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Intracranial stenosis in patients with post-ischemic stroke: a case-control study

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ABSTRACT

Background: Despite its remained position as the main culprit of stroke worldwide, studies on intracranial stenosis in Indonesia are still very limited. It is necessary to research to measure the prevalence and risk factors of intracranial stenosis in post-ischemic stroke.

Method: We conducted case-control research with participants of 234 ischemic stroke patients. Each patient was listed for their risk factors and analyzed for their association with intracranial stenosis. Intracranial circulation was determined by transcranial doppler (TCD) sonography TD-DOP 9000 with a 2-MHz probe. A peak systolic velocity (PSV) of >140cm/s or mean systolic velocity of (MSV) >80cm/s were used as criteria for middle cerebral artery (MCA) stenosis. In contrast, PSV>90 cm/s or MSV>60cm/s were used to determine the posterior circulation stenosis. Statistical analysis used SPSS 18.0 software which The Independent t-test and chi-square test were used to assess significant differences in correlation to intracranial stenosis. P-value <0.05 was statistically significant.

Result: Intracranial stenosis cases were 38%, with the anterior circulation being the most common stenosis location. Hypertension, diabetes mellitus and dyslipidemia were the most often risk factors. Only hypertension with OR=2.97 (95%CI=1.76-4.98) and diabetes mellitus with OR=1.48 (95%CI=1.12-2.43) were positively correlated with increased risk intracranial stenosis.

Conclusion: The occurrence of intracranial stenosis in ischemic stroke patients was high and increased with the presence of hypertension or diabetes mellitus.

Keywords: stroke, stenosis, carotid arteries, risk factors.
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BACKGROUND

Intracranial stenosis remains the main culprit of stroke worldwide.[1,2] Earlier studies have shown that the association of intracranial stenosis and ischemic stroke is stronger in Asians than in Caucasian individuals.[3,4] In Asian populations, intracranial stenosis contributed to 33% to 84% of ischemic stroke cases, while only 8% to 10 % in Caucasians.[4,5] This reveals that the occurrence of vascular stenosis differs from one race to another.[6] Characteristic variance in terms of the race might explain the differences in the profile of vascular risk factor, genetic susceptibility and lifestyles.[4,7]

Previous studies reported intracranial stenosis in patients increased stroke recurrence risk and had a more severe stroke attack.[6,8] In Indonesia, there are only a few studies about intracranial stenosis. Therefore, risk factor profiles for intracranial stenosis have not been fully explained.[6,9-11] Better comprehension of the risk factors that contribute to intracranial stenosis in patients with ischemic stroke plays an important role in reducing the risk of stroke recurrence or vascular events.[4,12,13] To address this issue, we examined the prevalence of intracranial stenosis and its risk factors in ischemic stroke patients.

METHOD

Study Design

This case-control study was done in Bethesda Hospital, Yogyakarta, Indonesia. There were 234 ischemic stroke patients included in the study who fulfilled the following criteria: (1) patients with the event(s) of transient ischemic attack or acute ischemic stroke; (2) patients with no history of intracerebral hemorrhage; (3) patients who had taken brain CT/ magnetic resonance imaging (MRI)/

MR angiography (MRA) screening in temporary hospital admission. The case was defined according to the criteria of intracranial stenosis from the previous consensus of TCD study.[14,15] Patients who did not fulfill the criteria of stenosis were included in the control group. The institutional review board permitted research protocol approval.

Clinical Assessment

This study analyzed the distribution of intracranial artery abnormalities, which were divided into anterior (anterior cerebral artery and middle cerebral artery) and posterior circulation (vertebral segment and proximal basilar artery). This study used Transcranial Doppler (TCD) sonography to detect any narrowing or blockage in intracerebral arteries that may decrease or stop blood flow to the brain. Demographic characteristics, including comorbidity, complication and diagnosis, were collected. Hypertension was determined as 140 mmHg for systolic blood pressure, ≥90 mm Hg for diastolic blood pressure, or a patient taking antihypertensive drugs. Diabetes mellitus was stated as fasting blood glucose of >126 mg/dl or 2-h postprandial blood glucose of >200 mg/dl, HbA1C of >6.5, or diabetes treated with medication before admission. Dyslipidemia was defined as serum low-density lipoprotein level of ≥ 100 mg/dL, high-density lipoprotein level of <45 mg/dL, triglycerides ≥ of 150 mg/dLmmol/l, or a history of treatment with a cholesterol-lowering drug. Smokers had a history of continuous or cumulative smoking for ≥6 months and finished ≥1 cigarette per day.

Imaging Procedures

TCD sonography is a safe, non-invasive technique that utilizes a pulsed Doppler transducer to determine intracerebral blood flow. TCD sonography's probe was placed and held at various areas on the head of the subject, usually at each temple, over each eye, and at the skull base.[14]

TCD studies were performed by TDOP-TC9000P unit with a 2-MHz probe. The diagnostic criteria for intracranial stenosis were based on the peak systolic flow velocity (PSV) or mean systolic velocity (MSV). PSV ≥ 140 cm/s or MSV ≥ 80 cm/s were used as criteria for Middle cerebral artery (MCA) stenosis in this study. Stenosis in the anterior cerebral artery was diagnosed with PSV ≥ 120 cm/s. While PSV ≥ 90 cm/s or MSV ≥ 60 cm/s were used to determine stenosis in the posterior circulation.[15-17]

Table 1. Frequency of vascular risk factors in stroke patients with intracranial stenosis (n = 52)

Variable	Frequency
Age (mean)	Mean 58.35
Age > 60 years old	35%
Male	52 %
Hypertension	72 %
Diabetes mellitus	24 %
Dyslipidemia	38 %
Smoking	22 %

Table 2. Distribution of the stenosis in patients with intracranial stenosis (52 patients)

Variable	Frequency
Anterior circulation	63 %
Posterior circulation	17 %
Both	20 %

Table 3. The risk factors of intracranial stenosis in acute ischemic stroke patients

Variable	Case (n=52)	Control (n=182)	OR	95% CI	p-value
Age > 60 years old	18	54	1.25	0.65-1.67	0.83
Male	27	96	0.96	0.55-1.36	0.53
Hypertension	37	88	2.62	1.76-4.98	< 0.05
Diabetes mellitus	12	34	1.48	1.12-2.43	< 0.05
Dyslipidemia	19	62	1.32	0.82-1.74	0.41
Smoking	11	38	1.14	0.69-1.73	0.86

Statistical Analysis

This study performed univariate analysis to examine the demographic characteristics. The Independent t-test and chi-square test were used to assess significant differences in variables studied in correlation to intracranial stenosis. Statistically significant differences only if $p < 0.05$. We performed statistical analysis with SPSS 18.0 software.

Result

There were 234 participants in total, 58.35 years old as mean age, 52% male and 48% female. Table 1 shows all patients' demographic data. Younger subjects dominated this study, with 65% age ≤ 60 years old and 35% age ≥ 60 years old. One hundred eighty-two patients received complete examinations of TCD (77.7%). The most common reason for incomplete data were the poor temporal window and bedridden-ventilated patients. The results of the TCD studies are demonstrated in Figure 1. Among ischemic stroke patients, the proportions of abnormalities were 37% stenosis, 31% atherosclerotic, and 21% hypoperfusion. Only 11% had normal vascularization.

The distribution of intracranial stenosis using TCD ultrasonography is summarised in Table 2. In comparison to the posterior circulation (17%), stenosis in the anterior circulation (63%) was more common, followed by patients with stenosis in both anterior and posterior circulation (20%). Figures 2 and 3 show stenosis in the middle cerebral artery. We analyzed the risk factors distribution in patients with intracranial stenosis and

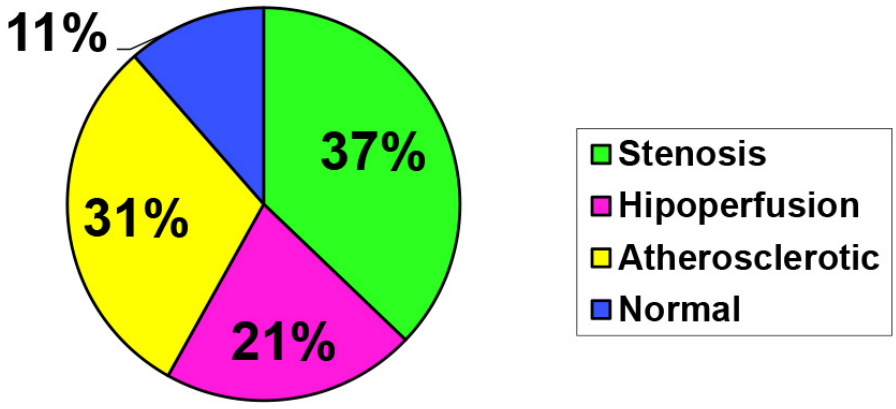

Figure 1. **Distribution of abnormalities of TCD results in patients with acute ischemic stroke**

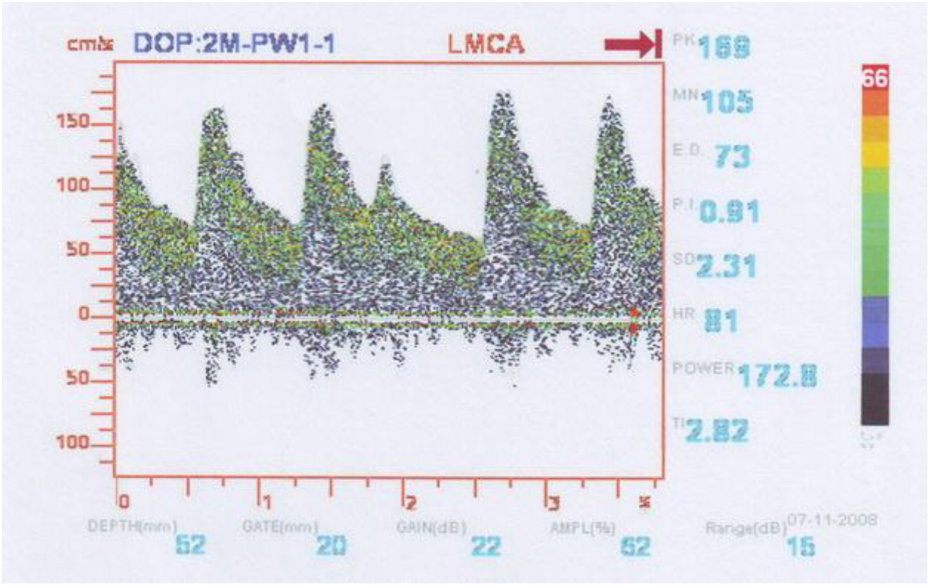

Figure 2. **Stenosis in the left middle cerebral artery**

those without stenosis. Hypertension (72%), dyslipidemia (38%), and diabetes mellitus (24%) were the most common modifiable risk factors in patients with intracranial stenosis.

A significant correlation was found between hypertension and diabetes mellitus with intracranial stenosis. Both hypertension and diabetes (OR=2.97; 95%CI=1.76-4.98 and OR=1.48; 95%CI=1.12-2.43, respectively) were associated with an increased risk of stenosis ($p<0.05$). Age, gender, smoking and the presence of dyslipidemia were not significantly associated with intracranial stenosis (Table 3).

DISCUSSION

Our study revealed that 37% of intracranial lesion cases in ischemic stroke patients were intracranial stenosis. This study demonstrated that the occurrence of intracranial stenosis was more common than that reported in earlier studies.[6,9,18] Intracranial stenosis was found to be more common in the anterior circulation. However, this figure may be an overestimation because we excluded patients with poor temporal windows (mostly older women) and moribund patients with severe stroke. Moreover, hypertension and diabetes mellitus were found to have a significant association with intracranial stenosis.

Consistent with previous studies, intracranial stenosis was frequently found.[3-6] Our data showed that MCA included in the anterior circulation was the most frequent stenotic intracranial artery. Regarding the location of intracranial stenosis, MCA has the highest percentage of patients presenting with stroke.[19] In patients with MCA stenosis, the risk of recurrent stroke increased with microemboli within three days of stroke onset. This study also accounts for the increased risk of TIA >8-fold over the next year after controlling the confounders.[20]

Identifying the risk factors associated with intracranial stenosis is essential because intracranial stenosis patients have a high stroke recurrence rate.[19] There is 38% rate of recurrence at two years for stroke due to intracranial stenosis.[21] Several risk factors such as age, gender, hypertension, diabetes mellitus, dyslipidemia, and smoking, are regarded as major contributors to intracranial stenosis.[4,12,13,22] Previous studies suggested that individuals aged ≥ 60 years had an increased risk of intracranial stenosis, which was not found in this study.[6] Moreover, Turan et al., who studied the risk factors concerning intracranial stenosis, reported that age was positively associated with basilar stenosis.[19]

Despite some previous suggestions, we did not find a statistical difference in the frequency of intracranial lesions between males and females. In contrast, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial reported that females were at higher risk for recurrent ischemic stroke.[23] The explanation for this finding is complex. Women have many risk factors prone to metabolic abnormalities (e.g., hypertension, diabetes and high body mass indexes). Smaller intracranial arteries seem to be found more frequently in women than men, which could expose a greater risk for stroke in the stenotic intracranial artery.[24]

In the present study, intracranial stenosis was found more frequently in patients with a history of either hypertension or diabetes mellitus. Previous studies revealed that hypertension and diabetes mellitus are risk factors for isolated intracranial stenosis and extracranial carotid stenosis, while

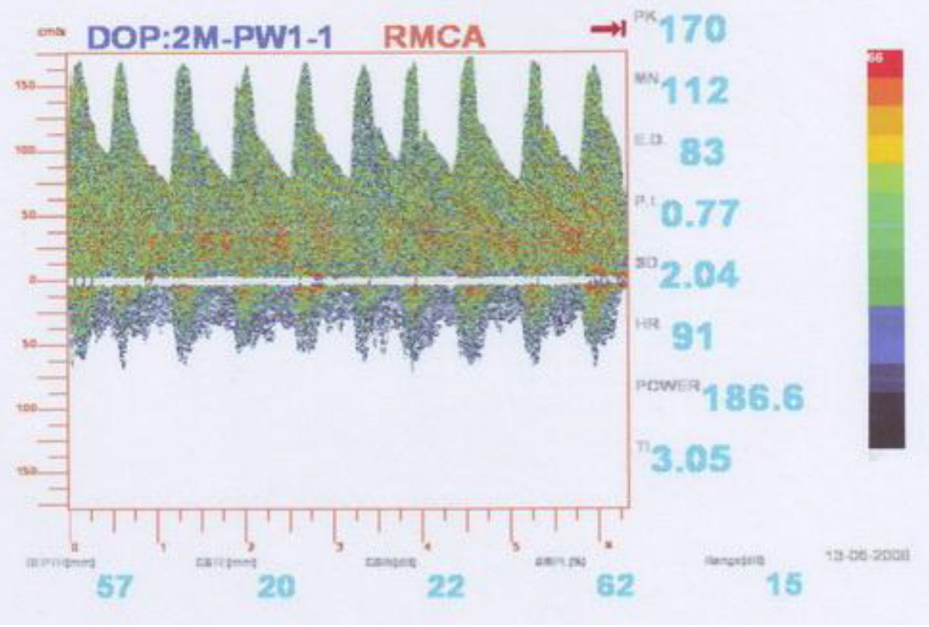

Figure 3. **Stenosis in the right middle cerebral artery**

diabetes mellitus is the major determinant of isolated intracranial stenosis.[4] Hypertension may harden arteries and accelerate artery disease progression, which increases the risk of vascular events and recurrent stroke.[25] Diabetes Mellitus may be linked to increased oxidative stress and decreased antioxidant capacity, which in consequence leads to endothelial dysfunction and more severe inflammation that advance atherogenesis.[4,26]

Dyslipidemia was not considered a risk factor for intracranial stenosis in the present study; unlike that reported in a research conducted by Chen et al.[6] In contrast, a previous study found that a history of a lipid disorder had significant association with severe (70% to 99%) intracranial stenosis.[19] In a WASID trial, the total mean cholesterol of >200 mg/dL during follow-up was also related to a higher risk of stroke.[20,27] Although smoking is a well-known risk factor that increases the event of atherosclerotic arteries,[28] it was not found to be associated with intracranial stenosis in the present study. Ding et al. and Park et al. found that in Asian and Korean populations, smoking had a stronger correlation with extracranial arterial stenosis than with intracranial arterial stenosis.[29,30]

Since we can now detect intracranial occlusive disease safely and reliably with TCD, studying the prevalence of intracranial stenosis in patients with multiple risk factors is feasible.[31] Identifying patients with intracranial stenosis may enable us to implement preventive measures in this high-risk population. Our study's main limitation is that this study was conducted retrospectively, and the responses might have been confounded by recall bias. Furthermore, this study was based in a single hospital; therefore, it may not represent the whole country.

CONCLUSION

This study shows a high occurrence of intracranial stenosis in ischemic stroke patients. Furthermore, this study observed that hypertension and diabetes mellitus had a significant association with intracranial stenosis prevalence.

DISCLOSURE

Author Contribution

All authors were involved in all the study processes, including preparation, data gathering, analysis, drafting and publication approval of this manuscript.

Ethics Consideration

Ethics approval was obtained from the Ethics Committee, Faculty of Medicine, Duta Wacana Christian University, Yogyakarta, Indonesia, before the study (Ethical clearance number: 448/C.16/FK/2019).

Conflict of Interest

No conflict of interest was involved in this study.

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