A Study Design to Evaluate Association between Smoking and Intracranial Atherosclerotic Stenosis

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Purpose: Smoking is a well known risk factor for stroke. The cerebral arteries may be uniquely susceptible to the atherosclerotic effects of smoking, such that it has a different risk profile for stroke compared with other atherosclerosis risk factors. It remains uncertain whether smoking is associated specifically with intracranial (IC) or extracranial (EC) atherosclerotic cerebrovascular disease. The aim of this study design will be to evaluate the association between smoking and severe IC stenosis, adjusting for other atherosclerosis risk factors, particularly age distribution.

Study design: This is a retrospective cohort study design. Participants are patients (n=1714) with severe atherosclerotic stenosis undergoing cerebral catheter angiography because of stroke or transient ischaemic attack. All atherosclerotic steno-occlusive lesions are described in terms of location (anterior versus posterior circulation, IC versus EC, or intradural versus extradural). The atherosclerotic or stroke risk factors for analysis include age, gender, smoking history, number of lesions (single versus multiple), cardiac disease, diabetes mellitus, hypertension, family history, dyslipidemia, history of previous stroke, alcohol intake, metabolic syndrome and body mass index. Statistical analysis includes univariate analysis followed by multivariate logistic regression. The relationship between IC atherosclerotic stenosis and smoking will be assessed. Differences in risk factor distribution is analysed according to age at intervals of 10 years. Significant risk factors associated with IC atherosclerotic stenosis will also be assessed by multivariate logistic regression analysis.

Summary: This is an analytical study design that intends to measure the association between IC or EC atherosclerotic stenosis and smoking and other risk factors. We anticipate that it will have the power to detect any relationship between smoking and IC atherosclerotic lesions especially in younger patients.

Key Words : Smoking; Stenosis; Atherosclerosis; Risk Factors

Intracranial (IC) atherosclerosis is more common in Asians than Caucasians. According to a study from South Korea, the distribution of symptomatic, severe stenotic lesions was 52% in IC arteries and 48% in extracranial (EC) arteries [1]. Single stenotic lesions were more likely to be located in an IC artery and were associated with a poor clinical outcome [2, 3]. It is unclear why IC atherosclerosis is more common in Asians than Caucasians. Age, male gender and hyperlipidaemia were reported to favour EC atherosclerosis, while an association between metabolic syndrome and IC atherosclerosis was reported only for posterior circulation strokes [4]. IC stenotic lesions in young patients are predominantly located in the anterior circulation and occur more frequently in young women [5]. The presence of a lipid disorder was reported to be associated with the severity of the IC stenotic lesion, whereas the lesion's location depended on the nature of the risk factor and demographic features [6].

Cigarette smoke is an aerosol that contains >4000 chemicals, including nicotine, carbon monoxide, acrolein and oxidant compounds [7]. Smoking reduces flow-mediated dilatation (FMD) of systemic arteries in healthy young adults [8]. Smoking was reported to be a significant risk factor for carotid atherosclerosis and may accelerate the development and/or progression of atherosclerosis [9, 10]. However, a study revealed that smoking and hypertension may be more closely associated with IC atherosclerosis than EC atherosclerosis after adjusting for potential confounding by other risk factors [11]. It should be noted that the criterion for significant cranial atherosclerotic stenosis in the previous studies was defined as being greater than 50% as evaluated by magnetic resonance angiography, and the definition of the IC anatomical border was not described clearly.

Although smoking in Korea has decreased recently, the smoking rate in subjects aged over 20 years was about 26% (male versus female = 43.7% vs. 7.9%) in 2012 [12]. Young adults who are involved in gambling are more likely to report cigarette smoking [13]. In South Korea, a large number of young adolescents spend approximately 2 h per day in computer game rooms, which may increase their exposure to tobacco smoke [14]. This is because smoking among Korean men is still a socially sanctioned behaviour in many indoor workplaces and commercial hospitality venues, including bars, nightclubs, restaurants and computer game rooms [14].

Few studies have examined the association between smoking and IC stenosis in young patients. IC stenosis was suggested to be more common in young patients, especially in those with a single, severe stenotic lesion [11, 15]. In addition, the IC artery is not clearly defined anatomically. Therefore, we are planning to elucidate the association between smoking and IC atherosclerosis based on an exact anatomical location defined angiographically. Furthermore, we aim to examine whether this association is confounded by age, number of lesions and other atherosclerotic risk factors.

MATERIALS AND METHODS

Overall design

Participants in this retrospective cohort study include patients with severe cerebral artery atherosclerotic stenosis or occlusion undergoing cerebral angiography because of stroke or transient ischaemic attack. The diagnosis of occlusion or the degree of stenosis is made using high-resolution, biplane digital subtraction angiography (DSA) (Siemens Axiom Artis Zee biplane angiography system, Siemens AG, Medical Solutions, Erlangen, Germany) of the internal carotid artery (ICA), common carotid artery (CCA), vertebral artery (VA) and/or proximal subclavian artery. All lesions are describe in terms of location (anterior (AC) vs. posterior (PC) circulation, IC vs. EC and intradural (ID) vs. extradural (ED)).[16] Risk factors for atherosclerosis or stroke include age, gender, smoking history, number of lesions (single or multiple), cardiac disease, diabetes mellitus (DM), hypertension (HTN), family history of stroke, hyperlipidaemia, previous stroke, alcohol intake, metabolic syndrome and body mass index (BMI). The independent association between all risk factors and the outcome of IC atherosclerotic stenosis is assessed using univariable analysis. IC atherosclerotic stenosis is then modelled using multiple logistic regression, with smoking as the explanatory variable, examining for potential confounding by all risk factors that survived after univariable analysis.

The Institutional Review Board approves the study design and the use of clinical data, and all patients provide written informed consent for the angiographic procedures. Because of the retrospective and observational nature of this study, the need for written informed consent for retrospective analysis is waived.

Patients

We review the records of 1714 consecutive patients diagnosed with atherosclerotic severe stenosis or

occlusion involving a cerebral artery in prospective neurointervention database at Asan Medical Centre, Seoul, Korea between January 2002 and December 2012.

Patients aged between 30 and 80 years old are included in the study. Among patients who underwent cerebral angiography due to TIA/stroke, severe stenosis of cerebral artery $\geq 70\%$ or occlusion in the carotid artery, the VA and the subclavian artery and the IC cerebral arteries to the A1, M1 and P1-2 lesions are included [17−19]. We assume that severe stenosis of the cerebral artery $\geq 70\%$ or occlusion is clinically the most critical degree of stenosis related with certain and definite pathophysiology related with presenting symptom and prognosis. Mild to moderate stenosis is excluded because mild to moderate stenosis is a common finding on cerebral catheter angiography in the elderly patients, even in asymptomatic patients and clinical significant is uncertain.

The following patient groups are excluded: patients aged >80 or <30[20]; patients with lesions located beyond A1 of ACA, M1 of MCA or P2 of PCA; patients who had undergone revascularisation with thrombolysis or thrombectomy because of acute onset of symptoms, dissection or other vascular disease such as vasculitis or moyamoya disease, restenosis after stenting/angioplasty, or endarterectomy of extra endovascular removal of a cardiac embolism. The presence of cardioembolism is determined by angiographic finding of embolism as a filling defect in the vessel and also underlying severe atherosclerotic stenosis or occlusion as well as cardiac evaluation for the source of the embolism [17, 19, 21, 22].

DEFINITIONS

Patient age groups

Patients are classified as being young (30?55 years) or old (>55−80 years) at the time of DSA examination [23]. We also determine the age distribution in 10 year intervals.

Stenosis location in the ICA

To aid the precise identification of a lesion's location, the ICA is divided into its embryological vascular segment and corresponding remnant branch. ICA segments are then defined based on the three anatomical parts of occlusion levels: supraclinoid-terminal (Supra-T), petrocavernous (PC) and bulb-cervical (BC) [16].

Single vs. multiple lesions

All patients underwent selective angiography of the ICA, CCA, VA and/or proximal subclavian artery. A single lesion is defined as when there is only one occurrence of a severe cerebral artery stenotic lesion ($\geq 70\%$) or occlusion on cerebral angiography. The presence of multiple lesions is defined as the occurrence of at least two severe stenotic lesions or occlusions. In patients with multiple lesions, the one responsible for the patient's symptom presentation is deemed to be their main lesion.

Angiographic evaluation of lesion location (IC vs. EC and ID vs. ED)

The junction between ID and ED arteries is set as the angiographic dural margin just below the ophthalmic artery. The junction between IC and EC arteries is set as the ICA segment of the lower margin of the carotid canal in the petrous bone for the ICA, and as the level of foramen magnum for the VA [16].

Smoking

Smoking definition and classification follows those of the US Centers for Disease Control and Prevention. Non-smokers are defined as those who currently do not smoke cigarettes, including both former smokers and never smokers. Never smokers are defined as those who have never smoked or who have smoked fewer than 100 cigarettes in their entire lifetime. Former smokers are defined as those who have smoked at least 100 cigarettes in their lifetime but currently do not smoke. Current smokers are defined as those who have smoked 100 cigarettes in their lifetime and currently smoke cigarettes every day (daily) or some days (nondaily) [24]. Heavy smokers are defined as those who smoke 20 or more cigarettes per day, or 20 or more pack-years according to a recent report in the *International Journal of Environmental Research and Public Health* [25].

Other risk factors

Cardiac disease risk factors include myocardial infarction, angina and a history of coronary artery bypass graft or percutaneous coronary intervention. Diagnosis of DM is established if the patient met at least one of the following criteria [26]: (1) past history of known DM; (2) glycated haemoglobin (HbA1c) $\geq$ 6.5%; (3) serum glucose level after an 8h fast ≥ 126 mg/dL; (4) glucose level 2h after a 75goral glucose tolerance test ≥ 200 mg/dL; and (5) serum glucose level ≥ 200mg/dL on random testing. Diagnosis

of hypertension is established if the patient had a history of known hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mm Hg) or is on antihypertensive treatment. Diagnosis of dyslipidaemia is established if the patient met at least one of the following criteria: (1) past history of known hyperlipidaemia and on hyperlipidaemia treatment; (2) total cholesterol ≥200 mg/dL; (3) triglycerides ≥200 mg/dL; and (4) low-density lipoprotein ≥130 mg/dL (5) high-density lipoprotein ≤40 mg/dL.

Stroke includes having a past history of ischaemic stroke, haemorrhagic stroke or transient ischaemic attack. Family history is recorded as positive if apparent or sibling suffered IC or EC atherosclerotic stenosis. A history of alcohol intake is defined as those who currently drank alcohol or who had quit drinking less than 6 months previously. BMI ≥30 kg/m² is defined as a positive risk factor.

Metabolic syndrome is defined by the criteria of the National Cholesterol Education Program as the presence of three or more of the following: (1) abdominal obesity; (2) elevated triglyceride levels (≥150 mg/dL); (3) decreased high-density lipoprotein cholesterol (HDL-C) levels (<40 mg/dL for men and <50 mg/dL for women); (4) high blood pressure (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg or use of antihypertensive medication); and (5) elevated fasting glucose levels (≥ 110 mg/dL).[27] Abdominal obesity is defined as a waist circumference of ≥90 cm for men and ≥80 cm for women according to the revised Asia-Pacific criteria suggested by the World Health Organization Western Pacific Region [28].

Clinical data collection

The physician responsible for consideration of the patient for DSA fills out a standardised data collection form to collect information on age, gender, pattern of cerebral atherosclerosis (lesion location and severity), cardiac disease, DM, HTN, family history, dyslipidaemia, previous stroke history, alcohol history, metabolic syndrome and BMI, medical history and current medication. Patients' angiographic findings and medical records are recorded prospectively to assess patient demographics; however, additional smoking history is assessed retrospectively by telephone to obtain the data in sufficient detail.

Statistics and Study outcome

Distribution of patient age, gender, lesion location (AC vs. PC, IC vs. EC, and ID vs. ED) and number

(single vs. multiple) are correlated with the history of smoking. We also evaluate the proportion of patients with IC atherosclerotic stenosis among smokers and compare this with the proportion in patients stratified by the other risk factors. Differences in risk factor distribution are analysed according to age in 10 year intervals.

Categorical variables are presented as frequencies and percentages, and continuous variables are expressed as mean and SD. The t test is used to compare continuous variables, and the chi-square test or Fisher exact test are used to compare categorical variables, as appropriate. Associations between risk factors (age, gender, location, multiplicity, smoking, etc.) and IC atherosclerosis stenosis are tested by using the univariate logistic regression model followed by the multivariable logistic regression model with backward elimination. All reported p-values are two sided, and P <.05 is considered statistically significant. Statistical analyses are conducted using SPSS 21 software (SPSS Inc., Chicago, IL, USA).

SUMMARY

This analytical cohort study is designed to investigate the association between IC atherosclerotic stenosis and smoking, adjusting for confounding by other risk factors. We anticipate that it will have the power to detect any relationship between smoking and IC atherosclerotic lesions especially in younger patients.

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