Patient Survival on PAN/AN69 Membrane Hemodialysis: A Ten-Year Analysis[1]

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ABSTRACT

Survival characteristics over a 10-yr period of 352 patients on hemodialysis (HD) with polyacrylonitrile membranes in a single center were retrospectively analyzed and compared with national data collected by the U.S. Renal Data System (USRDS). Only those patients who stayed on HD for longer than 3 months were included. Any outcome other than death was considered as lost to follow-up. The number of expected deaths in the entire patient population according to the USRDS data base was 203, whereas the observed actual rate was only 132, reaching high statistical significance. Several subgroups of patients, stratified on the basis of age and time on starting HD, diabetes mellitus as the cause of original renal disease, *etc.*, also exhibited significantly better survival. HD with a biocompatible membrane, providing adequate removal of low- as well as "middle"-molecular-weight uremic toxins, may be one important explanation for improved survival.

Key Words: *Mortality, patient survival, hemodialysis, nutrition, biocompatibility*

Both concern and controversy surround the mortality rate in the U.S. dialysis patient population. This may be increasing (1), but others maintain that when mortality is corrected for the increasing age and incidence of diabetes in the ESRD population, it is remaining constant (2). Held *et al.*, in their recently published report (3), showed that mortality was negatively associated with the duration of dialysis treatment, using the Cox model, adjusting for patient and dialysis unit covariates. In contrast, despite increased acceptance of elderly and diabetic patients, gross mortality (10% annually) has changed little between 1980 and 1987 for European patients (4). During the same time, hemodialysis (HD) patients' mortality rate in Japan has stayed around 9% (5), and in Australia between 8 and 16% (6), but in Canada, it is 20% (7). In the United States, the gross mortality rate was 20.7% in 1983 (1), 23.7% in 1989, and 22.9% in 1990 (8). There was clearly an upward trend, as discussed later.

It has been our impression, as early as 1981, that, in addition to low-molecular-weight solute clearance, there might be other factors, such as the biocompatibility of the membrane, the removal of uremic "middle molecules," and the volumetric control of ultrafiltration for fluid removal, capable of positively influencing the well-being, morbidity, and mortality of HD patients. This retrospectively completed analysis of our HD population explores the survival over a 10-yr span of all patients using the polyacrylonitrile (PAN/AN69) membrane.

MATERIALS AND METHODS

From March 1981 to December 1991, 352 patients were hemodialyzed exclusively with the PAN/AN69 membrane (manufactured by Hospal Corporation, Lyon, France). Both parallel-plate and hollow-fiber dialyzers were used. Some patients were dialyzed with other membranes before the availability of PAN in March 1981. No patient was dialyzed on cellulose-based membranes during the study period. Survival characteristics of all patients were compared with national data collected and processed by the U.S. Renal Data System (USRDS) (8). Similar to the USRDS database, no patient who had a failed renal transplant and returned to HD was entered into this analysis. Only those patients who stayed on HD for longer than 3 months were studied. Any outcome other than death was considered as lost to follow-up. The duration of hospitalization for medical or surgical problems, if any, was included in the total length of observation for each patient. However, data on morbidity or hospitalization were not tracked. No patient was dialyzed at a blood flow greater than 250 mL/min and at a dialysate flow greater than 500 mL/min. Dialysate sodium concentration was maintained around 143 mmol/L. Volumetric control was used for ultrafiltration. In the prescription for dialysis, high flux took precedence over high efficiency,

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in the sense that blood flows faster than 250 mL/min were not used in order to enhance lower molecular weight solute clearance. Convective transport was presumed to facilitate higher molecular weight solute clearance. The average weekly duration of HD was 9 h, with acetate dialysate in 75% of patients, albeit, another variable. Fewer than 10% of patients were dialyzed for 12 h weekly. Hemodialyzers were not reused during 9 of the 10 yr. Recombinant human erythropoietin became available for use only in July 1989. Routinely, each patient was seen by a physician during each HD session. Excluding the head nurse and the charge nurse, the staff-to-patient ratio was 1:3. The ratio of nurses to patient-care technicians was 1.2:1. In general, patients exhibited a high degree of compliance with regard to dietary restrictions, medications, and adherence to dialysis schedule. In a group of prevalent 66 patients, forming a subset of the original 352 patients, percent reduction in urea, Kt/V, normalized protein catabolic rate (nPCR), and serum albumin were compiled. These parameters were compared with those of another group of prevalent 43 patients dialyzed on cellulosic membrane in a different dialysis facility in Iowa that shared the same staffing and medical care characteristics. These parameters were drawn from a total of 6 months of observation per patient in both groups. All patients were stable, having not been hospitalized for the duration of the 6 months. Delivered Kt/V and PCR were measured with software based on variable-volume, single-pool urea kinetic modeling (9), taking into account BUN levels (pre/post/predialysis), weight changes, hematocrit, and actual dialyzer clearance. Dialysis treatment time, however, was seldom guided by Kt/V or PCR values.

USRDS tables are organized such that, knowing the age of the patient, the race, the diagnostic category (diabetes, hypertension, glomerulonephritis, and other entities), and the duration on HD at risk of death, one can calculate a risk factor representing expected mortality for each patient. Adding up the individual expected risks of death gives the total number of expected death for the entire population through the study period. This can be compared with the observed deaths to determine the significance of the difference by χ^2 test. The USRDS tables account for varying case mixes and comorbid conditions, and their compilation is drawn from actual observations of almost the entire U.S. dialysis population. The stated purpose of the tables is to allow individual dialysis units to perform valid comparisons of local experience with the national database (8).

Our analysis also included an estimation of patient survival rates using the Kaplan-Meier method for incomplete observations (10). The gross mortality was also compared with national figures (1,8). The individual cause of death was unfortunately not tracked in this study. In addition, no efforts were made to correlate dialysis treatment time to patient mortality.

RESULTS

The diagnostic categories in the patient population were: diabetic nephropathy (30% of patients), glomerulonephritis (23.5%), hypertensive nephrosclerosis (18.5%), and other entities (28%). The mean (± SE) duration of HD at risk of mortality was 920.1 ± 50.2 days (range, 150 to 4,557). The mean age when starting HD was 56.83 ± 0.9 yr (range, 15 to 90). Table 1 shows the respective distribution of age, Kt/V, nPCR, serum albumin, and HD time in 66 patients on PAN/AN69 membranes in our center and in another 43 patients on cellulosic membrane from a different unit in Iowa. There was at least one observation per patient per month. Although our patients were slightly younger and had been hemodialyzed for the same weekly duration, their percent reduction in urea and Kt/V were lower than the same values for those on cellulosic dialyzers ($P < 0.001$). However, their PCR and albumin levels were higher than in the latter group ($P < 0.001$ and <0.005, respectively). Serum albumin levels were measured by bromocresol purple. No observable downward or upward trend could be noted in any of these parameters during the 6 months of observation.

The number of expected deaths in 352 patients under our care (Group 1), according to the USRDS database, was 203, whereas the number of actual deaths was only 132. This difference was found to be significant at a P value of <0.001 (Table 2). We further subdivided the patient population as follows: Group 2 consisted of patients who started on long-term HD on or after January 1, 1986. Group 3 included the patients who were on HD between January 1, 1986, and December 31, 1988. Group 4 included patients who were 60 yr or older when starting hemodialytic therapy. Group 5 included patients who were aged 60 yr or more on HD between January 1, 1986, and December 31, 1988. All diabetic patients were put together in Group 6, and those diabetics on HD between January 1, 1986, and December 31, 1988, were in Group 7. As shown in Table 2, in each group with the exception of Group 7, the difference between expected and observed mortality was statistically highly significant.

Patients were stratified as described above for the following reasons: (*1*) the original USRDS survival data were tabulated for the prevalent ESRD population between January 1, 1986, and December 31, 1988; (*2*) an examination of the survival trend for all study patients as well as the prevalent population contemporaneous with the USRDS database seemed relevant; (*3*) the survival trend for high-risk patients,

TABLE 1. Profile of two groups of patients[a]

Membrane	N	Age (yr)	Percent Reduction in Urea (%)	Kt/V	nPCR (g/kg·day)	Serum Albumin (g/dL)	Time on HD (min)
Cellulosic	43	62.11 ± 2.1	69.1 ± 0.59	1.46 ± 0.02	0.91 ± 0.02	3.72 ± 0.04	184.8 ± 4.26
PAN	66	57.16 ± 2.12	54.05 ± 0.8	0.93 ± 0.02	1.08 ± 0.01	3.84 ± 0.03	179.2 ± 1.42
P		<0.5	<0.001	<0.001	<0.001	<0.05	NS

Values are mean ± SE. NS, nonsignificant.

TABLE 2. Patient survival on PAN/AN69 membrane HD[a]

Group No.	Total No. of Patients	Age (yr) (Mean ± SE)	Duration on HD (days)	Expected Mortality	Observed Mortality	*P*
1	352	55.89 ± 0.9	920.1 ± 50.2	203.74	132	<0.001
2	299	57.82 ± 0.99	285.92 ± 6.81	160.42	114	<0.001
3	181	56 ± 1.28	278.95 ± 9.3	72.24	45	<0.005
4	197	69.78 ± 0.54	259.87 ± 8.7	149.17	96	<0.001
5	105	69.7 ± 0.76	277.02 ± 12.5	53.46	30	<0.005
6	130	56.56 ± 1.21	235.27 ± 10.7	63.19	47	<0.05
7	51	55.18 ± 2	244.92 ± 17.8	22.39	16	<0.1

[a] Group 1, all patients; Group 2, those who started on HD on or after January 1, 1986; Group 3, patients who were on HD between January 1, 1986, and December 31, 1988; Group 4, those who were 60 yr or older when starting HD; Group 5, patients who were 60 yr or older on HD between January 1, 1986, and December 31, 1988; Group 6, all diabetic patients; Group 7, those diabetics on HD between January 1, 1986, and December 31, 1988.

like that for the elderly and diabetics, was also deemed important. Results of all analyses performed are shown in Table 2 regardless of the statistical significance of the outcome.

Kaplan-Meier survival estimates for all 352 patients are shown in Figure 1. Most deaths appeared to have occurred during the first 2 yr after starting HD. Briefly, 84% of the patients were alive at 1 yr, 60% at 3 yr, 48% at 5 yr, and 33% at the end of 10 yr.

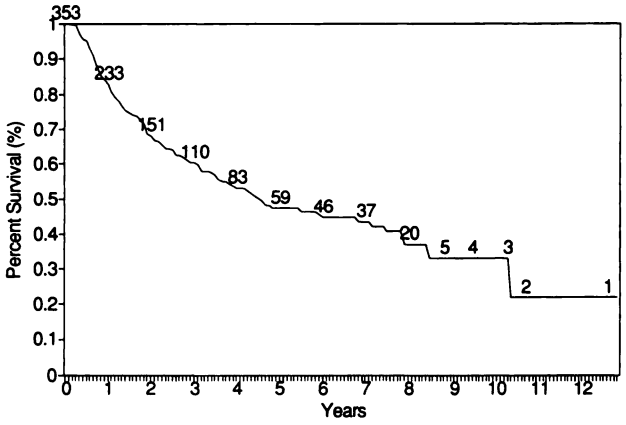

Figure 1. Actuarial patient survival estimates by Kaplan-Meier method in 352 patients.

The gross mortality rates of our HD population are indicated in Table 3; corresponding national rates are also shown. Gross mortality rate is the percentage of deaths in the HD population expressed in relation to the average number of patients on HD and peritoneal dialysis in the respective year. The average number is obtained from the number of patients on each modality at the beginning of the year and at the end. The national rates include deaths in the peritoneal

TABLE 3. Gross patient mortality rate[a]

Year	USRDS	Nephrology Clinic
1981	20.5	0 (0/26)
1982	20.1	0 (0/38)
1983	20.6	2.8 (2/70)
1984	20.7	10.5 (12/114)
1985	22.2	6.9 (9/130)
1986	22.8	14.5 (19/131)
1987	23.4	7.0 (10/141)
1988	24.3	11.8 (17/144)
1989	23.7	13.1 (19/145)
1990	22.9	13.3 (21/157)
1991	NA	11.1 (15/135)

[a] Values are percents. NA, not available.

dialysis population; data from our center do not. Even so, it can be seen that the risk of death was much lower for our patient population.

DISCUSSION

Admittedly, because this is a retrospective analysis, it is subject to its inherent limitations. It is a single center's experience. We also recognize the lack of a control arm in our study consisting of patients dialyzing on "nonbiocompatible" membranes. Nevertheless, problems posed by variability in case mix and dominant comorbid conditions are minimized by comparing patient survival with that derived from the tables constructed by the USRDS. It is our understanding, based on communications with USRDS, that if the Cox model of regression with multiple covariates were to be performed, the results would not greatly differ from the expected risk of death (calculated per 1,000 patient years at risk) for the total number of days the sample patients were on HD, based on the USRDS tables. We are unable to say at this state of the USRDS database how many patients nationally have been dialyzing on biocompatible membranes exclusively.

The purpose of the unrandomized comparison between the two groups of patients in Table 1 (43 on cellulosic membrane and 66 on PAN) was merely to show differences in the indices of the adequacy of HD. Because both patient groups are drawn from Iowa, it is unlikely that any possible genetic homogeniety might be favorably or unfavorably influencing these indices. These patients were not separately tracked as to their morbidity and mortality, and therefore, we are unable to indicate the existence of relevant differences. In addition, we more than realize that the 66 patients modeled are only about 19% of our whole study population and that data collected from them could not be extrapolated to the entire patient base. Furthermore, it is also conceivable that our patient population received better dialysis than the USRDS sample, even in terms of lower molecular weight solute clearance. Yet, as shown in Table 1, for the same duration of dialysis and for a lower Kt/V, patients on PAN seemed to achieve higher nPCR and serum albumin levels.

The adequacy of HD remains a controversial topic. The National Cooperative Dialysis Study (NCDS) focused on the level of BUN as the statistically most powerful predictor of mortality and morbidity (11). The PCR was the second most significant predictor of morbidity and mortality, and therefore, the NCDS report of 1983 strongly recommended an adequate dietary protein intake. In light of the NCDS data, Gotch and Sargent later advocated a threshold Kt/V of >0.8 at a PCR of >0.8 g/kg per day for adequate therapy (12). Whether or not the optimization of dialysis with the use of Kt/V values of >1 affects patient mortality could be answered at best by stating that most of the evidence that exists examining this question is circumstantial and dependent on comparisons of mortality in patients with different settings. This kinetic analysis showed that BUN cannot be considered to be a prescription control parameter, because it is a dependent variable of Kt/V (dialyzer clearance times treatment time, divided by the volume of total body water) and nPCR, the two primary prescription control parameters. Underdialysis can occur with low levels of predialytic BUN if treatment time is reduced, if there is a low PCR. Later studies by Lindsay and Spanner (13) suggest the dependence of dietary protein intake and PCR on Kt/V. These studies also indicated that this relationship may be dependent on the membrane used: dialysis with the PAN/AN69 membrane required a lower Kt/V to obtain a given PCR than did dialysis with a cellulosic membrane. This difference may be explained by the beneficial effect of the removal of "middle-molecular-weight" uremic toxins by the AN69 membrane, which has a different solute clearance profile than a cellulosic membrane. Their data suggested that the NCDS conclusions may be reinterpreted by assigning a major relationship between the nutritional status of patients and their morbidity. A satisfactory nutritional status is attained only in patients receiving adequate dialysis, which, in turn, ensures the control of predialytic BUN levels. Studies by the same authors later confirmed the hypothesis that the relationship between Kt/V for urea and PCR is membrane dependent (14). This observation has to be seen in the light of the recently published study of Delmez et al. (15), revealing that in 617 HD patients in the metropolitan St. Louis area, for a mean Kt/V of 1.03, the PCR obtained was 0.9 g/kg per day. All of these patients were on conventional hemodialyzers made of cuprammonium cellulosic membranes.

The interaction between blood and dialyzer membranes induces biologic effects such as the stimulation of the complement system, the aggregation of granulocytes, transient leukopenia, the release of granulocytic enzymes, clotting, and thrombocyte activation (16). Several of the side effects of HD may be attributed to the increased release of cytokines from monocytes during dialysis, as a result of complement activation, toxins, or acetate in the dialysate (17). HD has been shown to lead to monokine production (18,19). One such factor is interleukin-1 (IL-1), which with other monokines, is synthesized and released by monocytes after stimulation by exogenous pyrogens or by complement activation through C5a (20). Concentrations of IL-1 are elevated in dialysis patients before HD and rise further during and after HD with regenerated cellulosic membranes (19,21). There is a close correlation between the intradialytic

increase in IL-1 production and C3a levels in dialysis patients on regenerated cellulosic membranes (22). In contrast, in patients using PAN/AN69 membranes, IL-1 remained at basal levels during HD. Among the known effects of monokines, the induction of protein catabolism probably results from the local release of prostaglandin E2 in skeletal muscle, which in turn stimulates lysosomal protein degradation. The interaction between blood and regenerated cellulosic membranes leads to accelerated net protein breakdown, as measured by increased amino acid efflux from leg tissues (23). Sham HD with PAN/AN69 membranes did not result in such an increased amino acid efflux, implying that the protein catabolic effect of blood-membrane contact depends on the biochemical properties of the dialyzer. Indeed, Rotellar *et al.* rather elaborately demonstrated the profound catabolic effects of the HD procedure using hollow-fiber cellulose acetate dialyzers (24). However, it should be pointed out that in another study, by Herbelin *et al.*, IL-1 levels rose with HD in patients both on cellulosic-cuprophane and on PAN/AN69 membranes (25).

Given these observations, it is tempting to propose a link between the bioincompatibility of the hemodialyzer membrane, the repetitive protein catabolic effects of dialysis, and patient morbidity and mortality. In keeping with this, low mortality rates have been reported with high-flux dialysis and short treatment time guided by urea kinetic modeling (26–28). Gotch and Uehlinger (28) reported an annual mortality rate of 14.2% with an average treatment time of 2.25 h.

In the evolution of our results of improved patient survival, urea kinetic modeling had only incidental importance. We do not imply that kinetic modeling is unimportant or unhelpful. We believe that our results could best be explained by a combination of a number of factors such as biocompatibility of the dialyzer membrane, adequate clearance of "middle molecules" as well as smaller molecular toxins, volumetric control of ultrafiltration, patient compliance, and close surveillance of patients' well-being by the staff and physicians of the dialysis unit. It is, indeed, only a single center's experience.

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