Mode of Dialysis Therapy and Mortality in End-Stage Renal Disease

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Abstract. Despite considerable differences in technique and blood purification characteristics, hemodialysis and peritoneal dialysis have been thought to have similar patient outcomes. An inception cohort of 433 end-stage renal disease patients was followed prospectively for a mean of 41 mo. The outcomes of hemodialysis (HD) and peritoneal dialysis (PD) patients were compared using intention to treat analysis based on the mode of therapy at 3 mo. After adjustment for PD patients less likely to have chronic hypertension and more likely to have diabetes, ischemic heart disease, and cardiac failure at baseline ($P < 0.05$), a biphasic mortality pattern was observed. For the first 2 yr, there was no statistically significant difference in mortality. After 2 yr, mortality was greater among PD patients with an adjusted PD/HD hazard ratio of 1.57 (95% confidence interval [CI], 0.97 to 2.53). Both the occurrence (adjusted hazards ratio 6.87 [95% CI, 2.01 to 23.5]) and the direction (toward PD, adjusted hazards ratio 6.25 [95% CI, 1.54 to 25]) of a therapy switch were subsequently associated with mortality after 2 yr. Progressive clinical and echocardiographic cardiac disease were not responsible for this late mortality. Lower mean serum albumin levels in PD patients in the first 2 yr of therapy (3.5 ± 0.5 *versus* 3.9 ± 0.5 g/dl, $P < 0.0001$) accounted for a large proportion of the increase in subsequent mortality. Hemodialysis has a late survival advantage over peritoneal dialysis; antecedent hypoalbuminemia is a major marker of the increased late mortality in PD patients. (J Am Soc Nephrol 9: 267–276, 1998)

The advent of peritoneal dialysis was a major addition to the therapeutic armamentarium available to treat end-stage renal disease (ESRD) (1–3). Peritoneal dialysis and hemodialysis are very different in terms of dialysis technique. Peritoneal dialysis is associated with a lower overall clearance of traditional markers of solute removal, such as urea and creatinine; however, clearance with standard peritoneal dialysis is continuous, as opposed to markedly intermittent for hemodialysis (4). Peritoneal dialysis is associated with a slower loss of endogenous renal function than hemodialysis (5). As in hemodialysis patients, uremic solute clearance has recently been shown to have a considerable impact on patient outcome in a large prospective study of peritoneal dialysis patients (6), as is the case in hemodialysis patients (7–12). It has been suggested that peak levels of uremic solutes, rather than the time-averaged levels, determine toxicity. Using urea as a marker for other toxins, it has been suggested that the failure to show mortality differences between hemodialysis and peritoneal dialysis reflects the fact that the prehemodialysis urea levels are similar to the relatively constant urea levels of peritoneal dialysis (13).

There are major technical and metabolic differences between hemodialysis and peritoneal dialysis. Both earlier and more recent studies have shown inconsistent results for comparative mortality (14–27). For example, a multicenter study from Italy showed a lower mortality among older patients treated with peritoneal dialysis (22). On the other hand, recent large epidemiologic studies from the United States have shown an excess mortality among older diabetic patients treated with peritoneal dialysis (23), and among peritoneal dialysis patients in general (24,25) compared with their hemodialysis counterparts. Similarly, registry data from Australia and New Zealand (26) suggest that peritoneal dialysis patients have higher mortality. In contrast, a recent report from the Canadian Organ Replacement Registry suggests that peritoneal dialysis confers a survival advantage (27). All of these studies are observational, and therefore inconsistent results may be due to unavoidable and varying selection biases that are seen in nonrandomized studies.

The logistic and ethical barriers to performing a randomized trial to determine whether the treatments differ in patient outcome are many. Consequently, longitudinal epidemiologic studies are necessary. There are several methodological issues to consider if epidemiologic studies are to be used to help us answer this question: (*1*) potential imbalances in baseline age and comorbidity in groups treated by hemodialysis or perito-

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neal dialysis; (2) inadequate follow-up time that may preclude the possibility of observing different survival characteristics over time; (3) crossover effects between treatments that may mask the potential impact of treatment modality on mortality. In this regard, it is well known that a switch of modality from peritoneal dialysis to hemodialysis is a common occurrence. For example, in the CANUSA study, 17% of peritoneal dialysis patients eventually transferred to hemodialysis (6).

We have demonstrated previously that clinical and echocardiographic cardiac disorders, present on initiation of dialysis, have an adverse influence on the survival of patients with chronic uremia (28,29). We have described the natural history of cardiac failure and ischemic heart disease during dialysis therapy (30,31), and we have assessed the impact of anemia, hypoalbuminemia, and hypertension on cardiac morbidity and mortality (32–34). In this article, we report on the impact of mode of dialysis therapy on the progression of echocardiographic disorders, cardiac morbidity, and overall mortality in an inception cohort of ESRD patients, followed prospectively for long periods of time.

Materials and Methods

Patients

This prospective cohort study was started in the following locations: the Royal Victoria Hospital, Montreal, Quebec, in 1982; the Health Sciences Centre, St. John's, Newfoundland, in 1984; and the Grace Hospital, St. John's, Newfoundland, in 1985. Patients were eligible for entry into the study if (1) they survived for 6 mo after starting renal replacement therapy and (2) they had a technically satisfactory echocardiogram within 1 yr of starting renal replacement therapy. Patient recruitment was completed in June 1991. The mean patient follow-up was 41 mo.

Of 518 patients who survived at least 6 mo from the start of ESRD therapy, a cohort of 433 (83.6% of those eligible) entered the study. A total of 85 patients was excluded for the following reasons: failure to obtain a technically adequate echocardiogram within 1 yr of starting therapy (71 patients), started therapy elsewhere (seven patients), charts mislaid (five patients), and refusal to participate (two patients).

Data Collection

At baseline and at yearly intervals thereafter, a clinical assessment was undertaken to detect the presence of cardiovascular disease. At monthly intervals, the data collected included BP, hemoglobin and serum albumin levels, and interdialytic weight gain in hemodialysis patients. BP and blood tests were carried out immediately before dialysis in hemodialysis patients. BP was measured sitting in the contralateral arm in patients with patent arteriovenous fistulae or grafts. The BP and blood work recorded were single values taken at the start of each month of dialysis therapy. At yearly intervals, all changes related to renal replacement therapy, admissions to hospital, and autopsy notes were recorded.

Peritoneal dialysis consisted of 8 L of dialysate for the vast majority of patients in the study. We did not routinely record hemodialysis time, membrane type, dialysate, and blood flow rates or urea reduction ratios at all centers. Hemodialysis times were recorded systematically from 1986 onward in one center. In the first week of January of each year, the total hemodialysis times in hours at this center were as follows (mean/SD/median): 1986: 12.2/2.3/12.0; 1987: 12.1/2.1/12.0; 1988: 10.2/2.0/10.5; 1989: 10.0/2.0/10.5; 1990: 9.9/1.8/9.5; and 1991: 9.1/1.8/9.0. Dialysis prescription was similar in the other two centers.

Baseline and annual echocardiography were performed using M-mode and two-dimensional ultrasonography. Left ventricular mass index was calculated according to the Penn convention (35). Left ventricular cavity volume was calculated by the formula of Pombo *et al.* (36). The initial echocardiogram was performed (mean ± SD) 3 ± 4 mo (median, 0 mo) after the start of ESRD therapy. A total of 298 patients were alive and still on dialysis 1 yr after starting dialysis therapy. Of these, 275 (92%) had a repeat echocardiogram at a median interval of 13 mo after the initial study. This patient subset was almost identical to the parent group of 433 patients, with no statistically or clinically significant differences in terms of baseline clinical and echocardiographic parameters (32).

Treatment Analysis

Mode of dialysis therapy was defined as the treatment modality in use at the end of 3 mo. We chose this time period, as opposed to the day of first dialysis, because many peritoneal dialysis patients are temporarily treated with hemodialysis, although the intention is that they will use peritoneal dialysis as maintenance therapy. The following clinical outcomes were studied (see Appendix for definition of terms): time to death, new-onset ischemic heart disease, and new-onset cardiac failure. We looked at deaths before and after 2 yr. This cutoff point was chosen arbitrarily in advance as the time point that split the number of deaths in two. Patients were censored on transplantation or reaching final follow-up for mortality analyses. We examined mortality after 2 yr in a multivariate model that included mode of therapy at 3 mo, whether a switch of therapy had taken place between 3 mo and 2 yr and an interaction variable between mode of therapy at 3 mo and switch of therapy. We also performed analyses in which patients were called "peritoneal dialysis" if they switched from hemodialysis to peritoneal dialysis, provided the switch occurred more than a given time (the period of grace) before final follow-up on dialysis; similarly, patients were called "hemodialysis" if they switched from peritoneal dialysis to hemodialysis more than the period of grace before outcome assessment. The periods of grace chosen were 0, 1, 2, 3, 6, 12, and 18 mo. The conclusions made in this study regarding mode of therapy and mortality were unaltered when reaching final follow-up was the sole censoring event, and transplantation was no longer used as a censoring event. Transplantation, reaching final follow-up, and death were censoring events for the other clinical events. The echocardiographic outcomes studied were the changes in left ventricular mass index, cavity volume index, and fractional shortening between the baseline and first follow-up echocardiogram.

We examined the potential impact of three commonly measured variables on late mortality differences between hemodialysis and peritoneal dialysis. Mean arterial blood pressure, serum albumin, and hemoglobin were measured monthly as part of the protocol. The values obtained were averaged over the first 2 yr of dialysis therapy; these values were then tested for their association with mortality after 2 yr. In particular, we wished to test whether differences in these serial variables might account for differences in treatment efficacy. The rationale used was as follows: if one mode of dialysis therapy is associated with excess late mortality and different levels of a potential risk factor, and if the difference in efficacy changes when adjustment is made for this serial variable, then the direction of change can suggest whether differences in the potential risk factor are protective or harmful.

Statistical Analyses

Normally distributed continuous variables were compared using ANOVA. Categorical variables were compared using χ^2 analysis. All statistical tests are two-tailed, with a P value less than 0.05 taken to indicate statistical significance. The proportional hazard model was used to adjust the peritoneal dialysis-to-hemodialysis hazards ratios of clinical outcomes for baseline age, gender, and comorbidity. Echocardiographic outcomes were similarly adjusted, using ANOVA with covariate adjustment.

Results

Patient and Treatment Characteristics

The cohort was almost entirely Caucasian. During this time period, the vast majority of peritoneal dialysis patients were treated with 8 L of dialysate per day. Compared with hemodialysis patients, peritoneal dialysis patients were more likely ($P < 0.05$) to have diabetes, have a history of ischemic heart disease and cardiac failure, and have lower ejection fractions on baseline echocardiography, but were less likely to have a history of hypertension for more than 10 yr (Table 1).

Outcomes

Figure 1 shows that patients on peritoneal dialysis at 3 mo were much more likely to experience a treatment failure than hemodialysis patients ($P < 0.0001$). The proportion of patients transplanted was similar for both treatment modalities (32% PD *versus* 38% HD). Using survival analysis, there was no statistically significant difference in the time wait to transplantation.

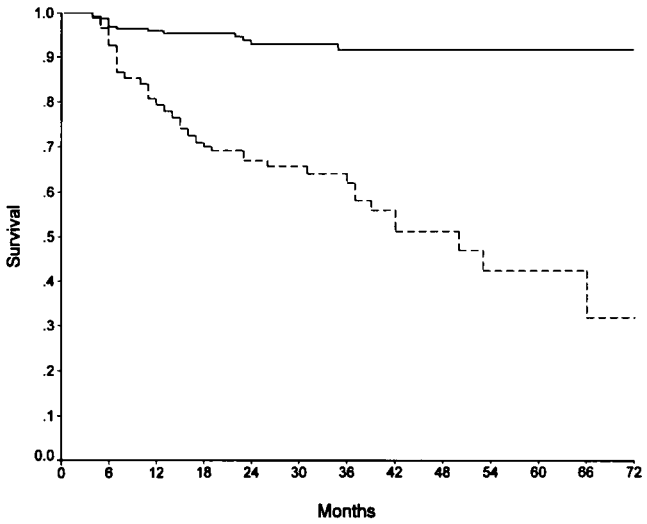

Figure 1. Time to treatment failure in patients on hemodialysis (solid line) and peritoneal dialysis (dashed line) at 3 mo. $P < 0.0001$ by the log rank test.

The overall median survival was 48 mo when patients were censored at the time of transplantation (Tables 2 and 3). The deaths observed in this study were attributed to myocardial infarction in 10.1%, other cardiac causes in 11.4%, sudden death in 25.5%, vascular disease in 10.7%, infection in 14.8%, treatment withdrawal in 12.1%, and other causes in 15.4%. The causes of death were similar in hemodialysis and peritoneal

Table 1. Baseline characteristics of hemodialysis and peritoneal dialysis patients[a]

Characteristic	Therapy at 3 mo	
	Hemodialysis (n = 248)	Peritoneal Dialysis (n = 185)
Age	51 ± 17	51 ± 17
Male gender (%)	66.9	61.1
Years of ESRD (%)		
1982 to 1984	22.6	17.3
1985 to 1986	19.4	14.6
1987 to 1988	23.8	32.4
1989 to 1991	34.3	35.7
Hypertension >10 yr (%)	30.2	20.5[b]
Diabetic (%)	21.4	34.1[b]
Ischemic heart disease (%)	18.1	27.0[b]
Cardiac failure (%)	26.7	36.2[b]
Echocardiogram–LV		
mass index (g/m^2)	160 ± 51	158 ± 45
cavity volume (ml/m^2)	84 ± 36	86 ± 40
fractional shortening (%)	35 ± 8	33 ± 8[b]

[a] Continuous variables are expressed as mean ± SD. ESRD, end-stage renal disease; LV, left ventricular.

[b] $P < 0.05$ comparing patients treated by hemodialysis or peritoneal dialysis.

Table 2. Principal outcomes observed while on dialysis therapy

Outcome	Therapy at 3 mo	
	Hemodialysis (n = 248)	Peritoneal Dialysis (n = 185)
Death on either therapy, all time frames	79/248 (31.9%)	71/185 (38.4%) $P = 0.16$
Death within 2 yr	41/248 (16.5%)	33/185 (17.8%) $P = 0.95$
Death after 2 yr	38/107 (35.5%)	38/75 (50.7%) $P = 0.04$
Treatment failure	14/248 (5.6%)	60/185 (32.4%) $P < 0.00001$
De novo ischemic heart disease	21/203 (10.3%)	19/116 (14.1%) $P = 0.30$
De novo cardiac failure	48/181 (26.5%)	23/118 (19.5%) $P = 0.16$
Change in LV[a]		
mass index (g/m^2)	32 ± 57	23 ± 58 $P = 0.24$
cavity volume (ml/m^2)	5 ± 33	−3 ± 34 $P = 0.06$
fractional shortening (%)	−1.3 ± 8.6	−1.3 ± 8.2 $P = 0.48$

[a] Second echocardiogram minus first echocardiogram. LV, left ventricular.

Table 3. Unadjusted and adjusted[a] outcomes of peritoneal dialysis (PD) patients compared with hemodialysis (HD) patients

Outcome	PD/HD Hazards Ratio[b] Unadjusted	PD/HD Hazards Ratio[b] Adjusted
Death, all time frames	1.30 (0.94 to 1.79) $P = 0.11$	1.14 (0.81 to 1.59) $P = 0.46$
Death within 2 yr	0.80 (0.49 to 1.31) $P = 0.36$	0.76 (0.45 to 1.27) $P = 0.28$
Death after 2 yr	1.70 (1.09 to 2.66) $P = 0.02$	1.57 (0.97 to 2.53) $P = 0.06$
Dialysis treatment failure	6.84 (3.76 to 12.4) $P < 0.001$	6.87 (3.74 to 12.6) $P < 0.001$
De novo ischemic heart disease	1.54 (0.43 to 0.32) $P = 0.17$	1.37 (0.72 to 2.63) $P = 0.33$
De novo cardiac failure	0.75 (0.45 to 1.24) $P = 0.25$	0.71 (0.41 to 1.20) $P = 0.18$

[a] Adjusted using the proportional hazards model for age, gender, hypertension >10 yr, diabetes mellitus, ischemic heart disease, and cardiac failure at baseline.

[b] A hazard ratio less than 1 indicates a survival advantage for peritoneal dialysis, greater than 1 a survival advantage for hemodialysis.

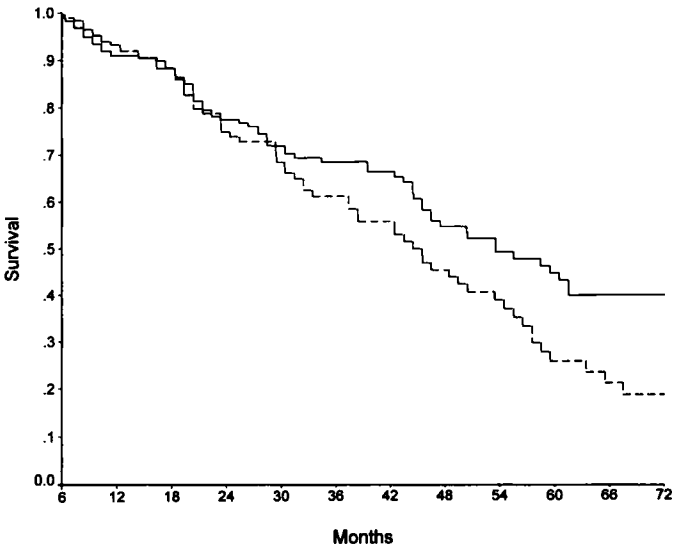

Figure 2. Survival, estimated by the product limit method of hemodialysis (solid line) and peritoneal dialysis (dashed line) patients. Patients were censored at transplantation. $P = 0.11$ by the log rank test.

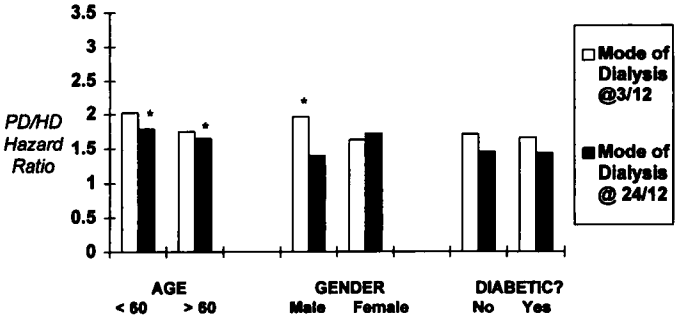

Figure 3. Risk of death using proportional hazards analysis after 2 yr on dialysis therapy according to age, gender, and diabetic status. A hazard ratio greater than 1 suggests a survival benefit for hemodialysis. *$P < 0.05$.

dialysis patients. A total of 86 patients were admitted because of ischemic heart disease, of which 47% were *de novo* episodes. A total of 143 of 432 (33%) patients developed cardiac failure during the study, half of which were *de novo* episodes; 259 subjects had evaluable serial echocardiograms. On follow-up echocardiography, the mean left ventricular mass index was 171 ± 58 g/m^2, cavity volume 91 ± 43 ml/m^2, and fractional shortening 31 ± 9 percent.

Within the first 2 yr of dialysis therapy, the proportion of deaths was similar in hemodialysis and peritoneal dialysis patients. After 2 yr, there were more deaths among peritoneal dialysis patients (50.7% *versus* 35.5%, $P = 0.04$). Figure 2 shows survival according to the mode of dialysis therapy at 3 mo. There was a clear divergence in survival after approximately 2 yr. Figure 3 shows the risk of mortality after 2 yr in the major subgroups. The increased late mortality risk of peritoneal dialysis patients tended to be equally shared among all patient subgroups. Analyses of mortality after 2 yr, based on mode of therapy at 2 yr, showed similar results. The mortality comparisons were almost identical when transplanted patients were left uncensored.

There were no statistically significant differences between hemodialysis patients and peritoneal dialysis patients in the proportion that went on to develop new ischemic heart disease or cardiac failure while on dialysis therapy. Similarly, the progression of echocardiographic parameters was similar in both patient groups. A non-statistically significant trend toward more rapid progression of left ventricular dilation was seen in hemodialysis patients ($P = 0.06$).

Table 3 shows the unadjusted peritoneal dialysis-to-hemodialysis hazards ratios for the major clinical outcomes. Mortality hazards ratios after 2 yr were higher for peritoneal dialysis (PD/HD hazards ratio 1.70, $P = 0.02$). Treatment failure was much more likely for peritoneal dialysis (PD/HD hazards ratio 6.84, $P < 0.001$). There were no statistically significant differences between hemodialysis and peritoneal dialysis patients in the rates of *de novo* ischemic heart disease and cardiac failure.

Multivariate Analyses

The disparities in patient outcome seen on bivariate analysis were not fully accounted for by differences in baseline age, gender, or comorbidity. When adjustment was made for baseline age, gender, and the presence of chronic hypertension, diabetes mellitus, ischemic heart disease, and cardiac failure (Table 3), the conclusions drawn from bivariate analysis were unchanged, except that the late mortality effect did not quite reach conventional thresholds of statistical significance (adjusted PD/HD hazard ratio 1.57; 95% confidence interval [CI],

0.97 to 2.53; $P = 0.06$). Adding year of study entry as a covariate had no effect on the late survival advantage seen in hemodialysis patients in either model. There were no statistically significant differences between hemodialysis and peritoneal dialysis patients in the adjusted hazards ratios of *de novo* ischemic heart disease and cardiac failure. There were no statistically significant covariate-adjusted differences between hemodialysis and peritoneal dialysis patients in the changes in left ventricular mass index, cavity volume, and fractional shortening between the baseline and the first annual follow-up echocardiogram (data not shown).

In Table 4, the outcome variable was mortality after 2 yr among patients still on dialysis therapy at 2 yr. Mode of dialysis in use at 3 mo, a switch in therapy occurring between 3 mo and 2 yr, and an interaction variable between the 3-mo therapy and a switch in therapy were incorporated in a single proportional hazards model. After adjustment for age, sex, chronic hypertension, diabetes mellitus, ischemic heart disease, and cardiac failure at baseline, this model suggested, in terms of later mortality, the following independent effects: (*1*) patients on hemodialysis at 3 mo tended ($P = 0.079$) to have a better prognosis than those on peritoneal dialysis, which did not reach statistical significance; (*2*) as a group, patients who switched therapies were subsequently 6.87 times more likely to die than patients who did not switch therapies; and (*3*) patients who switched from peritoneal dialysis to hemodialysis had a 6.25 (=1/0.16) times lower subsequent mortality than patients who either switched from hemodialysis to peritoneal dialysis or had no switch in therapy. In an analysis of mortality after 2 yr (using hemodialysis patients without a therapy switch between 3 and 24 mo as reference category; group I), the adjusted hazards ratios were 1.81 (95% CI, 0.82 to 4.02; $P = 0.14$) for patients on peritoneal dialysis at 3 mo who switched to HD between 3 and 24 mo (group II), 6.87 (95% CI, 2.00 to 23.5; $P = 0.002$) for patients on HD at 3 mo who switched to PD between 3 and 24 mo (group III), and 1.56 (95% CI, 0.97 to 2.50; $P = 0.07$) for patients on PD at 3 mo, without a therapy switch between 3 and 24 mo (group IV). Combining groups I and II (hemodialysis at 2 yr) and groups III and IV (peritoneal dialysis at 2 yr) produced an adjusted hazards ratio of 1.56 (95% CI, 0.97 to 2.50; $P = 0.07$).

Table 5 shows mortality according to the final mode of dialysis therapy. In these models, patients who switched therapies were assigned to the new therapy, provided the interval between the switch and final follow-up exceeded arbitrarily chosen "periods of grace." After adjustment for differences in baseline comorbidity, patients using peritoneal dialysis as the final mode of dialysis therapy had a higher mortality after 2 yr. The associations were very similar when final mode of dialysis was tested as a time-dependent covariate (data not shown).

The hypothesis was tested that differences in potential risk factors such as hemoglobin, serum albumin, and mean arterial BP might account for the superior late survival of hemodialysis patients (Figure 4). In patients treated exclusively with one or another dialysis modality, peritoneal dialysis patients had lower mean serum albumin levels (3.4 ± 0.5 g/dl *versus* 3.9 ± 0.4 g/dl, $P < 0.0001$), higher hemoglobin levels (9.7 ± 1.7 g/dl *versus* 8.3 ± 1.3 g/dl, $P < 0.0001$), and similar mean arterial BP levels (102 ± 10 mmHg *versus* 99 ± 13 mmHg, $P = 0.12$) averaged over the first 2 yr of dialysis therapy. At baseline, peritoneal dialysis patients had similar serum albumin levels (3.4 ± 0.6 g/dl *versus* 3.5 ± 0.6 g/dl, $P = 0.2$), higher hemoglobin levels (9.0 ± 1.7 g/dl *versus* 8.1 ± 1.7 g/dl, $P < 0.01$), and similar mean arterial BP levels (107 ± 107 mmHg *versus* 104 ± 15 mmHg, $P = 0.3$) compared with the levels seen in hemodialysis patients. The baseline factors independently associated with mortality after 2 yr were age, diabetes mellitus, and cardiac failure. When adjustment was made for these factors using the proportional hazards model, peritoneal dialysis was associated with a 2.03-fold increase in late mortality (column I). Adding mean hemoglobin levels (column II) and mean arterial BP levels (column III) measured in the first

Table 4. Mortality after 2 yr[a] of patients still on dialysis therapy at 2 yr according to mode of therapy received after third month of dialysis and switches of therapy before 2 yr

Variable	Comparison Group	Mortality after 2 yr Hazards Ratio (95% CI)
Peritoneal dialysis[b] at 3 mo ($n = 75$)	Hemodialysis[b] ($n = 107$)	1.61 (0.95 to 2.72) $P = 0.079$
Therapy switch[c] between 3 and 24 mo ($n = 27$)	No therapy switch[c] between 3 and 24 mo ($n = 155$)	6.87 (2.01 to 23.50) $P = 0.002$
(Mode of therapy at 3 mo)[b] × (Switch)[c] interaction variable		
On peritoneal dialysis at 3 mo, switch to hemodialysis between 3 and 24 mo ($n = 22$)	On hemodialysis at 3 mo with switch to peritoneal dialysis between 3 and 24 mo or no therapy switch ($n = 160$)	0.16 (0.04 to 0.65) $P = 0.01$

[a] The variables entered in the proportional hazards model were age, gender, hypertension >10 yr, diabetes mellitus, ischemic heart disease, cardiac failure at baseline, mode of dialysis therapy at 3 mo, switch of therapy between 3 and 24 mo, and an interaction variable between mode of therapy at 3 mo and switch of therapy between 3 and 24 mo.

[b] Mode of dialysis therapy was entered in the proportional hazards model as 0 for "hemodialysis" and 1 for "peritoneal dialysis."

[c] Switch of dialysis therapy was entered as 0 for "No" and 1 for "Yes."

Table 5. Survival according to final[a] mode of dialysis therapy

Period of Grace[b] (mo)	Adjusted[c] PD[a]/HD[a] Hazards Ratio All Time Frames (95% CI)	Adjusted[c] PD[a]/HD[a] Hazards Ratio ≤2 yr (95% CI)	Adjusted[c] PD[a]/HD[a] Hazards Ratio >2 yr (95% CI)
0	1.30 (0.91 to 1.85) $P = 0.15$	0.70 (0.40 to 1.20) $P = 0.19$	1.95 (1.19 to 3.20) $P = 0.008$
1	1.37 (0.97 to 1.94) $P = 0.08$	0.79 (0.46 to 1.34) $P = 0.37$	2.00 (1.23 to 3.27) $P = 0.006$
3	1.45 (1.02 to 2.05) $P = 0.04$	0.82 (0.50 to 1.37) $P = 0.45$	1.99 (1.22 to 3.26) $P = 0.006$
6	1.64 (1.16 to 2.30) $P = 0.005$	1.00 (0.61 to 1.65) $P = 0.99$	1.99 (1.22 to 3.26) $P = 0.002$
12	1.49 (1.06 to 2.08) $P = 0.02$	0.94 (0.57 to 1.53) $P = 0.79$	1.78 (1.09 to 2.89) $P = 0.02$
18	1.45 (1.03 to 2.03) $P = 0.03$	0.85 (0.52 to 1.39) $P = 0.52$	1.91 (1.18 to 3.09) $P = 0.009$

[a] If no switch of therapy occurred after 3 mo, the final mode of therapy was the one in use at 3 mo. If a switch of therapy occurred in a patient on PD at 3 mo and the interval between the switch and final follow-up exceeds the period of grace, the final mode of dialysis therapy was considered to be HD. If a switch of therapy occurred in a patient on HD at 3 mo and the interval between the switch and final follow-up exceeds the period of grace, the final mode of dialysis therapy was considered to be PD.

[b] Time interval between switch of therapy and final follow-up while on dialysis therapy.

[c] The variables entered in the proportional hazards model were age, gender, hypertension >10 yr, diabetes mellitus, ischemic heart disease, cardiac failure at baseline, and final mode of dialysis therapy.

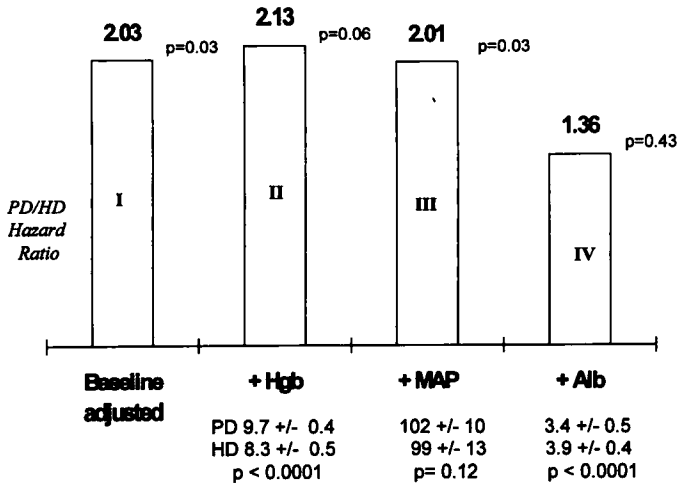

Figure 4. Patients treated exclusively by hemodialysis or peritoneal dialysis. Column I shows the risk of death after 2 yr using proportional hazards analysis, comparing peritoneal dialysis to hemodialysis, adjusted for age, diabetes mellitus, and cardiac failure at baseline. Columns II, III, and IV show how the addition of mean hemoglobin, mean arterial BP, and serum albumin (measured during the first 2 yr and shown below each column for hemodialysis and peritoneal dialysis patients) influences mortality after 2 yr. A hazard ratio greater than 1 suggests a survival benefit for hemodialysis.

2 yr of therapy as covariates had little impact on the stability of this estimate. In contrast, when serum albumin levels were added to the model (column IV), the adjusted peritoneal dialysis/hemodialysis hazard ratio fell from 2.03 to 1.36. This analysis suggests that, in terms of late mortality, peritoneal dialysis would have efficacy approaching that of hemodialysis were it not for factors leading to differences in serum albumin levels. Stated differently, this analysis suggests that 65% (100 times [(2.03 − 1.36) ÷ (2.03 − 1.00)]) of the excess late mortality associated with peritoneal dialysis could be explained by the factors leading to disparity in mean serum albumin levels.

Discussion

It has recently been suggested that peritoneal dialysis patients may have an increased mortality compared with hemodialysis patients (23–26).This hypothesis was tested in a large cohort of dialysis patients followed from a uniform time point in the natural history of renal replacement therapy; this study involved very lengthy patient follow-up, collected routine clinical data prospectively, and examined echocardiographic outcomes, cardiac morbid events, and mortality. The principal conclusion drawn from this study was that peritoneal dialysis patients had an increased mortality compared to hemodialysis patients, which became apparent after approximately 2 yr of dialysis therapy. This adverse outcome was associated with antecedent hypoalbuminemia.

Ideally, a randomized clinical trial would be needed to determine whether hemodialysis and peritoneal dialysis are equivalent in terms of patient mortality. Even if the logistic, social, and ethical issues inherent in such a study could be overcome, several methodological issues would remain. Large patient numbers and considerable patient follow-up would be required, the latter to exclude a multiphasic mortality response. Given that technique failure is common in peritoneal dialysis, the problem of how to deal with imbalanced crossover between treatments would arise.

Treatment modality effects were considerable in this longitudinal study, with mortality differences emerging after approximately 2 yr of therapy. Differences in measurable baseline comorbidity or transplantation rates did not account for the difference in outcome. The strong association with late mortality between a switch of therapy and the direction of switch, as well as the observation that final mode of therapy shows a stronger association with late mortality than initial mode of dialysis therapy, lends support to the hypothesis that treatment crossover differences need to be considered in comparing the two modes of therapy. In addition, the study presented here showed that the relative death rates of peritoneal dialysis compared with hemodialysis increases over time, violating the most basic assumption of the proportional hazards model. The latter model has been used for most, although not all, comparisons of mortality between the two treatment modalities. The data from this study suggest (but do not prove) that a risk-accentuating effect of a switch from hemodialysis to peritoneal dialysis, as well as the assumption of constant hazards ratios over time, conceals considerable differences in late mortality.

The study does not tell us the antecedent and direct cause of the excess mortality seen in peritoneal dialysis patients. Compared with hemodialysis patients, peritoneal dialysis patients showed a non-statistically significant tendency toward slower progression of echocardiographic disorders and fewer admissions for new-onset cardiac failure. Both of these manifestations of cardiac failure are predictors of subsequent death (28–30). There were no clear differences in the cause of death seen in the two treatment modalities. These data are similar to those of Bloembergen *et al.*, who showed that the excess mortality among peritoneal dialysis patients is spread out across several causes of death, although the discrepancy seemed to be greatest in mortality from infectious causes (37).

In this study, serum albumin levels were lower and hemoglobin was higher in peritoneal dialysis patients than in hemodialysis patients. We have reported previously that hypoalbuminemia was a very potent predictor of cardiac outcomes, as well as mortality in both hemodialysis and peritoneal dialysis patients (33). Multivariate analysis suggested that the lower serum albumin level of peritoneal dialysis was associated with much of the excess late mortality. It is worth reiterating that low serum albumin levels preceded subsequent mortality. Whether this observation is a fortuitous statistical association or a true cause-and-effect association cannot be determined from this study. It is noteworthy that low serum albumin levels have been repeatedly implicated as major markers of poor prognosis in both peritoneal dialysis and hemodialysis patients (6,7,33,38–41), although the causal mechanisms are not yet known. It is certainly possible that hypoalbuminemia could favor the development of ischemic heart disease through alteration in the lipid profile (perhaps by mechanisms similar to those seen in the nephrotic syndrome and other states of profoundly negative protein balance), increased oxidant stress, endothelial dysfunction, and alterations in endogenous vasoactive substances leading to a state of chronic vasodilatation (42–50). It is equally plausible that low albumin and late mortality in peritoneal dialysis patients could be linked by chronic inflammation or the impact of other (unmeasured) comorbidities (51). Recently, Lowrie *et al.* reported very similar findings in a large sample of dialysis patients: Peritoneal dialysis patients had higher mortality rates even after accounting for case-mix imbalances at baseline; this difference could be explained to a considerable degree by the lower serum albumin levels associated with peritoneal dialysis (25).

We did not measure dialysis urea removal, a surrogate marker for overall uremic solute clearance in this study, which reflects that these measurements were not in use at the time this study began. There is little doubt that uremic solute removal is one of several factors that affect the outcome of both hemodialysis (9–13) and peritoneal dialysis (6) patients. It is already known that conventional peritoneal dialysis is associated with considerably lower weekly urea removal than even moderate amounts of hemodialysis (4). It is likely that the intensity of hemodialysis delivered at the three institutions was, if anything, suboptimal by current standards (7–12). It is noteworthy that peritoneal dialysis is associated with a slower loss of native renal function than hemodialysis. Overall, urea clearance fell by almost one-fifth over 2 yr in the CANUSA study, almost entirely due to the loss of residual renal function, to levels independently associated with increased mortality (6). It is tempting to speculate that lower uremic solute clearance, particularly after the passage of 2 or more yr, may have accounted for some of the increase in late mortality seen in peritoneal dialysis patients in this study. There is little doubt that the "8 L of dialysate for all" CAPD performed in this study, which ran from the early 1980s through the early 1990s, would be considered inadequate for many patients in the post-CANUSA era. In many ways, our study tends to reaffirm the findings of the CANUSA study. A recent study showed no difference in outcome when adjustment was made for urea clearance, suggesting that the two modes of dialysis could have a similar outcome if CAPD urea clearance can be maintained at an optimal level (52). Another study showed a similar 2-yr survival when adjusted for Kt/V urea in accord with the peak-concentration hypothesis (53). No study to date can answer the critical question: What are the comparative outcomes of optimal hemodialysis and optimal peritoneal dialysis?

We did not routinely measure lipid subfractions or triglyceride levels in this study. It is clear that peritoneal dialysis patients have a different lipid profile than hemodialysis patients, with higher levels of serum cholesterol and triglycerides (54). The importance of these variables as cardiovascular risk factors in uremic patients is not yet clearly established, although recent studies suggest a potential role (55–58).

Known and unknown biases in how patients are initially assigned to a given therapy could account for much of the disparity in outcome of hemodialysis and peritoneal dialysis patients. On a relative basis, there was a 59% greater prevalence of diabetes, a 49% greater prevalence of ischemic heart disease, and a 36% greater prevalence of cardiac failure in peritoneal dialysis patients. The late mortality effect seemed to go beyond measured comorbidity. We say this because (*1*) adjusting for measured comorbidity had little impact on the mortality comparison and (2) the mortality effect was not

present until 2 yr or so; in this study, the impact of the major differences in comorbidity (ischemic heart disease, cardiac failure, diabetes mellitus) was seen immediately. Unmeasured baseline selection factors could similarly account for much of the disparity in outcome. In this study, we observed that patients who switched dialysis mode had a higher mortality than those who did not. In particular, a switch to peritoneal dialysis seemed to imperil hemodialysis patients. It would be difficult to incorporate complete knowledge of the factors leading to a therapy switch into available statistical models, even if it had been feasible to collect it. Undoubtedly, this limits how one study can be generalized to another set of patients. It is quite possible that social, demographic, geographic, educational, and psychological factors, and physician and center biases have an impact on (*1*) which therapy a patient chooses and (*2*) patient outcome. It is very difficult to quantify these factors accurately. It is therefore impossible to exclude the possibility that these factors accounted for the increased late mortality of peritoneal dialysis patients observed in this study. Except for an experimental design, there is no way to control for the impact of unmeasured factors that could account for the observed mortality differences. Similarly, because many selection bias factors cannot be measured, it is a truism that they cannot be compared between studies. This fact must necessarily limit the degree to which our findings can be generalized to other patient populations. Patient compliance with dialysis therapy was not measured. It bears reiteration that survival for 6 mo was a prerequisite for entry into this study, which is a significant difference from most other studies that have compared the relative outcomes of peritoneal dialysis and hemodialysis patients. It could be argued that this is a more fair comparison, because it avoids the "first therapy" bias, whereby patients, albeit with irreversible renal failure, are much more likely to use hemodialysis as initial therapy if they reach end-stage with an acute deterioration in renal function, or because of very late referral without predialysis planning. It could also be argued that peritoneal dialysis is intrinsically superior initially. Our study cannot address these issues.

This study, at first glance, seems to be at variance with recently published data from the Canadian Organ Replacement Therapy Registry (CORR) (27). This study differs in several important respects. The clock started ticking at 6 mo in this study, as opposed to initiation of dialysis therapy in the CORR study. Their findings of a superior survival for PD within the first 2 yr of therapy and our findings that after 2 yr, PD patients have poorer survival, are by no means mutually exclusive. It is conceivable that (*1*) relative mortality was higher in hemodialysis patients within the first 6 mo in our study and (2) relative mortality was greater after 2 yr in peritoneal dialysis patients in the CORR study. Hypothesis (*1*) could not be tested in our study; hypothesis (*2*) was not tested in the CORR study.

Our study has important implications. It suggests that crossover effects and violation of the proportional hazards assumption may conceal major differences in treatment efficacy between hemodialysis and peritoneal dialysis that only become apparent after approximately 2 yr of therapy. It suggests that peritoneal dialysis, at least as it was practiced until very recently, may be an inadequate long-term therapy for the average patient starting maintenance dialysis therapy. Lower serum albumin levels were a harbinger of the increased late mortality. These data indicate that studies designed to determine the causes of hypoalbuminemia and the efficacy of interventions aimed at reversing hypoalbuminemia are urgently needed, especially in peritoneal dialysis patients.

Appendix

Mean arterial blood pressure: Diastolic blood pressure + 1/3 (systolic blood pressure–diastolic blood pressure).

Coronary artery disease: Previous history of myocardial infarction, coronary artery bypass surgery, or percutaneous transluminal angioplasty.

Angina pectoris: Precordial chest pain precipitated by exertion or stress, relieved by rest or nitrate therapy.

Ischemic heart disease: Coronary artery disease or angina pectoris.

Cardiac failure: Dyspnea plus two of the following: raised jugular venous pressure, bibasalar crackles, pulmonary venous hypertension, or interstitial edema on chest X-ray requiring hospitalization or extra ultrafiltration.

New-onset cardiac failure: Cardiac failure while on dialysis therapy in a patient without a history of cardiac failure at baseline.

New-onset ischemic heart disease: Admission for ischemic heart disease while on dialysis therapy in a patient without a history of ischemic heart disease at baseline.

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