Clinical risk factors predictive of thrombotic stroke with large cerebral infarction

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Abstract

Large cerebral infarctions have high morbidity and mortality. Patients with large cerebral infarctions may have recurrent ischemia as high as 8.1% within 7 days; highest among other types of strokes. Data regarding risk factors for large cerebral infarction in Asian populations are still scant. All adult (age ≥15 years old) patients with the diagnosis of thrombotic ischemic stroke who were treated at Srinagarind Hospital, Khon Kaen University, Thailand from January 2012 to December 2013 were studied. Large cerebral infarctions are defined by clinical criteria of having cerebral cortical impairment, brain stem or cerebellar dysfunction with infarction sizes of more than 1.5 cm. The association of various stroke risk factors and large infarction strokes were calculated using multiple logistic regression analysis. There were 276 thrombotic stroke patients who met the study criteria; classified as large cerebral infarctions in 59 patients (21.38%) and small cerebral infarctions in 217 patients (78.62%). Baseline characteristics and risk factors for stroke were comparable between both groups. The large cerebral infarction group had a significantly larger proportions of right internal carotid artery stenosis, plaques on the left side, left internal carotid artery stenosis, and internal carotid artery stenosis at any side than the small cerebral infarction group. Among various stroke risk factors, only internal carotid artery stenosis at any side was the only significant factor associated with large cerebral infarction with an adjusted odds ratio of 11.14 (95% CI: 3.46, 35.82). In conclusion, significant internal carotid artery stenosis is associated with large cerebral infarction.

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Introduction

Approximately 6.7 million patients died from stroke in 2012 worldwide and it ranked as the second leading cause of death after ischemic heart disease.[1] It is also the leading cause of death in Thailand for both males (9.4%) and females (11.3%).[2] According to the Trial of Org 10172 in Acute Stroke Treatment classification, ischemic stroke can be defined as large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.[3]

Large cerebral infarction causes high mortality and severe disability. Patients with large cerebral infarctions may have recurrent ischemia as high as 8.1% within 7 days; highest among other types of stroke.[4] A study from Germany showed that factors associated with large cerebral infarction were male gender (66.2%), smoking (37.6%), and alcohol consumption (14.7%).[4] Data regarding risk factors for large cerebral infarctions in the Asian population are still scant. This study aimed to determine clinical risk factors predictive of thrombotic strokes with large cerebral infarctions in the Thai population.

Materials and Methods

The study was conducted at Srinagarind Hospital, Khon Kaen University, Thailand between January 2012 and December 2013. All adult stroke patients (aged more than 15 years) and admitted to the stroke unit were retrospectively reviewed. Patients were excluded if the final diagnosis were transient ischemic attack, cardioembolic stroke, or hemorrhagic stroke.

Eligible patients were classified into two groups; large and small infarction strokes by clinical criteria as follows. Large cerebral infarctions were defined by any of the following: cerebral cortical impairment apparent as aphasia, neglect, restricted motor involvement, etc.; brain stem or cerebellar dysfunction; brain imaging findings showed cortical, cerebellar, brain stem, or subcortical hemispheric infarction greater than 1.5 cm in diameter on computer tomography or magnetic resonance imaging. The small cerebral infarctions were defined by clinical syndromes of lacunar infarction without evidence of cerebral cortical dysfunction plus normal computer tomography/ magnetic resonance imaging or relevant brain stem or subcortical hemispheric lesions with a diameter of less than 1.5 cm in diameter.

Baseline characteristics of all eligible patients were retrieved from medical records and admission notes. Risk factors of stroke were also recorded including hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, coronary artery disease, and tobacco smoking. Laboratory results including carotid duplex ultrasound and imaging of the brain were also recorded.

Risk factor definition

Hypertension was defined as history of elevated blood pressure >140/90 mm Hg at 2 independent readings before stroke or when on antihypertensive medication.[5] Diabetes mellitus was defined by the presence of the following findings: fasting plasma glucose more than or equal to 126 mg/dL on two occasions, HbA1C more than or equal to 6.5% on two occasions, or random plasma glucose more than or equal to 200 mg/dL plus clinical evidence of hyperglycemia before the stroke or on antidiabetic medication.[6] Dyslipidemia was defined by the presence of any following findings; total cholesterol more than 200 mg/dL, low density lipoprotein more than 100 mg/dL, or high density lipoprotein less than 40 mg/dL at 2 independent readings before stroke or on lipid-lowering medication.[7]

Carotid duplex ultrasound parameters

Carotid duplex ultrasonography data included carotid intimal thickness, plaque formation, degree of internal carotid stenosis according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[8] Carotid plaques were defined as local thickening of carotid intimal–media thickness of more than 50 % compared to the surrounding vessel wall. Significant internal carotid artery (ICA) stenosis was classified as stenosis above 70 percent measured by carotid duplex ultrasonography and magnetic resonance angiography was used to confirm the location and severity of the lesions in this subgroup of patients.

Statistical analyses

Descriptive statistics were used to detect significant differences between large and small cerebral infarction. The Wilcoxon rank sum test was used for comparison of the group median values expressed as continuous variables. The Fisher exact test was used to compare categorical variables between groups.

Univariate logistic regression analysis was applied to calculate the crude odds ratios (ORs) of individual variables for large cerebral infarction. All variables with a P<0.20 in univariate analysis or those that were clinically significant were included in subsequent multivariate logistic regression analyses. The final model was composed of factors associated with large infarction stroke. Analytical results are presented as adjusted ORs, and 95% confidence intervals (CIs). All analyses were performed by STATA version 10.1 (College station, Texas, USA).

Ethical statement and data availability

The study protocol was approved by the ethic committee in human research of Khon Kaen University. The research data is available per requested.

Results

There were 362 patients reviewed during this study period. Of those, 86 patients were excluded from the study because of cardioembolic stroke in 31 patients, transient ischemic attack in 30 patients, hemorrhagic stroke in 9 patients, and diagnosis other than stroke in 16 patients. In total, 276 thrombotic stroke patients were in the analyses and classified as large cerebral infarction in 59 (21.38%) patients and small cerebral infarction in 217 (78.62%) of the patients.

Baseline characteristics and stroke risk factors of patients with large and small cerebral infarctions were comparable (Table 1). There were 59 patients (21.38 %) and 217 patients (78.62 %) who had large and small cerebral infarction. The mean age of all patients was 62.5 years old and approximately three fourths of the subjects were men.

Regarding the carotid duplex ultrasound parameters (Table 2), there were 199 patients (72.1%) had carotid plaque. The prevalence of significant ICA stenosis was found in 16 patients (5.79 %); 4 patients had both sides of significant ICA stenosis and 12 patients had large cerebral infarction. The large cerebral infarction group had significantly larger proportions of right ICA stenosis (10.17% *vs* 0.92%); P value = 0.002, plaques on left side (59.32% *vs* 40.09%); P=0.012, left ICA stenosis (16.95% *vs* 0.92%); P<0.001, and ICA stenosis at any side (20.39% *vs* 1.84%); P<0.001 than the small cerebral infarction group.

Among various stroke risk factors, only

Table 1. Baseline characteristics of thrombotic stroke patients classified by infarct size.

Baseline characteristics	Overall (n=276)	Large infarction (n=59)	Small infarction (n=217)	P value
Median age	62.5 (53-71)	65 (55-72)	62 (53-70)	0.134
Male gender, n (%)	192 (69.57)	46 (77.97)	146 (67.28)	0.150
Acute ischemic stroke, n (%)	171 (61.96)	20 (33.90)	132 (60.83)	0.546
Diabetes mellitus, n (%)	94 (34.06)	23 (38.98)	71 (32.72)	0.439
Hypertension, n (%)	186 (67.39)	42 (71.19)	144 (66.36)	0.534
Dyslipidemia, n (%)	137 (49.64)	29 (49.15)	108 (49.77)	0.299
Coronary artery disease, n (%)	30 (10.87)	6 (10.17)	24 (11.06)	0.999
Previous stroke, n (%)	43 (15.58)	12 (20.34)	31 (14.29)	0.310
Current smoking, n (%)	128 (46.38)	32 (54.24)	96 (44.24)	0.187

Acute ischemic stroke indicated the diagnosis of stroke was made within 6 months.

Table 2. Carotid duplex ultrasound parameters of thrombotic stroke patients classified by infarct size.

Ultrasound parameter	Overall (n=276)	Large infarction (n=59)	Small infarction (n=217)	P value
Mean (SD) Right CIMT	0.67 (0.14)	0.69 (0.13)	0.67 (0.14)	0.464
Plaque on right side	135 (48.91%)	15 (25.42%)	120 (55.30%)	<0.001
ICA stenosis right	8 (2.90 %)	6 (10.17 %)	2 (0.92%)	0.002
Mean (SD) Left CIMT	0.72 (0.19)	0.77 (0.25)	0.70 (0.16)	0.010
Plaque on left side	122 (44.20%)	35 (59.32%)	87 (40.09%)	0.012
Left ICA stenosis	12 (4.35%)	10 (16.95%)	2 (0.92%)	<0.001
Plaque at any side	199 (72.1%)	38 (64.41%)	161 (74.19%)	0.182
ICA stenosis at any side	16 (5.79%)	12 (20.39%)	4 (1.84%)	<0.001

CIMT: carotid intimal media thickness, Plaque combine: total patients who had plaque left or right, ICA stenosis combine: total patients who had internal carotid artery stenosis left or right.

Table 3. Factors associated with large cerebral infarction by multivariate logistic regression analysis.

Risk factor	Adjusted odds ratio	95 % confidence interval	P value
Age	1.00	0.98-1.03	0.69
Male	1.60	0.68-3.76	0.27
Diabetes mellitus	1.08	0.56-2.10	0.82
Hypertension	1.16	0.55-2.46	0.69
Dyslipidemia	1.28	0.86-1.91	0.23
Smoking	1.15	0.54-2.46	0.72
Coronary artery disease	0.81	0.28-2.34	0.70
Previous stroke	1.11	0.46-2.67	0.82
Plaque at any side	0.59	0.32-1.08	0.08
ICA stenosis at any side	11.14	3.46-35.82	<0.001

ICA stenosis combine: total patients who had internal carotid artery stenosis left or right.

ICA stenosis at any side was the only significant factor associated with large cerebral infarction with an adjusted odds ratio of 11.14 (95% CI: 3.46, 35.82) as shown in Table 3.

Discussion and Conclusions

This study showed that ICA stenosis at any side was the only significantly factor associated with large cerebral infarction. Note that large cerebral infarctions in this study were defined by clinical criteria unlike the TOAST criteria.[3] It can be interpreted that either persons with ICA stenosis may have a higher risk to develop large cerebral infarction or stroke patients with large cerebral infarction tended to have accompanied large cerebral infarction. The causal relationship between ICA stenosis and large cerebral infarction needs further studies.

Unlike the earlier study from Germany, hypertension, male gender, or smoking was not the independent factors associated with large cerebral infarctions in this study.[4] This study using multiple logistic regression analysis to study the association between factors and large cerebral infarctions, while the German study used the Chi-square test. This statistical method is more robust and can control confounding factors. In addition, carotid duplex ultrasonography parameters were not included in the previous study. These findings indicated that ICA stenosis may be a stronger indicator for large cerebral infarction than others.

The carotid plaque has been shown to be a marker for generalized atherosclerosis.[9] In this study, it was not an independent factor for large cerebral infarctions. This may indicate that carotid plaques may be associated with diffuse atherosclerosis but not the cardiovascular event of large cerebral infarctions in particular. The overall prevalence of ICA stenosis in this study was quite low at 5.79%; but was mostly on left side (Table 2). A previous study from Thailand showed that ICA stenosis may be found somewhat higher than this study; 8.3% of large artery stroke patients.[10] The prevalence of ICA stenosis is also varied by countries, race, and age.[11,12] In Taiwan, the ICA stenosis in acute ischemic stroke is slightly higher at 10.1%.[11] While, male native American had the highest prevalence of carotid stenosis than other races.[12]

Recent stroke guidelines recommend carotid endarterectomy to be performed in patients with a TIA or ischemic strokes within 6 months and in patients who have the ipsilateral carotid artery with a severe occlusion of 70-99% stenosis as documented by noninvasive imaging if the operative risk less than 6%.[13,14] As a result of this study results, carotid doppler ultrasonography should be performed in patients at risk for stroke or stroke patients. Carotid endarterectomy as a treatment option when appropriate.

The strength of this study is that the classification of cerebral infarction was made by clinical criteria. Clinicians are able to classify patients with cerebral infarction more easily. Some limitations exist. Risk factors for stroke are categorized instead of using numerical data. These factors may reduce the quality of data but it should still be significant if the factors are really relevant. Some risk factors for stroke are limited due to the retrospective study design such as sleep apnea which has recently been added in the guideline as a risk factor for stroke.[15]

Significant ICA stenosis is associated with large cerebral infarction.

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