Ischemic Stroke among the Patients with End-Stage Renal Disease Who Were Undergoing Maintenance Dialysis

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Purpose: In spite of higher incidence of stroke in end-stage renal disease (ESRD) patients compared to general population, the risk factor for stroke which is specific to ESRD is not fully understood. The ESRD patients who develop stroke may have certain additional risk factors compared to ESRD patients without stroke. We used registered data of Hallym Stroke Registry to elucidate the factors which affect development of ischemic stroke among the dialysis patients. **Materials and Methods:** We recruited patients with acute ischemic stroke in ESRD patients undergoing maintenance dialysis. Dialysis patients without stroke were selected as control group with age and gender matching. We compared the demographic features, stroke risk factors, and laboratory findings in ESRD patients with or without ischemic stroke. **Results:** The total of 25 patients with ESRD developed ischemic stroke. Fifty ESRD patients without stroke were chosen as the control group. The mean age of acute ischemic stroke patients was 59.80±9.94 and male gender was 48%. The most common ischemic stroke subtype was small vessel occlusion (n=12), followed by large artery atherosclerosis (n=7). The patients with stroke had more frequent history of hypertension and higher systolic/diastolic blood pressure at the time of admission than the ESRD patients without stroke. Total cholesterol and LDL-cholesterol levels were significantly lower in the stroke group. In multivariate analysis, LDL-cholesterol was found to be the only risk factor for ischemic stroke. **Conclusion:** The results of our study reveal that LDL-cholesterol is associated with greater risk for ischemic stroke in the patients on dialysis.

Key Words: Cholesterol, hypertension, end-stage renal disease, ischemic stroke

INTRODUCTION

Stroke is one of the most debilitating disorders and carries high level of socioeconomic burden. Korean society has been changing from developing country to developed country and also rapidly changing to the aged society. The high prevalence of stroke is a major concern in Korea, and stroke ranks as one of the leading causes of death along with cancer and ischemic heart disease.[1,2] On the other hand, chronic kidney disease (CKD) is also an another form of end-artery disease and shares many vascular risk factors with stroke in their pathogenesis. Thus, the pa-

tients with CKD, especially end-stage renal disease (ESRD), are prone to develop stroke.[3,4] Several studies have reported a 5- to 10-fold higher stroke risk for hospitalized stroke among the patients undergoing dialysis.[5,6] There are a number of possible explanations for this excessively higher risk for stroke among these CKD patients. Previous studies have demonstrated that traditional risk factors for stroke, such as diabetes, hypertension, cardiac disease, and prior stroke, are much more common among the dialysis population than general population.[7,8] Regarding the enormously elevated incidence of stroke in these patients, traditional risk factors seem to account for much but not all of this excessive risk.[9] Additional factor responsible for the higher stroke rates may be accelerated atherosclerotic vascular disease caused in part by uremia itself, and ESRD may act as an independent factor for development of stroke.[10]

In ESRD, some risk factors of stroke show unusual patterns of contribution in the development of stroke. In a recent study,[11] for example, hypertension, the most important risk factor for stroke showed J-shaped curve of stroke hazard in patients with decreased renal function. The influence of lipid on stroke is still inconclusive in the patients with ESRD.[9,12] Atorvastatin failed to show effectiveness on prevention of stroke in those patients who are undergoing hemodialysis (HD).[13]

In spite of higher incidence of stroke in dialysis patients than general population, the risk factor for stroke which is specific to dialysis patients is not fully understood. The patients with ESRD who develop stroke may have certain additional risk factors compared to ESRD patients without stroke. Moreover, strokes in patients with ESRD are known to have peculiar clinical conditions and laboratory findings.[14] We used data collected by the Hallym Stroke Registry (HSR) to identify patient characteristics associated with acute ischemic stroke in ESRD patients who underwent dialysis, with special concern on risk factors and stroke pattern.[15]

MATERIALS AND METHODS

This study is a retrospective case-controlled clinical study, and has been reviewed and approved by the Institutional Review Board of Hallym University Medical Center (HUMC), Seoul, Korea. From July 2003 to June 2007, we evaluated 1013 consecutive patients with acute stroke who were admitted to the Stroke Unit at Kangnam Sacred Heart Hospital (an affiliated hospital of HUMC) and who were registered

in the HSR. Among these stroke patients who registered in the HSR, we selected the patients who developed acute ischemic stroke and underwent maintenance dialysis as the stroke group. Dialysis patients who had never developed stroke were chosen as the control group (non-stroke group) with age and gender adjustment. We classified the patients with acute stroke according to the modified Trial of Org 10172 in Acute Stroke Treatment classification and evaluated their neurological manifestations, clinical outcomes, and radiologic findings on magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA).[16] To evaluate clinical outcome, we assessed in-hospital mortality and the National Institutes of Health Stroke Scale (NIHSS) score at the time of admission and discharge. We defined clinical improvement as a decrease of three or more points in NIHSS score, and clinical worsening as an increase of two or more points of NIHSS score during the hospitalization.

We also compared the characteristics of patients of the stroke group to those of the non-stroke group. Evaluated characteristics of both groups included demographic factors, laboratory findings, clinical findings (cause of the renal disease, type of the dialysis treatment and the duration of dialysis) and other measurements including height, weight, body mass index, initial blood pressure, hemoglobin, albumin, blood urea nitrogen, creatinine and lipid profiles.

All data were expressed as mean±standard deviation or median. Statistical analysis was conducted using chi-square and paired t-test for univariate test appropriately. We also performed conditional logistic regression analysis to find out independent factors for the development of stroke in the ESRD patients. p values less than 0.05 were accepted as statistically significant.

RESULTS

During the recruitment period, total 1013 of acute stroke patients were registered to the HSR. Among them, 25 patients with acute ischemic stroke had been diagnosed as having the ESRD. All the ESRD patients had been undergoing dialysis. Nineteen patients were on HD and 6 patients were on peritoneal dialysis. Fifty ESRD patients without stroke were chosen as the control group who were vitally stable with maintaining dialysis. All of the control group were HD patients and most cases were admitted for arteriovenous fistula operation.

The demographic factors of both ESRD groups (stroke

vs. non-stroke) are shown in Table 1. The mean age of the stroke group was 59.80±9.94 years (range: 44-82) and male gender was 48%. The most common underlying cause for stroke with the ESRD patients was combined hypertension and diabetes mellitus (n=15), followed by hypertension in 8 and diabetes in 2. Underlying diseases of the non-stroke ESRD patients were combined hypertension and diabetes in 17, hypertension in 15, diabetes in 10, and primary glomerulonephritides and others were found in 8 patients. The percentages of patients who had been taking aspirin, statin and various types of anti-hypertensive agents are also listed, and there were no significant differences between the stroke group and the non-stroke group.

There were significant differences between the two groups in the presence of hypertension history and initial systolic/diastolic blood pressures. The stroke patients also had higher frequency of hypertension history (92% vs. 64%, $p=0.01$) and showed higher systolic blood pressure (169.20±34.75 vs. 148.20±23.88 mm Hg, $p=0.003$) and diastolic blood pressure (98.00±18.03 vs. 87.60±10.41 mm Hg, $p=0.003$) at the time of the admission. Total cholesterol ($p=0.006$) and low-density lipoprotein (LDL)-cholesterol ($p<0.001$) were significantly lower in the stroke group.

Otherwise, no remarkable results were found in the laboratory tests (Table 2).

To evaluate the correlation between stroke development and various conditions of ESRD, we conducted multivariate logistic regression analysis. Although several factors were significant in univariate analyses, lower level of LDL-cholesterol was a risk factor which was associated with the development of stroke (odds ratio=0.956, 95% confidence interval 0.926-0.986, $p=0.004$) (Table 3). Although the clinical meaning of relationship was weakened because of marginal statistical significance, the relationship between the development of stroke and LDL-cholesterol level showed reverse correlation compared to general population.

Clinical properties and neuro-radiological features of infarctions in ESRD are shown in Table 4. The most common type of ischemic stroke in the patients with ESRD was small vessel occlusion (SVO, n=12), followed by large artery atherosclerosis (LAA, n=7) and stroke of undetermined etiology (n=6). Motor weakness was the most common neurological manifestation (n=16), followed by sensory symptoms (n=9). Other symptoms and signs were dysarthria, dizziness, ataxia, dysmetria, eyeball deviation and seizure etc. Regional distribution of lesions is also shown in Table 4. Lesions of

Table 1. Demographic Properties of Patients with ESRD with or without Ischemic Stroke

	ESRD with ischemic stroke (n=25)	ESRD without stroke (n=50)	p value
Age (yrs, range)	59.80 (44-82)	61.00 (39-83)	0.644
Age >60 yrs (%)	13 (52.0)	25 (50.0)	0.809
Male gender (%)	12 (48.0)	24 (48.0)	1.000
Duration of dialysis (yrs)	3.30±2.63	2.10±2.30	0.055
Weight (kg)	61.49±8.45	58.18±9.93	0.171
BMI (kg/m²)	24.10±3.73	22.70±3.14	0.101
SBP at admission (mm Hg)	169.20±34.75	148.20±23.88	0.003*
DBP at admission (mm Hg)	98.00±18.03	87.60±10.41	0.002*
Smoking (%)	9 (36.0)	12 (24.0)	0.271
Hypertension (%)	23 (92.0)	32 (64.0)	0.012*
Diabetes mellitus (%)	17 (68.0)	27 (54.0)	0.322
Hyperlipidemia (%)	9 (36.0)	19 (38.0)	0.999
Cardiac embolism (%)	1 (4.0)	0 (0.0)	0.999
Statin (%)	9 (36.0)	10 (20.0)	0.164
Aspirin (%)	15 (60.0)	30 (60.0)	1.000
ACEI/ARB	15 (60.0)	19 (38.0)	0.088
Calcium channel blocker	15 (60.0)	28 (56.0)	0.808
Beta blocker	10 (40.0)	18 (36.0)	0.803
Diuretics	11 (44.0)	26 (52.0)	0.626
Anti-coagulants	0 (0.0)	0 (0.0)	1.000

BMI, body mass index; n, number of patients; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease.
*$p<0.05$.

Table 2. Comparison of Laboratory Data among the Patients with ESRD with and without Ischemic Stroke

	ESRD with ischemic stroke (n=25)	ESRD without stroke (n=50)	p value
White blood cell (/mm^3)	7689±3182	7032±2759	0.359
Hemoglobin (g/dL)	9.45±1.54	9.82±1.20	0.266
Hematocrit (%)	28.09±4.36	29.26±3.71	0.229
Total cholesterol (mg/dL)	142.83±30.80	173.38±47.58	0.006*
HDL-cholesterol (mg/dL)	34.55±12.84	36.09±10.30	0.596
Triglyceride (mg/dL)	138.27±71.73	143.13±121.15	0.863
LDL-cholesterol (mg/dL)	76.95±24.67	109.11±35.50	<0.001*
aPTT (sec)	33.87±4.56	33.83±6.68	0.980
Prothrombin time (INR)	1.03±0.09	1.01±0.14	0.393
Fasting blood sugar (mg/dL)	134.36±77.21	176.45±82.70	0.052
HbA1C (%)	6.35±0.93	6.86±1.42	0.288
Albumin (g/dL)	3.40±0.39	3.58±0.61	0.178
Total protein (g/dL)	6.34±0.83	6.29±0.50	0.787
Blood urea nitrogen (mg/dL)	57.69±36.34	69.79±35.12	0.169
Creatinine (mg/dL)	8.03±3.08	8.18±3.10	0.846

HDL, high density lipoprotein; LDL, low density lipoprotein; aPTT, activated partial thromboplastin time; INR, internatinal normalized ratio; ESRD, end-stage renal disease.
*$p<0.05$.

Table 3. Risk Factors of Ischemic Stroke in ESRD Patients

Variables	Odds ratio (95% CI)	p value
Age >60 yrs	0.954 (0.229-3.983)	0.949
Duration of dialysis (per months)	1.026 (1.000-1.052)	0.053
SBP at admission (per 10 mm Hg)	0.948 (0.654-1.374)	0.779
DBP at admission (per 10 mm Hg)	1.889 (0.829-4.301)	0.130
Blood urea nitrogen	1.002 (0.982-1.023)	0.817
LDL-cholesterol	0.956 (0.926-0.986)	0.004*

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; CI, confidence interval; ESRD, end-stage renal disease.
*$p<0.05$.

anterior circulation were found in 17 patients, and those of posterior circulation were found in 6 patients. Two patients had lesions on both circulations.

The NIHSS at the time of admission and discharge were 5.33±3.08 and 3.58±1.93, respectively. The average hospital stay was 22.6±19.78 days. Two patients (8%) expired due to sepsis and transtentorial herniation resulting from increased intracranial pressure, and the others were discharged either in clinically improved (n=17, 68%) or unchanged state (n=6, 24%).

DISCUSSION

This study is based on the HSR which is a Korean multi-hospital based stroke registry. While a community-based stroke study gives valid epidemiological information of stroke, a hospital-based study such as the HSR can provide more precise clinical information, accurate classification of stroke and proper etiologic mechanisms.[17] Although previous studies performed with HD patients focused on the higher incidence of stroke, including cerebral hemorrhage in HD patients compared to general population,[18,19] we analyzed the risk factors and clinical findings of cerebral infarction in the ESRD patients and also tried to elucidate the factors which can affect the development of ischemic stroke in ESRD which may act as an independent risk factor for stroke. Among the stroke patients with ESRD, we chose only the ischemic stroke patients because some factors are known to affect the development of stroke whether it is ischemic or hemorrhagic.[20,21]

The stroke patients in this study had significantly more frequent history of hypertension and showed higher systolic/diastolic blood pressure at the time of admission. Even though elevated initial blood pressure in stroke patients might be attributable to stroke itself, more common history

Table 4. Summary of Characteristics of Stroke in ESRD (n=25)

Parameters	
Stroke subtypes (%)	
Large artery atherosclerosis	7 (28)
Small vessel occlusion	12 (48)
Stroke of undetermined etiology	6 (24)
Stroke of other determined etiology	0 (0)
Cardioembolism	1 (4)
Neurological outcomes	
Average hospital stays (days)	22.6±19.78
Motor weakness (%)	16 (64)
Motor power (grade/5)	3.71 (upper)/3.82 (lower)
Sensory change (%)	9 (36)
Babinski sign (%)	6 (24)
Increased deep tendon reflexes (%)	4 (16)
NIHSS (points)	5.33±3.08 (admission) 3.58±1.99 (discharge)
Distribution of infarcts	
Anterior circulation (%)	17 (68)
Posterior circulation (%)	6 (24)
Both (%)	2 (8)
Location of infarcts	
MCA territory (%)	6 (24)
ACA territory (%)	1 (4)
Basal ganglia (%)	7 (28)
Pons (%)	3 (12)
Thalamus (%)	2 (8)
Internal capsule (%)	2 (8)
Cerebellum (%)	1 (4)
Corona radiate (%)	1 (4)
Multi-lacunes (%)	2 (8)

ESRD, end-stage renal disease; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ACA, anterior cerebral artery.

of hypertension in stroke group suggests a critical role of hypertension in the development of ischemic stroke among the ESRD patients. It is consistent with the data from general population, in which the elevated blood pressure was associated with an increased risk for stroke.[22] Thus, our result did not support the U- or J-shaped association of blood pressure with the incidence of stroke which was shown in the previous studies conducted in chronic kidney disease patients.[11]

Our results show some similarities and discrepancies with the previous reports. Age, race, comorbid conditions, diabetes mellitus, and previous stroke were associated with increased risk of cerebrovascular events in the CHOICE study.[23] Whereas the history of hypertension and higher blood pressure was associated with the development of stroke in the ESRD patients,[10,19] anemia which was previ-

ously shown in ARIC study[24] was not a significant risk factor for stroke in our ESRD patients.

A Japanese study found markedly increased incidence of strokes in the vertebrobasilar system,[19] however, our study showed more common stroke events in the territories supplied by the anterior circulation. The HSR revealed less common ischemic stroke in the posterior circulation (39.8%) in general population.[25] On the other hand, SVO was the most common subtype of stroke classification, which was different from the result of general population in the HSR. The most common type in the HSR was LAA followed by SVO. This difference may be due to micro-inflammatory change of small vessel of the ESRD patients associated with malnutrition, as indicated previously.[19]

In our study, lower level of total cholesterol and LDL-cholesterol were found in the patients with ischemic stroke. It is opposite to the studies performed in general population. Various studies indicate that low LDL-cholesterol level may have certain relationship with the development of cerebral hemorrhage,[20] and high LDL-cholesterol is associated with increased incidence of ischemic stroke.[26] Thus, the underlying mechanism is not yet clearly understood. Low cholesterol levels may increase the incidence of hemorrhagic stroke, possibly through disturbed integrity of endothelial cells in intracranial small vessels.[27]

The association between ischemic stroke and low LDL-cholesterol level of dialysis patients has not been discovered. Many patients with ESRD are malnourished and have chronic inflammation. It is, therefore, possible that the mechanism which leads to the association of inflammation and stroke in general population[28] exerts a similar effect in the dialysis population and might explain the observed association between malnutrition and stroke in the present study. However, none of inflammatory markers were associated with stroke risk in the CHOICE study.[29]

There should be some caution in interpretation of positive relationship between blood pressure and ischemic stroke. It is possible that the effects of blood pressure were confounded by the use of anti-hypertensive medications. In our study, however, the patients in both groups regularly underwent dialysis and had similar opportunities for the control of hypertension. Although high systolic and diastolic blood pressure in the stroke group might be the effect of stroke itself, more frequent history of hypertension may be more important in the interpretation of the relationship between hypertension and ischemic stroke among the ESRD patients.[30]

All patients with ischemic stroke should have risk factors

controlled. The 2011 American Heart Association/American Stroke Association recommend blood pressure reduction, anti-platelet therapy and statins in patients with an ischemic stroke.[31] In patients with hyperlipidemia, statin therapy decreases the risk of stroke, but hypercholesterolemia is not a strong risk factor for stroke. Therefore, it seems plausible that the protective effects of statins are not mediated by cholesterol lowering, but rather by anti-atherothrombotic properties.[32] Other strategies include glucose control in diabetes patients, smoking cessation, oral anticoagulation in patients with cardiac embolism, and endarterectomy in patients with carotid artery stenosis. Nevertheless, there are no guidelines on prevention of stroke in patients with chronic kidney disease. Especially in hemodialysis patients, warfarin should be used very cautiously due to increased hemorrhagic stroke.[33]

There are several limitations in our study. Because of its retrospective design, we were unable to perform well controlled, blinded study. Moreover, relatively small size of the patients could prevent us from drawing conclusion that LDL cholesterol has the protective effect for stroke in the patients with ESRD. We also did not evaluate the inflammatory markers such as high-sensitivity C-reactive protein and interleukin-6. Well-controlled prospective study with large size of subjects should be performed to draw more relevant conclusion in the future.

In conclusion, we found that the history of hypertension and the levels of systolic/diastolic blood pressure are important in the development of ischemic stroke in the ESRD patients. Especially, low LDL-cholesterol was the only risk factor for ischemic stroke. The stroke subtype classification also has a preference for small vessel disease in our ESRD patients, showing a different pattern from that of Korean general population.

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