Ischemic Stroke in Patients with Renal Transplantation

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<ABSTRACT>

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Impaired renal function may contribute to development of stroke and small vessel pathology in the brain. We investigated whether stroke subtype, initial stroke severity, early neurologic outcomes, time to cerebral infarction occurrence, and the presence of small vessel pathology in the brain are different between patients with end stage renal disease (ESRD) receiving dialysis treatment (DT) and those with renal transplantation (RT). From January 1995 to January 2011, a total of 57 consecutive RT patients (RT group) and 120 patients undergoing dialysis treatment due to ESRD (DT group) who developed a first-ever acute cerebral infarction were enrolled. We compared stroke subtypes, presence of small vessel pathology on MRI, stroke severity based on the National Institutes of Health Stroke Scale (NIHSS) and in-hospital mortality between the groups. The stroke subtypes, NIHSS scores at

admission and in-hospital mortality were not different between the two groups. On multivariate analysis, the presence of high grade periventricular white matter changes tended to be more frequently detected in the DT group than the RT group (p=0.078). The stroke patterns, severity and short term outcomes were not different between RT and DT groups. The risk of cerebral infarction and high grade periventricular white matter changes may be reduced after RT in patients with ESRD.

Key words: renal transplantation, end stage renal disease, stroke, cerebral infarction, cerebral microbleeds, leukoaraiosis

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I. INTRODUCTION

Cerebral infarction occurs often in patients with end stage renal disease (ESRD).[1] Most patients with ESRD who are treated with hemodialysis (HD) have classic risk factors for ischemic stroke,[2] and HD itself is an independent risk factor for stroke.[2] Patients who are treated with continuous ambulatory peritoneal dialysis (CAPD) may have a greater risk of ischemic and hemorrhagic strokes because high blood pressure is often less well controlled due to excessive hydration during CAPD.[3] Cerebral small vessel pathology including silent lacunar infarction (SLI),[4] leukoaraiosis (LA),[5] and cerebral microbleeds (CMBs)[6] were reported as being associated with impaired renal function possibly due to the hemodynamic similarities between the vascular beds of the kidney and those of the brain.[7]

Renal transplantation (RT) is the best treatment for overcoming many clinical

problems associated with ESRD. Endothelial vascular damage and oxidative stress, which are caused by renal dysfunction and uremic toxin, are decreased after RT. Arterial stiffness, which is associated with small artery disease and intracranial cerebral atherosclerosis,[8] is improved.[9,10] Additionally, the risk for vascular events is decreased in RT recipients with sustained graft function.[11] However, underlying vascular risk factors may be present in spite of RT, and the immunosuppressive agents that are used in patients with RT may aggravate vascular diseases and hypertension through catecholamine-related vasoconstriction.[12] Therefore, RT may both positively and negatively affect stroke occurrence and outcomes.

Considering that impaired renal function is associated with small vessel disease and that the renal function can be improved after RT, stroke types, small vessel pathologies and outcome may be different between received RT and continuing dialysis treatment (DT). There have been several reports on the characteristics, incidence and classification of cerebral infarction in patients with ESRD [2,13,14] and RT.[15-19] However, no study has investigated differences in stroke type and outcomes between RT and DT patients. The aim of this study was to compare stroke subtype, initial stroke severity and early neurologic outcomes between these groups. We also investigated whether the frequency of small vessel pathologies such as CMBs, SLI, and LA are different between the groups.

II. MATERIALS AND METHODS

1. Subjects

We retrospectively reviewed medical records of patients treated with dialysis (HD or CAPD) or those who received a first renal transplantation between January 1995 and January 2011 at a single university hospital. Among the 2,321 patients who received a renal transplantation, 57 patients were identified as having a first-ever acute cerebral infarction. Among the 6,999 ESRD patients treated with HD or CAPD during the same study period, 120 patients with a first-ever acute cerebral infarction were identified. All enrolled patients were confirmed as cerebral infarction by brain CT and/or magnetic resonance image. Patients with transient ischemic attack were excluded. This study was approved by the Severance Hospital Institutional Review Board of the Yonsei University Health System.

2. Demographic and laboratory data collection

Demographic characteristics, laboratory findings, and time intervals from the initiation of dialysis or RT to stroke onset were compared between patients with RT (RT group) and those undergoing dialysis due to ESRD but who did not receive RT (DT group). The stroke subtype was determined based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification[20] based on a neuroradiologist's report and the consensus of stroke specialists. Severity of neurologic deficits was determined using the National Institutes of Health

Stroke Scale (NIHSS) at admission. Data for in-hospital mortality was obtained from medical records.

3. Definition of small vessel disease and silent lacunar infarction

Small artery pathologies were evaluated using MRI. CMBs were defined as punctuate hypointense lesions less than 10 mm in size on gradient echo (GRE) MRI images, which were based on previously reported methods.[21] Silent lacunar infarction (SLI) was defined when a small (<15 mm) lesion in the perforating artery territory showed a high signal intensity on fluid attenuated inversion recovery (FLAIR) or T2 weighted and iso- or low signal intensity on T1 weighted image.[22] We also assessed the severity of LA. The extents of LA in the periventricular white matter (PVWM) and deep white matter (DWM) were determined on the FLAIR images according to the Fazekas' scoring system.[23] Briefly, LA in PVWM was categorized as: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; and grade 3, irregular PVWM extending into DWM. LA in DWM was categorized as: grade 0, absent; grade 1, punctuate foci; grade 2, beginning confluence of foci; and grade 3, large confluent areas. PVWM and DWM changes were dichotomized into high grade (2 – 3) or low grade (0 – 1) LA.

4. Definition of risk factors

Hypertension was diagnosed when a patient had been taking anti-hypertensive

medication or had resting systolic blood pressures ≥140 mmHg or diastolic blood pressures ≥90 mmHg on repeated measurements. Diabetes mellitus was diagnosed if the patient had fasting blood glucose ≥7.0 mmol/L or was being treated with anti-diabetic medications or insulin. Hyperlipidemia was diagnosed if the patient had low-density lipoprotein cholesterol ≥4.1 mmol/L, total cholesterol ≥6.2 mmol/L, or if the patient was treated with lipid lowering agents after diagnosis of hyperlipidemia. Patients were defined as smokers if they were current smokers or had stopped smoking within one year prior to the index ischemic stroke.

5. Statistical analysis

Statistical analysis was performed with SPSS (version 18.0, SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation and categorical variables were reported as frequency and percentage. The variables were compared by independent t-tests, Chi-square tests, or Fisher's exact test, as appropriate. A two-tailed value of $P < 0.05$ was considered significant. Adjusting the age and sex factors, variables with $P < 0.1$ in the univariate analysis were entered for multivariate binary logistic regression analyses were performed to determine independent factors for cerebral small vessel pathologies.

III. RESULTS

1. Comparison of demographic characteristics

The demographic data is shown in Table 1. When compared with the RT group, the DT group was older, more frequently female, and had higher creatinine levels. Previous use of statins and hemodialysis were more frequently observed in the RT group. The cause of renal disease was different between the two groups in that hypertensive and diabetic nephropathy were more frequently observed in the DT group while glomerulonephritis was more frequently observed in the RT group (Table 1).

Table 1. Demographic data of enrolled patients.

	RT (n=57)	DT (n=120)	*P* value
Sex, male	43 (75.4)	63 (52.5)	0.005
Age, years	53.8 ± 9.2	61.1 ± 12.3	0.001
Risk factors			
Hypertension	54 (94.7)	108 (90.0)	0.392
Diabetes mellitus	36 (63.2)	76 (63.3)	0.982
Atrial fibrillation	7 (12.3)	24 (20.0)	0.290
Dyslipidemia	29 (50.9)	49 (40.8)	0.209
Smoking	13 (22.8)	19 (15.8)	0.260
Coronary artery occlusive disease	14 (24.6)	53 (44.2)	0.012
Previous statin use	39 (68.4)	46 (38.3)	0.001

Previous antiplatelet medication	15 (26.3)	58 (48.3)	0.006
Hemodialysis	48 (84.2)	67 (56.8)	0.001
Serum creatinine level, mg/dL	1.6 ± 1.2	7.0 ± 2.4	0.001
Serum albumin level, mg/dL	3.7 ± 0.7	3.8 ± 0.7	0.399
Causes of end stage renal disease			0.004
Diabetic nephropathy	27 (47.4)	68 (56.7)	
Hypertensive nephropathy	11 (19.3)	40 (33.3)	
Glomerulonephritis	12 (21.1)	10 (8.4)	
Eclampsia	3 (5.3)	0 (0.0)	
Tuberculous nephritis	2 (3.5)	0 (0.0)	
APCKD	1 (1.8)	1 (0.8)	
Drug induced	1 (1.8)	1 (0.8)	

Data are shown as mean ± standard deviation or number (%). RT: renal transplantation, DT: dialysis treatment, APCKD: adult polycystic kidney disease

2. Comparison of clinical characteristics

The results of comparison for clinical characteristics are shown in Table 2. In the RT group, the mean time interval from starting dialysis to stroke onset was 129.9 ± 60.9 months, and that from RT to stroke onset was about 102.2 ± 60.3 months. These intervals were significantly longer than that in the DT group (51.1 ± 46.1 months) (Table 2).

Table 2. Comparison for the time interval for stroke onset.

	RT (n=57)	DT (n=120)	*P* value
Time interval from ESRD, months	129.9 ± 60.1	51.1 ± 46.1	0.001
Time interval from RT, months	102.2 ± 60.3		

Data are shown as mean ± standard deviation. RT: renal transplantation, DT: dialysis treatment, ESRD: end stage renal disease

3. Comparison of stroke subtypes

Large artery atherosclerosis was most common in the RT group (31.6%) and small vessel occlusion was most common in the DT group (26.7%); however, there was no statistical difference between the two groups (Table 3).

Table 3. Comparison for stroke subtypes.

TOAST classification	RT (n=57)	DT (n=120)	*P* value
			0.070
Large artery atherosclerosis	18 (31.6)	25 (20.87)	
Cardioembolism	11 (19.2)	30 (25.0)	
Small vessel occlusion	10 (17.5)	32 (26.7)	
Undetermined negative	12 (21.1)	25 (20.8)	
Multiple causes	3 (5.3)	8 (6.7)	
Undetermined incomplete	3 (5.3)	0 (0.0)	

Data are shown as number (%).TOAST: trial of Org 10172 in Acute Stroke Treatment, RT: renal transplantation, DT: dialysis treatment

4. Comparison of small vessel pathology

Brain MRI was performed in 160 (90.3%) patients [52 (91.2%) patients in the RT group and 108 (90.0%) patients in the DT group]. GRE images were available in 124 (70.0%) patients [44 (77.1%) patients in the RT group and 80 (66.7%) in the DT group]. On univariate logistic analysis, ESRD (p=0.018), high grade DWM changes (p=0.001), SLI (p=0.001), CMBs (p=0.001), older age (p=0.002) and diabetes mellitus (p=0.021) were associated with high grade PVWM changes (Table 4).

Table 4. Comparison for small vessel pathologies.

Imaging findings	RT (n=57)	DT (n=120)	*P* value
High grade PVWMC	18 (34.6)	60 (55.6)	0.018
High grade DWMC	17 (32.7)	52 (48.1)	0.088
Silent lacunar infarction	22 (42.3)	64 (59.3)	0.062
Cerebral microbleeds	5 (11.4)	23 (28.8)	0.042

Data are shown as number (%). RT: renal transplantation, DT: dialysis treatment, PVWMC: periventricular white matter change, DWMC: deep white matter change

5. Multivariate analysis for small vessel pathology

On multivariate analysis, SLI and CMBs were not entered because of their multicollinearity with LA. After adjusting for sex and significant factors on univariate analysis, ESRD tended to be associated with high grade PVMW changes (p=0.078) (Table 5).

Table 5. Factors associated with periventricular white matter changes.

	High grade PVWM change	
	OR (95% CI)	*P* value
Sex, male	0.987 (0.500 – 1.950)	0.970
Age, years	1.043 (1.010 – 1.078)	0.011
Diabetes mellitus	2.585 (1.277 – 5.233)	0.008
ESRD	1.962 (0.962 – 4.155)	0.078

PVWM: periventricular white matter, OR: odds ratio, CI: confidence interval, ESRD: end stage renal disease

6. Comparison of neurologic severity and outcomes

The NIHSS scores at admission did not differ between the RT (median 3 [2 – 8] and DT (median 3 [1 – 7]) groups (p=0.565). In-hospital mortality (12 patients in RT versus 16 patients in DT, p=0.194) also did not differ between the two groups.

IV. DISCUSSION

This study showed that the high grade PVWM changes tended to be more frequently detected in DT patients than in RT patients. Our findings, along with findings in previous studies, suggest that impaired renal function is associated with small vessel pathology in the brain,[4-6] and its risk may be reduced when

renal function is improved by RT. Arterial stiffness, which is associated with vessel wall damage in the microvessels of the end-organs and intracranial artery atherosclerosis, improved after RT.[9,24] RT can improve endothelial dysfunction induced by a state of continuous renal dysfunction because uremic toxins cause oxidative stress on vasculature, endothelial damage, and acceleration of atherosclerosis.[10,25] Those changes may underlie a decreased risk of small vessel pathologies following RT in ESRD patients.

The incidences of stroke and cardiovascular disease were lower in the RT group than the DT group.[26,27] Renal dysfunction increases the risk of ischemic and hemorrhagic stroke in the general population.[28] Function of kidney on admission appears to be a significant independent prognostic factor for long term mortality and new cardiovascular morbidity.[29] In contrast, RT with sustained graft function seems to reduce the risk for stroke.[11] In this regard, recovery of renal dysfunction following RT could reduce the risk of stroke. The time from starting dialysis to stroke onset was longer in the RT group than in the DT group in our study. The longer time interval in the RT group might be related to the reduced risk of stroke following RT in patients with ESRD.

In our study, there were no differences in initial stroke severity and in-hospital mortality after stroke between the two groups. These findings suggest that stroke severity as well as short term outcomes were not substantially affected by

renal transplantation and recovery of renal dysfunction, although stroke onset could be delayed. Renal dysfunction is associated with more severe stroke at admission and is a strong negative predictor of 30-day survival after acute ischemic stroke.[30,31] Although renal transplantation may improve clinical outcomes by improving renal and endothelial function,[10] which may positively affect stroke severity, the use of immunosuppressive agents may produce neurotoxicity,[24] which may offset the protective effect of RT. The small sample size in our study may be in part responsible for the absence of differences between the groups.

Our study has limitations. First, the size of population of our study was not large, which might be due to few events of cerebral infarction in both RT and dialysis patients. Therefore, all subtypes of stroke might not be represented sufficiently for the purpose of our study which includes comparison of the differences in occurrence of stroke subtypes between the groups. Second, although the longer time intervals from starting dialysis to stroke onset in the RT group in our study were speculated to be associated with a reduced risk of stroke after RT, the incidence of stroke could not be investigated by our study design. Therefore, our speculation regarding this issue is inconclusive and further studies may be necessary to determine whether RT is protective for stroke.

V. CONCLUSION

The stroke patterns, severity and short term outcomes were not different between RT and DT groups. The risk of cerebral infarction and high grade periventricular white matter changes may be reduced after RT in patients with ESRD.

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<국문요약>

신장이식환자에서 발생하는 뇌경색증

<지도교수 허지회>

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송태진

신장기능의 이상은 뇌경색증 및 소혈관질환 (백질변성, 미세출혈 또는 무증상 열공성 뇌경색) 발생과 밀접한 관련이 있다. 본 저자들은 신장이식을 받은 환자와 투석치료중인 말기신장질환 환자 사이에 뇌경색증 및 소혈관질환의 특성에 차이가 있는지와, 뇌경색증 이후의 예후는 어떠한지에 대하여 비교연구를 진행하였다. 1995년 1월부터 2011년 1월까지 세브란스병원에 입원하였던 뇌경색증 환자들 중 신장이식을 받은 환자 57명과 투석치료중인 말기신장질환 환자 120명을 선별하여 후향적 연구방법으로 조사하였다. 결과적으로, 뇌경색증의 아형, 입원 당시의 뇌경색증의 중증도, 원내 사망률은 신장이식을 받은 환자군과 투석치료중인 말기신장질환 환자군 사이에 차이가 없었으나, 소혈관질환은 투석치료중인 말기신장질환 환자군에서 더 흔

하게 관찰되었다. 또한 소혈관질환 중 뇌실 옆 백질변성의 경우는 다변량 분석에서도 투석치료중인 말기신장질환이 연관되어있는 경향성을 보였다 (p=0.078). 결론적으로, 본 연구의 결과는, 신장이식을 받은 환자군과 투석치료중인 말기신장질환 환자군 사이에 뇌경색증의 아형, 입원당시의 중증도, 원내 사망률에는 차이가 없으나 신장이식을 받게 되면 뇌경색증 및 소혈관질환의 발생가능성이 감소할 가능성이 있음을 시사한다.

핵심되는 말 : 신장이식, 말기신장질환, 뇌졸중, 뇌경색증, 소혈관질환, 백질변성, 미세출혈, 무증상 열공성 뇌경색