Outcome of Stroke in Patients Undergoing Hemodialysis

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Background: While elevated levels of serum creatinine have been shown to be a risk factor for diminished survival after stroke, it is unknown how renal replacement therapy may affect the outcome.

Methods: Strokes occurring in 26 consecutive patients undergoing hemodialysis at our institution were reviewed and clinical and laboratory variables and outcome were compared with those of patients who had a stroke but had normal renal function.

Results: Twenty-four strokes in the patients undergoing hemodialysis were ischemic while only 2 were hemorrhagic. Virtually all the patients had hypertension, half had diabetes mellitus, and most had some prior evidence of cardiovascular disease at the time of their stroke. Fifty percent of the patients undergoing hemodialysis had a good outcome (defined as being discharged home) while the remainder had a poor outcome (defined as dying or being discharged to a nursing facility). The combined presence of hypertension and coronary artery disease had a sensitivity of 91.2% for identifying patients with a poor outcome, while male sex, the presence of coronary artery disease, and the combined presence of hypertension, coronary artery disease, and/or congestive heart failure had sensitivities greater than 80% but low specificity. The outcome of patients undergoing hemodialysis was comparable with that of a control group of patients who had a stroke but had normal renal function, although the length of hospital stay was greater (mean [±SEM] 29.8±6.4 days vs 12.7±1.1 days, respectively; P<.01).

Conclusions: Hospitalized patients undergoing hemodialysis in whom stroke occurs appear to have as good an outcome as that of patients with normal renal function, although they are hospitalized longer. In addition, certain clinical variables seem to be associated with a worse outcome. Aggressive measures to prevent and treat stroke seem as warranted for patients undergoing hemodialysis as for patients with normal renal function, although interventions to reduce the length of hospital stay are needed.

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Chronic renal failure appears to be a significant risk factor for the development of stroke, as well as other complications of accelerated cardiovascular disease. While renal replacement therapy may ameliorate many of the metabolic derangements of end-stage renal disease as well as other variables, such as platelet dysfunction, it does not diminish the risk of cardiovascular disease, which remains substantially higher in this group than in the general population. Some, in fact, have argued that hemodialysis may actually accelerate atherogenesis, although this is controversial. Among the cardiovascular complications seen in patients with end-stage renal disease, stroke is the third leading cause of death, ranking behind heart disease and infection. In particular, several studies have reported an alarmingly high incidence of hemorrhagic stroke in patients undergoing hemodialysis. These data have demonstrated an important role for renal disease in predisposing to stroke.

While the presence of renal failure appears to have a significant impact on the development of stroke as well as other cardiovascular complications in both patients not receiving dialysis and those receiving dialysis, Friedman has reported that patients with renal insufficiency who are not receiving dialysis have diminished survival after stroke. This study strongly suggests that renal insufficiency can not only impact the risk of stroke but can also affect the outcome as well. However, it is unknown how renal replacement therapy might affect the outcome of stroke, although it is plausible that it might help by controlling platelet dysfunction, fluid overload, and other variables. In the
**PATIENTS AND METHODS**

With the aid of a computerized medical record search using the *International Classification of Diseases, Ninth Revision (ICD-9)*, discharge codes, we identified 26 consecutive patients receiving maintenance hemodialysis who had a discharge diagnosis of stroke at our institution over a 10-year period (January 1987 to December 1996). Two patients were admitted to other hospitals for their stroke and is it from there that we obtained their data. Maintenance hemodialysis was defined as a requirement for supportive dialysis therapy for at least 30 days and continuation of dialysis in the outpatient setting in accordance with the definition of the Health Care Financing Administration. Patients received dialysis using single-pass machines with cellulose acetate–hollow fiber dialyzers and standard tubing. There was no dialyzer reuse. Patients underwent dialysis 3 times weekly using bicarbonate or acetate-based dialysate solutions of standard composition. All dialysis machines were cleaned between treatments using standard methods. After human recombinant erythropoietin became generally available in 1989, the majority of our patients were treated with this agent.

Clinical data, including age, race, sex, and the presence of diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, left ventricular hypertrophy, cardiac dysrhythmia, and peripheral vascular disease, were recorded. All computed tomographic and/or magnetic resonance imaging scans of the brain, including follow-up examinations, were interpreted by an attending neuroradiologist. Existence of coronary artery disease was defined by 1 or more of the following criteria: prior myocardial infarction or angina, abnormal results on thallium stress testing, and/or documentation by cardiac catheterization. Congestive heart failure was considered to be present if patients had a clinical history consistent with congestive heart failure and/or if there was evidence of congestive heart failure on chest radiographs, echocardiograms, or nuclear ejection fraction studies. Left ventricular hypertrophy was diagnosed using standard electrocardiographic and/or echocardiographic criteria.

A history of cardiac dysrhythmia was determined by review of patients' medical records, including Holter monitor reports or cardiac rhythm recordings during prior hospitalizations. Peripheral vascular disease was considered present if there was a history of claudication, arterial bypass, gangrene, amputation, and/or abnormal findings of duplex or arteriographic studies. Blood pressure and laboratory data obtained before dialysis during the month prior to the stroke were recorded. Duration of stay in the hospital, disposition (discharge home [defined as a good outcome] or discharge to a nursing facility or death [defined as a poor outcome]), and the presence of a residual neurological deficit at the time of discharge were all recorded.

A control group of 87 consecutive cases of stroke in hospitalized patients at our institution with normal renal function (defined as a serum creatinine level ≤124 mmol/L [1.4 mg/dL]) were examined as well.

Continuous variables are reported as mean (±SEM).

For comparison of continuous variables, an unpaired Student t test was used. To compare proportions of patients with or without a given finding, a Fisher exact test or the X² test with Yates continuity correction was used as appropriate. Statistical significance was defined as P < 0.05.

The most common cause of end-stage renal disease in our patients was diabetic nephropathy in 11 (42.3%), while hypertension was the cause in 8 (30.8%). The remainder of the patients had end-stage renal disease secondary to other causes, including chronic interstitial nephritis, renal papillary necrosis, vasculitis, and administration of intravenous radiocontrast. The cause was unknown in 2 patients.

Patients' mean (±SEM) systolic blood pressure was 160.9±7.9 mm Hg, while mean diastolic blood pressure was 87.0±4.5 mm Hg. Laboratory studies disclosed the following mean (±SEM) values: serum sodium ion, 137.2±2.0 mmol/L; potassium, 4.8±0.2 mmol/L; serum urea nitrogen, 25.2±2.5 mmol/L (70.6±6.9 mg/dL); and creatinine, 875±71 µmol/L (9.9±0.8 mg/dL). Levels of serum albumin were decreased at 34±2 g/L and serum cholesterol levels were 5.30±0.33 mmol/L (204.8±12.8 mg/dL). Serum aminotransferase levels were within normal limits overall, and mean hematocrit was 0.30±0.02.

The types of strokes and outcomes are summarized in the following: 24 strokes (92.3%) were ischemic in origin, with only 2 hemorrhagic strokes occurring. Half of the patients were left with some neurological deficit (ratio of residual deficit, 13:13 or 50%). Thirteen (50%) of the patients were eventually discharged home while 7 (23.1%) went to a nursing home and 6 patients (23.1%) died in the hospital. The mean (±SEM) length of stay for patients who survived was 29.8±6.4 days. The sensitiv-
ties and specificities of clinical variables for poor outcome after stroke in these patients are summarized in Table 1. Among the variables, the combined presence of hypertension and coronary artery disease had a 91.7% sensitivity for identifying patients with a poor outcome, although the specificity was low. Male sex, the presence of coronary artery disease with or without hypertension, and the combined presence of hypertension, coronary artery disease, and/or congestive heart failure yielded sensitivities of greater than 80% for identifying patients with poor outcome, but had low specificity.

Table 2 provides a comparison of outcomes between patients undergoing hemodialysis and patients with normal renal function in whom stroke occurred. There was a tendency for the control patients to be somewhat older than the patients receiving hemodialysis (70.5±1.2 years vs 65.3±2.7 years, respectively), although this did not meet statistical significance (P=.05). The proportions of male and female patients did not differ between the groups (P=.11), but the racial makeup of the groups differed significantly in that there was a greater proportion of African American patients in the hemodialysis group, consistent with the greater proportion of African Americans in the overall population receiving hemodialysis compared with the general US population. When outcomes were compared, the proportions of patients with a good outcome were virtually identical: 43 (49%) control patients and 13 (50%) patients undergoing hemodialysis. The remainder of patients were discharged either to a nursing facility or died, and there was no difference in these 2 outcomes between the 2 groups (Table 2). While the outcome was comparable between patients undergoing hemodialysis and those with normal renal function, there was a substantial difference in length of stay because the patients receiving hemodialysis required hospitalization for about twice the number of days (29.8±6.4 days vs 12.7±1.1 days, respectively; P<.01).

While previous studies have shown that elevated serum creatinine levels appear to place patients at greater risk for stroke as well as a poor outcome after stroke, it is unknown whether renal replacement therapy might affect such an outcome. Such data could have clinical utility because if it were known that stroke had a dismal outcome in patients undergoing hemodialysis, it would suggest that stroke should be regarded as a preterminal event and hence one could argue that aggressive therapy would perhaps not be indicated in that setting. Although hemodialysis ameliorates many of the metabolic disturbances of uremia, these patients remain at substantially higher risk of death from cardiovascular and cerebrovascular disease compared with the general population. Thus, it does not appear that hemodialysis can attenuate the risk of vascular disease to any significant extent. While it has been suggested that hemodialysis itself might accelerate arterogenesis, it seems more likely that other risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, play a predominant role in this process. Virtually all our patients who developed stroke could be considered as having been at increased risk for this event, with all but one having hypertension and/or some evidence of cardiovascular disease. Half our patients had diabetes mellitus. Hypertension is well known to be associated with an increased risk of stroke, therefore, it is not surprising that virtually all our patients with stroke had a history of hypertension. Iseki and Fukiyyama have shown in patients undergoing hemodialysis that hypertension is an important predictor of stroke. Therefore, it is clear from the current literature that for patients with renal insufficiency not requiring renal replacement therapy as well...
as patients undergoing hemodialysis, the risk of stroke is significantly greater compared with the general population and it remains the third leading cause of death in these patients.

The present data suggest that the outcome of stroke in patients undergoing hemodialysis may be as good as the outcome in those with normal renal function. While the patients in the control group were slightly older and one might argue that this worsened the outcome in this group, even if the difference in mean age of 5 years were significant, it is doubtful that such a small difference in age would completely negate any difference in stroke outcome that might exist. Given the very high prevalence of preexisting vascular disease in the group of patients undergoing hemodialysis, it seems likely that as a whole this group might be expected to have a worse outcome. Regarding the difference in racial makeup between the groups, it should be noted that the proportion of African American patients in our hemodialysis group is fairly representative of the general population undergoing hemodialysis in the United States. African Americans are also well known for having a higher incidence of end-stage renal disease. Therefore, this difference in racial composition between control and hemodialysis groups is not surprising. Furthermore, given the worse outcome reported for a variety of diseases in African American patients, it seems doubtful that the stroke outcome was as good in the patients undergoing hemodialysis as in the control patients because of a high proportion of African Americans in the hemodialysis group.

While the patients undergoing hemodialysis appeared to have an outcome comparable with that of control patients who had normal renal function, there was a substantially longer period of hospitalization for these patients. Perhaps hospital care for such patients is more complex because of the frequent multitude of associated medical problems that make radiologic testing, drug administration, and other procedures more difficult and hazardous. Many of the patients undergoing hemodialysis developed complications, such as pneumonia, respiratory failure, sepsis, arrhythmia, and other problems, that probably contributed to the longer hospital stay. It would seem that given the reasonably good outcome of stroke in these patients, additional efforts would best be directed at finding interventions that can effectively and safely shorten their length of stay.

Several variables demonstrated fair sensitivity in identifying patients undergoing hemodialysis with a poor outcome after stroke. In our patients factors such as male sex, coronary artery disease, and the presence of hypertension with coronary artery disease and/or congestive heart failure had fairly good sensitivities for identifying poor outcome, although the specificities were low. While more work is needed in large groups of patients undergoing hemodialysis with stroke to find predictors of poor outcome with high sensitivity and specificity, these data suggest that male sex in addition to the presence of atherosclerotic disease of other vascular beds portends a worse outcome.

One somewhat atypical finding in our patients was that, in contrast to the very high proportion of hemorrhagic stroke reported by Iseki et al\(^\text{14,15}\) and Onoyama et al\(^\text{16}\), our population of predominantly African American and white patients undergoing hemodialysis almost always had ischemic stroke. There are certainly reasons for concern that patients undergoing hemodialysis might be at increased risk of hemorrhagic stroke given their platelet dysfunction and need for systemic heparinization. Other reports have also raised fears that hemodialysis might impose an inordinate hemorrhagic stroke risk\(^\text{21-23}\). However, the general Japanese population has a significantly higher risk of hemorrhagic stroke compared with that of US and European populations, an increased risk in some series of as much as 10-fold.\(^\text{21-23}\) By contrast, in the United States about 80% of strokes are ischemic rather than hemorrhagic. Therefore, it is plausible that the differences in the types of strokes experienced by different populations of patients undergoing hemodialysis are a reflection of the types of strokes prevalent in these different populations, although we cannot make definitive inferences regarding this based on our sample size. Furthermore, our findings suggesting comparable outcomes in patients undergoing hemodialysis and in control patients with stroke may have relevance only to hemodialysis populations with a predominance of ischemic stroke.

The percentage of ischemic stroke in our patients undergoing hemodialysis appeared to be somewhat higher than in the general population (92.3% vs approximately 80%). This could be because of the high prevalence of atherosclerotic vascular disease, making a stroke more likely to be due to a vascular occlusive event rather than hemorrhage. However, caution must be exercised given our relatively small sample size. It is also unclear whether a significant difference actually exists because a difference in status of only a few of our patients could substantially change our proportion of ischemic strokes. Nonetheless, our data are consistent with a predominance of ischemic strokes.

If hemodialysis does have a salutary impact on the outcome of stroke, it is not clear by what mechanism this may occur. Among a number of potential mechanisms, amelioration of platelet dysfunction (perhaps limiting the extent of stroke or conversion to hemorrhagic stroke) and control of extracellular fluid volume overload (perhaps lessening the risk of increased intracranial pressure or hemorrhage in contrast to the patient with renal failure who is not receiving dialysis) could minimize the risk of complications related to stroke and therefore improve the outcome, although this is highly speculative. In addition, these mechanisms could potentially lower what otherwise might have been a higher incidence of hemorrhagic stroke in these patients.

If, indeed, patients undergoing hemodialysis have the potential to have an outcome after stroke as patients without renal disease, the question arises whether aggressive therapies, including thrombolytic therapy, are indicated. Our data do not have implications regarding either the safety or efficacy of thrombolytic therapy and further studies are needed to resolve this important issue.
In summary, the present study suggests that while renal insufficiency predisposes to stroke and a poor outcome after stroke, patients undergoing hemodialysis may have the potential to do as well after stroke as patients with normal renal function. Hence, aggressive therapy and rehabilitation efforts in these patients seem indicated, as well as measures to reduce how long they stay in the hospital.

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REFERENCES