Risk of Fatal Cerebrovascular Accident in Patients on Peritoneal Dialysis versus Hemodialysis

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Abstract. Several reports have suggested that the incidence of hemorrhagic stroke may be greater on hemodialysis as compared with that among the general population and that patients with intracranial hemorrhage should be treated with peritoneal dialysis rather than hemodialysis. However, whether the risk of fatal stroke is greater on hemodialysis versus peritoneal dialysis has not been systematically examined. In this study, the case of a diabetic patient with extensive peripheral vascular disease who, after 7 years on hemodialysis, was changed to peritoneal dialysis and subsequently suffered two strokes over a 5-month period, is reported. Recent data from the United States Renal Data System, which allow a comparison of death rates from stroke in large numbers of hemodialysis versus peritoneal dialysis patients, are reviewed. These data suggest that the risk of death from stroke may actually be greater for patients on peritoneal dialysis versus hemodialysis in spite of their having a lesser prevalence of preexisting cerebrovascular disease. This risk was greatest for elderly diabetic black patients and women, who experienced a nearly twofold-greater odds favoring death from stroke on peritoneal dialysis versus hemodialysis. Selection of a dialysis modality for a patient beginning renal replacement therapy may require the consideration of such data, particularly in those patients with extensive preexisting vascular disease. (J Am Soc Nephrol 8: 1342-1347, 1997)

Stroke remains the third leading cause of death in the general population and the risk of this disorder is significantly greater in the end-stage renal disease (ESRD) population (1,2). The role of diabetes mellitus, hypertension, lipid derangements, hemostatic abnormalities, and other variables in the development of accelerated atherosclerosis in these patients has been reviewed at length elsewhere (1,2). Whether one dialysis modality versus the other might differentially impact on the development of stroke has never been systematically addressed. Several reports in the literature have suggested, though, that in selected neurological circumstances, peritoneal dialysis (PD) may be a preferred therapy to hemodialysis (HD), such as in the setting of intracranial hemorrhage (3,4). Several reports have also suggested an increased occurrence of cerebrovascular accident in patients on HD, particularly hemorrhagic stroke (5-8), compared with the general population, but it is unknown whether this represents a higher stroke risk relative to PD.

We report the case of a patient with extensive peripheral vascular disease but no history of stroke who, after being changed to PD after 7 years on HD, suffered two strokes within a 5-month period. We also review the literature on cerebrovascular disease in patients with ESRD, with particular emphasis on data from the USRDS, data that suggest that the risk of fatal stroke may actually be greater with PD compared with HD.

Case Report
A 53-year-old Hispanic man with diabetic nephropathy and ESRD had been on HD for 7 years, during which time virtually all vascular access for HD had been exhausted. He suffered from severe peripheral vascular disease of both the upper and lower extremities but had never suffered symptomatic cerebrovascular disease. A Tenckhoff PD catheter was inserted, and PD was begun. One month after beginning PD, the patient was doing well and had no neurological deficits. Four months after PD was begun, the patient had an episode of slight dizziness after being out in the hot weather, at which point he laid down. After about 30 minutes, his wife found him unable to speak or move his right-sided extremities. In the hospital, his blood pressure was 160/90 mmHg. He was found to be severely dysarthric with a dense right facial palsy and right-sided weakness. Computed tomography of the head confirmed the presence of a cerebral infarct in the distribution of the left middle cerebral artery, involving the left operculum and superior frontal cortex and underlying white matter. Although no cardiac source of embolism could be identified on transesophageal echocardiography, inferobasal asynergy was noted and, hence, warfarin therapy was initiated. Four months later, the patient presented again to the hospital with dysphagia, dysphonia, and left upper-extremity weakness. Computed tomography of the head revealed a new infarct of the right cerebral peduncle. The patient was hospitalized for 5 days and then discharged, but he
required readmission 2 days later due to a worsening of his symptoms. No new infarct was documented. With intensive therapy, his speech and ambulation have improved marginally.

Discussion

Although stroke remains the third leading cause of death in the general population in the United States, the incidence of this disorder is increased in ESRD patients (1,2,9–11). The death rate from cerebrovascular disease ranks third behind cardiac disease and infection, excluding withdrawal from dialysis (12). This is believed to be due to variables such as hypertension (13), diabetes mellitus, and other factors that may promote accelerated atherogenesis as reviewed elsewhere (1). A recent report has implicated the LP(a) phenotype in accelerated cerebrovascular disease in ESRD patients (14), a finding that potentially might allow early identification and perhaps treatment of patients at high risk for stroke. A recent report, though, has questioned the magnitude of the impact of hyperlipidemia on carotid atherosclerosis (15). Whether hemodialysis itself may accelerate the progression of atherosclerosis has been subject to controversy (16–18). However, the incidence of cerebral hemorrhage has been reported to be increased in patients on HD compared with the general population (5–8), a factor that some researchers have attributed to heparinization. As such, HD is generally contraindicated in patients with intracranial hemorrhage who are typically changed to PD, as no systemic heparinization is required for this modality (3,4).

Other than studies demonstrating increased hemorrhagic stroke in HD patients (these studies did not compare the incidence with that on PD) and reports suggesting greater safety with PD for patients with intracranial hemorrhage, there had been until recently no large-scale data available to indicate whether the incidence of stroke is indeed greater on HD versus PD. Direct comparisons of overall stroke rates for each modality may be problematic because of patient-selection factors for one modality versus the other, such as age, race, sex, and presence of diabetes mellitus. In recent years, the USRDS has served as a unique resource for investigators wishing to examine data from large numbers of ESRD patients. The USRDS collects and annually reports clinical and demographic data on all patients treated for ESRD in the United States who survive for a minimum of 90 days on renal replacement therapy and who are approved for Medicare. Bloembergen et al. recently examined death rates by using the USRDS database and found patients on PD to be about 20% more likely to die from stroke than their counterparts on HD (19). This was in spite of the fact that, as the authors point out, the USRDS case-mix study has shown that patients on HD are 50% more likely to have underlying cerebrovascular disease, compared with those on PD (19). These data suggest that for patients on PD, in spite of their being less likely to have underlying cerebrovascular disease, they are at higher risk to die of stroke, compared with patients on HD.

The USRDS database allows the opportunity to look at cause-specific death rates depending on the presence of different clinical variables such as diabetes mellitus, age, race, and sex, and below we summarize and analyze some of these data (12). In this analysis, all patients on HD and PD from January 1, 1989, through December 31, 1991, were studied (12). Death rates due to cerebrovascular disease per 1000 patient-years exposure (PYE) were recorded in patients at risk until death, transplantation, or the end of the study’s time period as described above. Other variables recorded were patient age, gender, race, and cause of ESRD (diabetes mellitus or all others). The aim of our analysis of the USRDS data was to identify clinical variables potentially associated with higher cerebrovascular death rates on one modality versus the other. Data were available grouped in the following manner: (1) all dialysis patients (HD and PD), all causes of ESRD; (2) all dialysis patients with diabetic nephropathy; (3) all dialysis patients with ESRD not due to diabetes mellitus; (4) all HD patients with all causes of ESRD; (5) all HD patients with diabetic nephropathy; (6) all HD patients with ESRD not due to diabetic nephropathy; (7) all PD patients with all causes of ESRD; (8) all PD patients with diabetic nephropathy; or (9) all PD patients with ESRD not due to diabetic nephropathy (19). Death rates were calculated as the number of deaths due to cerebrovascular disease divided by the number of PYE and are recorded as rates per 1000 PYE. Age-adjustment of death rates was carried out using the combined HD and PD populations as the composite reference group and with the age-specific stroke death rates available for each age group in each category. For each variable, we then calculated an odds ratio for the odds of cerebrovascular death in the PD population versus the HD population. 95% confidence intervals (CI) were calculated using the Wolff approximation with Instat statistical software (GraphPad Instat, GraphPad Software version 2.04, Dr. Guth, Tulane University, New Orleans, LA). Because of the very large sample sizes available with the USRDS data, it is not unexpected that many comparisons will yield extremely small P values, even if these values are not truly of clinical significance. In this instance, 95% CI are likely to be a better measure of actual clinical significance of differences in cerebrovascular death rates in HD and PD patients, and we have therefore omitted further reference to P values from this analysis.

The overall unadjusted cerebrovascular death rate for all dialysis patients during this period was 11.5/1000 PYE in both HD and PD patients. Age-adjusted death rates for male, female, black, and white patients with and without diabetes mellitus are summarized in Table 1. For almost all of these clinical variables, the death rate for stroke on PD appears to exceed that of HD. In particular, female, black, and white diabetic patients appear to have a substantially higher cerebrovascular death rate on PD. Female diabetic patients on PD, for example, had a cerebrovascular death rate nearly one and one half times that of their counterparts on HD. Figure 1 illustrates the odds ratio for death of cerebrovascular disease on PD versus HD for male, female, black and white diabetic patients in different age ranges. Native American and Asian patients were not included in this analysis because the numbers in each category were too small and amounted to less than 2% of the study population. For diabetics in the 20- to 44-year-old age group, male patients and white patients appeared to have cerebrovascular death rates that were comparable on HD and
Table 1. Age-adjusted death rates from cerebrovascular disease in dialysis patients*

<table>
<thead>
<tr>
<th>Group</th>
<th>All HD</th>
<th>All PD</th>
<th>Diabetic Patients HD</th>
<th>Diabetic Patients PD</th>
<th>Nondiabetic Patients HD</th>
<th>Nondiabetic Patients PD</th>
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<tr>
<td>Male</td>
<td>9.9</td>
<td>10.8</td>
<td>14.0</td>
<td>16.2</td>
<td>8.6</td>
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<td>16.5</td>
<td>25.9</td>
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<tr>
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<td>13.5</td>
<td>14.4</td>
<td>18.9</td>
<td>9.9</td>
<td>10.4</td>
</tr>
<tr>
<td>White</td>
<td>11.3</td>
<td>13.9</td>
<td>16.3</td>
<td>22.1</td>
<td>9.3</td>
<td>10.5</td>
</tr>
</tbody>
</table>

* Data are derived from the US Renal Data System database and represent age-adjusted death rates in each category from cerebrovascular disease during the period January 1, 1989, through December 31, 1991, as described in the text. Data were recorded in patients at risk until death, transplantation, or the end of the time period of the study. Data are expressed as deaths due to cerebrovascular disease per 1000 patient-years exposure (PYE). HD, hemodialysis; PD, peritoneal dialysis; All, combined HD and PD patients.

PD. For black diabetic patients, though, there was a much higher cerebrovascular death rate on HD, and for female diabetic patients the death rate was higher on HD as well in this relatively young age range. These data suggest that young black and female diabetic patients might experience a higher incidence of cerebrovascular disease on HD versus PD. However, as this figure illustrates, diabetic patients appear to suffer a substantially higher cerebrovascular death rate on PD versus HD with advancing age. Elderly women and elderly black diabetic patients had an odds ratio of nearly 2 for having cerebrovascular death on PD, compared with HD. This risk was less for white patients, and the risk for men appeared to be comparable with both modalities. These data suggest that there may be significantly increased age-dependent stroke-related death risks for several subgroups of patients with diabetes, particularly blacks and women, that could significantly impact on their risk of fatal stroke on PD versus HD. For nondiabetic patients, the spectrum is a bit different, as illustrated in Figure 2. As shown here, for nondiabetic patients under the age of 65, death from cerebrovascular disease was more likely on HD compared with PD, with this risk appearing to be greatest for women. For those patients aged 65 and older, PD entailed a higher risk of cerebrovascular death, compared with HD, with similar odds ratios for male, female, black, and white nondiabetic patients. These data suggest that with the exception of women in the 45- to 64-year-old age group, nondiabetic patients below 65 may have lesser odds of death from stroke on

**Figure 1.** Odds ratios for death from cerebrovascular disease on peritoneal dialysis (PD) versus hemodialysis (HD) for patients with diabetes mellitus. Using the USRDS database from January 1, 1989, through December 31, 1991, an odds ratio was calculated for male, female, black, and white diabetic patients in the age ranges 20 to 44, 45 to 64, and 65 and older and represents the odds ratio of death from cerebrovascular disease on PD versus HD. Those points falling to the left of the line of unity suggest an odds ratio favoring death from cerebrovascular disease on HD. Those points falling to the right of the line of unity suggest a higher odds of death on PD versus HD. Error bars represent 95% confidence intervals calculated using the Wolff approximation.
Nondiabetics

Figure 2. Odds ratios of death from cerebrovascular disease for nondiabetic patients on PD versus HD. The USRDS database from January 1, 1989, through December 13, 1991, was analyzed by calculating the odds ratio of death due to cerebrovascular disease on PD versus HD for male, female, black, and white patients without diabetes mellitus in the age ranges 20 to 44, 45 to 64, and 65 and above. Those points falling to the left of the line of unity suggest a higher risk of death from cerebrovascular disease on HD, whereas those points to the right of the line favor death from cerebrovascular disease on PD, compared with HD. Error bars represent 95% confidence intervals calculated using the Wolff approximation.

PD, compared with HD, whereas those older than 65 have greater odds, although not to the extent in diabetic patients.

There are few means available to clinicians to minimize the occurrence of stroke in ESRD patients other than blood pressure control, pharmacologic attenuation of hyperlipidemia, and use of antiplatelet and other therapy in patients with documented cerebrovascular disease. The USRDS data suggest that stroke death rates may vary substantially between different patient subgroups, depending on whether they are on PD or HD, suggesting that one potential additional means by which death from stroke could theoretically be combated in the ESRD population might be by including the risk of stroke depending on their clinical profile into the decision-making process regarding choice of renal replacement modality. For example, as the odds ratio for death from stroke favors a substantially higher stroke rate on PD for the diabetic patient older than age 45, placing such a patient on HD might reduce that individual's stroke risk. By contrast, young patients, particularly nondiabetic women and black patients who appear to have a higher stroke death rate on HD, might do better if placed on PD instead. Although decisions regarding mode of renal replacement therapy are often left to the patient unless dictated by medical or surgical conditions, it is plausible that modality selection could potentially serve as an additional means of minimizing cerebrovascular complications of ESRD. These data, however, cannot be interpreted as having any implications regarding the overall safety and mortality associated with PD and HD, which is far beyond the scope of this review.

It should be pointed out that the USRDS data we have summarized provide information regarding fatal stroke. The data, although extremely useful in this regard, do not address other issues, such as the management of acute intracranial hemorrhage, the development of or progression of cerebrovascular disease, or the incidence of nonfatal stroke. Hence based on these data, it cannot be determined whether the overall incidence of stroke is greater in the PD population or whether the incidence is in fact the same or less but that a stroke in a PD patient is more likely to be fatal.

As Bloembergen et al. have pointed out, although the death rate from stroke was greater for PD compared with HD, stroke accounted for only about 8% of total excess deaths in these patients (19). Although stroke might not account for a large percentage of excess deaths, considering the marked morbidity associated with nonfatal stroke as well as the substantial expense of prolonged hospitalization, rehabilitation, nursing care, loss of income, and complications such as pneumonia, pressure ulceration, and other factors, increased stroke in PD patients could have considerable adverse consequences other than death. Studies to evaluate the extent of these adverse outcomes in the ESRD population have not been reported nor have either
prospective or crossover studies to compare stroke rates between PD and HD patients been carried out.

A recent study of nondiabetic patients with chronic renal failure has demonstrated that virtually all patients who have peripheral vascular disease have carotid artery disease (20). Undoubtedly, our patient, who had extensive peripheral vascular disease, had cerebrovascular disease at the time he was changed to PD, although he was asymptomatic at that time. It is plausible that differences in stroke incidence might be applicable only to patients with established cerebrovascular disease at the time dialysis is initiated or a change in modality is made. However, even relatively young nondiabetic patients, who would not be expected to have significant baseline cerebrovascular disease, did demonstrate a difference in fatal stroke incidence on PD versus HD (although in this instance the incidence was higher on HD).

It is unclear why the incidence of fatal stroke should be greater on PD compared with HD, although there are a number of potential contributing variables. Differences in the amount of dialysis delivered, lesser clearance of low-molecular-weight solutes via PD, losses of albumin and other proteins in PD, differences in potassium homeostasis, and use of heparin in hemodialysis patients could all potentially impact on the development of stroke. Other variables could play a role as well. It is well known that excessive blood pressure reduction can precipitate symptomatic cerebrovascular disease and, in general, blood pressure tends to be somewhat lower in PD patients. Another possibility is that the continual glucose load intrinsic to PD might accelerate the formation of advanced glycation end products, which are suspected to contribute to atherogenesis. If PD is ultimately demonstrated to entail a greater stroke risk in prospective and crossover studies, these and many other variables may require investigation. Until these factors are studied and until it can be clearly identified which subgroups might do better on PD or on HD, our only practical means of reducing the incidence of stroke in ESRD patients will remain vigorous counseling against smoking, and early detection and treatment of cerebrovascular disease. The available data do suggest, however, that although PD may be indicated in the setting of intracranial hemorrhage, it may be associated with a higher incidence of fatal stroke in other groups of patients.

Acknowledgments

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References

The Nephrology Training Program at Long Island Jewish Medical Center, New Hyde Park, the Long Island Campus for the Albert Einstein College of Medicine, Bronx, New York

The Long Island Jewish Medical Center in New Hyde Park, New York, is the Long Island Campus for the Albert Einstein College of Medicine, Bronx, New York. The renal division consists of five full-time faculty (three adult and two pediatric nephrologists). Although the first year of fellowship consists of clinical training, the second year is largely devoted to laboratory and/or clinical research. A third year is optional for those fellows interested in additional research training, and fellows have received support through research fellowship grants from the National Kidney Foundation of New York/New Jersey. The program is structured to prepare fellows for careers in academic medicine and/or patient care.

Fellows are exposed to a wide variety of renal disorders, including glomerular disease, tubulointerstitial disease, obstructive nephropathy, hypertension, and fluid-electrolyte disorders on the medical, surgical, obstetrical, and bone marrow transplant units. Conferences include a core curriculum series, renal grand rounds, weekly research journal club, combined conferences with the departments of urology, invasive radiology, nuclear medicine, and pediatric nephrology, renal biopsy conference, and weekly data club.

Research is given a high priority, the participation by fellows is required. Major research activities in the National Institutes of Health–supported laboratory include the mechanism by which opiates cause glomerulosclerosis, HIV-associated nephropathy, endocytosis by mesangial cells and macrophages, matrix degradation, modulation of mesangial cell proliferation and matrix synthesis by macrophages, matrix oxidation, and effects of glomerular hypertension on proliferation and apoptosis of mesangial cells and endothelial cells. Clinical research activities include studies evaluating survival and outcomes in subsets of patients on dialysis, rhabdomyolysis, and pharmacokinetics in dialysis patients. There are significant combined research efforts with the urology department as well. The research activities of the division result in 10 to 15 publications per year, as well as presentations at the American Society of Nephrology and Experimental Biology meetings.