantly during the study ($P < 0.001$). The decrease was significantly greater for the hemodiafiltration group than for the high-flux hemodialysis group ($P = 0.010$).

increased slightly but significantly over the course of the study (3250 ± 438 to 3577 ± 500 U/wk, $P = 0.031$). However, this increase was independent of the mode of therapy ($P = 0.123$).

Quality of Life

The patients in both groups had similar perceptions of their quality of life as assessed by the Kidney Disease Questionnaire (Table 4). The patients' assessment of their physical symptoms showed a significant improvement during the course of the study ($P < 0.001$); however, this increase did not depend on the mode of therapy ($P = 0.230$). None of the other dimensions of the Kidney Disease Questionnaire showed a change over the course of the study.

Discussion

The results of this study confirm the experience of other investigators that routine on-line hemodiafiltration can be performed safely in a large group of patients for an extended period (12–14). Our results also show that hemodiafiltration provides superior solute removal to high-flux hemodialysis over a wide range of solute sizes for blood flow rates in the range of 250 to 300 ml/min.

The improvement in solute removal with hemodiafiltration was relatively small for urea and creatinine; however, it may be helpful in treating large patients who tend to have a lower delivered Kt/V_{urea} than patients with a smaller body size (15,16). The difference in solute removal between the groups was more marked for β_2-microglobulin. However, this apparent difference in removal did not result in lower predialysis plasma concentrations with hemodiafiltration compared with high-flux hemodialysis after 1 yr of treatment. The pre- to posttreatment change in concentration of a solute is a good indicator of removal for solutes distributed in a single pool that includes plasma. A substantial rebound in plasma β_2-microglobulin concentrations, postdialysis, has been reported (17–20), suggesting that a single-pool model is not adequate to describe β_2-microglobulin kinetics, particularly in the face of efficient removal of β_2-microglobulin. In this case, the pre- to posttreatment change in concentration will overestimate actual β_2-microglobulin removal (21). That intrabody mass transfer rates limit β_2-microglobulin removal is supported by the results of other hemodiafiltration studies in which both longer follow-up periods and filtration volumes of up to 60 L have failed to lower pretreatment β_2-microglobulin concentrations below 18 to 20 mg/L (14,22,23). Additional studies of β_2-microglobulin kinetics during highly efficient therapies are needed to determine the point at which intrabody mass transfer begins to limit β_2-microglobulin removal. Increasing β_2-microglobulin removal beyond that point will not result in lower serum β_2-microglobulin concentrations unless treatment time or frequency is also increased (21). Support for the importance of increased frequency and treatment time over clearance comes from a recent report by Raj *et al.* (19), who switched patients from conventional thrice-weekly high-flux hemodialysis to nocturnal hemodialysis six nights per week with smaller surface area dialyzers and lower blood and dialysate flow rates. Over 9 mo, they observed a reduction in mean pretreatment serum β_2-microglobulin from 27.2 mg/L to 13.7 mg/L.

Failure to find a difference in pretreatment β_2-microglobulin concentration between high-flux hemodialysis and hemodiafiltration may also result from greater than anticipated removal of β_2-microglobulin by high-flux hemodialysis. In practice, high-flux hemodialysis represents a form of hemodiafiltration by virtue of the internal filtration and back-filtration that can occur in a dialyzer. Back-filtration flow rates are estimated to be up to 30 ml/min (24). Thus, back-filtration may generate 7 to 8 L of filtrate and substitution fluid flow within the dialyzer in a 4-h treatment, in addition to net fluid removal. That back-filtration in high-flux hemodialysis yields comparable β_2-microglobulin removal to hemodiafiltration at low filtration volumes is suggested by the observation of Lornoy *et al.* (25) that β_2-microglobulin removal with hemodiafiltration did not exceed that with high-flux hemodialysis until substitution fluid volumes exceeded approximately 10 L.

This study and others fail to show an advantage for hemodiafiltration over high-flux hemodialysis in terms of serum β_2-microglobulin concentrations. However, it should not be concluded from these data that hemodiafiltration is without benefit in terms of removing large-molecular-weight solutes. Complement factor D is a 24 kD protein involved in regulating the alternative pathway of complement. Serum complement factor D concentrations are increased in chronic renal failure (26), and at these elevated concentrations it enhances activity of the alternative pathway of complement (27) and inhibits

Table 4. Patient assessment of quality of life based on the Kidney Disease Questionnaire (11)[a]

	Hemodiafiltration		High-Flux Hemodialysis		*P* (Time)	*P* (Mode)
	6 Mo	12 Mo	6 Mo	12 Mo		
Physical symptoms	3.9 ± 0.3	4.8 ± 0.3	4.3 ± 0.3	4.8 ± 0.4	<0.001	0.657
Fatigue	4.6 ± 0.3	4.9 ± 0.4	4.7 ± 0.3	4.9 ± 0.3	0.083	0.910
Depression	5.6 ± 0.2	5.8 ± 0.2	5.6 ± 0.3	5.6 ± 0.3	0.086	0.684
Relationships	5.1 ± 0.3	5.2 ± 0.3	5.1 ± 0.3	5.1 ± 0.3	0.077	0.904
Frustration	5.3 ± 0.3	5.2 ± 0.4	5.3 ± 0.3	5.4 ± 0.4	0.648	0.851

[a] Each dimension of the Kidney Disease Questionnaire is scored on a seven-point scale, in which 1 is the worst possible score and 7 is the best possible score. *P* values represent the significance of changes with time (Time) or between hemodiafiltration and high-flux hemodialysis (Mode).

neutrophil degranulation (28). In renal failure, complement factor D accumulates in the intravascular compartment (29). As a result, the impact of intrabody mass transfer on solute removal will be minimal and should not limit the ability of hemodiafiltration to provide superior removal to high-flux hemodialysis. Indeed, we observed significantly greater pre- to posttreatment changes in serum complement factor D concentrations and decreased pretreatment serum concentrations in patients who were treated with hemodiafiltration relative to patients who were treated with high-flux hemodialysis. Unfortunately, heparin interferes with the assay used to measure complement factor D in this study, and the magnitude of the pre- to postdialysis concentration changes must be viewed with caution.

A recent report suggested that hemodiafiltration may improve anemia control with reduced erythropoietin doses (14). Such improvement has been ascribed to increased Kt/V_{urea} (30) or better removal of large-molecular-weight toxins. We could not confirm this observation; however, anemia control was not a primary outcome variable in our study and was not assessed rigorously.

Three patients withdrew from the study for reasons that may have been related to hemodiafiltration. These patients developed intratreatment hypertension that was not evident before their entry into the study. Two of the patients had a history of long-standing hypertension controlled by multiple-drug therapy, and the third had a history of borderline hypertension. Early in their experience with hemodiafiltration, Wizemann *et al.* (31) reported similar problems in a few patients. The reasons for the hypertension are not clear. Removal of sodium may be lower in hemofiltration and hemodiafiltration than in hemodialysis when the substitution fluid sodium concentration is the same as the dialysate sodium concentration (32,33). Thus, on-line hemodiafiltration may be associated with sodium retention, relative to high-flux hemodialysis. Sodium retention could cause vascular volume expansion during a treatment, particularly in fluid-overloaded patients. Alternatively, hemodiafiltration may efficiently remove antihypertensive drugs or endogenous vasodilators, leading to an increase in total peripheral resistance and intratreatment BP. Whatever the reason for hypertension in the three patients, there was no evidence of a generalized association between hemodiafiltration and hypertension.

Given the small number of patients and limited follow-up time of this study, it was not possible to address the question of whether the enhanced solute removal associated with hemodiafiltration improves clinical outcomes. There are indications, however, that enhancing the removal of larger solutes does improve outcomes. Leypoldt *et al.* (34) recently reported an analysis of the 1991 Case Mix Adequacy Study of the United States Renal Data System. After adjustments for case mix, comorbidities, and Kt/V_{urea}, they found that a 10% increase in vitamin B_{12} clearance was associated with a significantly reduced relative risk of mortality. Other investigators (35–37) have shown that therapies that increase the removal of β_2-microglobulin postpone the onset of β_2-microglobulin amyloid disease compared with conventional low-flux dialysis. Taken together, these data support the need for long-term studies, involving large numbers of patients, to address the hypothesis that increased removal of large-molecular-weight solutes improves patient outcomes. The results of the present study indicate that on-line hemodiafiltration may be the best means of providing increased removal of large-molecular-weight solutes for these studies.

Acknowledgments

The authors thank Christina Duhr and Jürgen Köbler for their help in sample collection and analysis and Walter Görgen and the nursing staff of the KfH Neuried dialysis center.

References

1. Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, Cohen AS, Schmid K: A new form of amyloid protein associated with chronic hemodialysis was identified as β_2-microglobulin. *Biochem Biophys Res Commun* 129: 701–706, 1985
2. Henderson LW, Colton CK, Ford CA: Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. *J Lab Clin Med* 85: 372–391, 1975
3. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schütterle G: Hemodiafiltration: A new alternative to hemofiltration and conventional hemodialysis. *Artif Organs* 2: 150–153, 1978
4. Ledebo I: On-line hemodiafiltration: Technique and therapy. *Adv Ren Replace Ther* 6: 195–208, 1999
5. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4: 1205–1213, 1993
6. Daugirdas JT, Schneditz D: Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. *ASAIO J* 41: M719–M724, 1995
7. Bergström J, Wehle B: No change in corrected β_2-microglobulin concentration after cuprophane haemodialysis. *Lancet* 1: 628–629, 1987
8. Leypoldt JK, Cheung AK, Deeter RB: Single compartment models for evaluating β_2-microglobulin clearance during hemodialysis. *ASAIO J* 43: 904–909, 1997
9. Oppermann M, Baumgarten H, Brandt E, Gottsleben W, Kurts C, Gotze O: Quantitation of components of the alternative pathway of complement (APC) by enzyme-linked immunosorbent assays. *J Immunol Methods* 133: 181–190, 1990
10. Keil LB, Jiminez E, Guma M, Reyes MD, Liguori C, DeBari VA: Biphasic response of complement to heparin: Fluid-phase generation of neoantigens in human serum and in a reconstituted alternative pathway amplification cycle. *Am J Hematol* 50: 254–262, 1995
11. Laupacis A, Muirhead N, Keown P, Wong C: A disease-specific questionnaire for assessing quality of life in patients on hemodialysis. *Nephron* 60: 302–306, 1992
12. Canaud B, Bosc JY, Leray H, Stec F, Argiles A, Leblanc M, Mion C: On-line haemodiafiltration: State of the art. *Nephrol Dial Transplant* 13(Suppl 5): 3–11, 1998
13. Pizzarelli F, Cerrai T, Dattolo P, Tetta C, Maggiore Q: Convective treatments with on-line production of replacement fluid: A clinical experience lasting 6 years. *Nephrol Dial Transplant* 13: 363–369, 1998
14. Maduell F, del Pozo C, Garcia H, Sanchez L, Hdez-Jaras J, Albero MD, Calvo C, Torregrosa I, Navarro V: Change from

conventional haemodiafiltration to on-line haemodiafiltration. *Nephrol Dial Transplant* 14: 1202–1207, 1999
15. Sherman RA, Cody RP, Solanchick JC: Body weight and adequacy of hemodialysis: Results of an ESRD network study. *ASAIO J* 39: 933–935, 1993
16. Ward RA, Buscaroli A, Schmidt B, Stefoni S, Gurland HJ, Klinkmann H: A comparison of dialysers with low-flux membranes: Significant differences in spite of many similarities. *Nephrol Dial Transplant* 12: 965–972, 1997
17. Maeda K, Shinzato T, Ota T, Kobayakawa H, Takai I, Fujita Y, Morita H: Beta-2-microglobulin generation rate and clearance rate in maintenance hemodialysis patients. *Nephron* 56: 118–125, 1990
18. Yasuhiro I, Eiichi N, Mineo O, Muneto Y, Toshihiro I, Masahiro F, Yoshifumi N, Masahito M, Ryuichi M: Removal of serum beta-2 microglobulin using high-performance membranes and analysis of changes in serum BMG levels after dialysis. *Am J Nephrol* 18: 228–232, 1998
19. Raj DSC, Ouwendyk M, Francoeur R, Pierratos A: β_2-microglobulin kinetics in nocturnal haemodialysis. *Nephrol Dial Transplant* 15: 58–64, 2000
20. Leypoldt JK, Cheung AK, Deeter RB: Rebound kinetics of β_2-microglobulin after hemodialysis. *Kidney Int* 56: 1571–1577, 1999
21. Clark WR, Leypoldt JK, Henderson LW, Mueller BA, Scott MK, Vonesh EF: Quantifying the effect of changes in the hemodialysis prescription on effective solute removal with a mathematical model. *J Am Soc Nephrol* 10: 601–609, 1999
22. Kerr PB, Argilés A, Flavier JL, Canaud B, Mion CM: Comparison of hemodialysis and hemodiafiltration: A long-term longitudinal study. *Kidney Int* 41: 1035–1040, 1992
23. Wizemann V, Lotz C, Techert F, Uthoff S: On-line haemodiafiltration versus low-flux haemodialysis: A prospective randomized study. *Nephrol Dial Transplant* 15[Suppl 1]: 43–48, 2000
24. Ronco C, Brendolan A, Feriani M, Milan M, Conz P, Lupi A, Berto P, Bettini MC, La Greca G: A new scintigraphic method to characterize ultrafiltration in hollow fiber dialyzers. *Kidney Int* 41: 1383–1393, 1992
25. Lornoy W, Becaus I, Billiouw JM, Sierens L, van Malderen P: Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. *Am J Nephrol* 18: 105–108, 1998
26. Volanakis JE, Barnum SR, Giddens M, Galla JH: Renal filtration and catabolism of complement protein D. *N Engl J Med* 312: 395–399, 1985
27. Pascual M, Paccaud JP, Macon K, Volonakis JE, Schifferli JA: Complement activation by the alternative pathway is modified in renal failure: The role of factor D. *Clin Nephrol* 32: 185–193, 1989
28. Balke N, Holtcamp U, Hörl WH, Tschesche H: Inhibition of degranulation of human polymorphonuclear leukocytes by complement factor D: *FEBS Lett* 371:300–302, 1995
29. Pascual M, Steiger G, Estreicher J, Macon K, Volanakis JE, Schifferli JA: Metabolism of complement factor D in renal failure. *Kidney Int* 34: 529–536, 1988
30. Ifudu O, Feldman J, Friedman EA: The intensity of hemodialysis and the response to erythropoietin in patients with end-stage renal disease. *N Engl J Med* 334: 420–425, 1996
31. Wizemann V, Birk HW, Techert F: Effects of a modified hemodiafiltration method on low-molecular-weight protein composition in plasma. *Blood Purif* 8: 45–51, 1990
32. Gotch FA, Evans MC, Keen ML: Measurement of the effective dialyzer Na diffusion gradient in vitro and in vivo. *Trans Am Soc Artif Intern Organs* 31: 354–357, 1985
33. Pedrini LA, Ponti R, Faranna P, Cozzi G, Locatelli F: Sodium modeling in hemodiafiltration. *Kidney Int* 40: 525–532, 1991
34. Leypoldt JK, Cheung AK, Carroll CE, Stannard DC, Pereira BJG, Agodoa LY, Port FK: Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patient survival. *Am J Kidney Dis* 33: 349–355, 1999
35. Küchle C, Fricke H, Held E, Schiffl H: High-flux hemodialysis postpones clinical manifestation of dialysis-related amyloidosis. *Am J Nephrol* 16: 484–488, 1996
36. Koda Y, Nishi S, Miyazaki S, Haginoshita S, Sakurabayashi T, Suzuki M, Sakai S, Yuasa Y, Hirasawa Y, Nishi T: Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int* 52: 1096–1101, 1997
37. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D: Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. *Kidney Int* 55: 286–293, 1999