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Original Articles

Risk Assessment of Smoking for Ischemic Stroke in Koreans

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Background and Purposes : Smoking is a well-known risk factor for ischemic stroke. It may contribute to stroke by inducing the aggregation of platelets and formation of atheroma, reducing cerebral blood flow, and increasing fibrinogen. However, the relative risk varies according to different ethnicity and area. Therefore, we performed this study to assess the risk of smoking for ischemic stroke in Korea.

Methods : Cigarette smoking habit was studied in 308 patients with ischemic stroke and in 348 age- and sex-matched control subjects who had no history of stroke using case control methods. In multiple logistic regression analysis, smoking had a significant value of odds ratio adjusted for hypertension, diabetes mellitus, and hyperlipidemia.

Results : The adjusted odds ratio (AOR) and 95% confidence interval (CI) was significant in the medium smokers (AOR, 1.92; 95% CI, 1.11 to 3.33: $p< 0.05$) and heavy smokers (AOR, 2.80; 95% CI, 1.64 to 4.78: $p< 0.05$). Furthermore, the OR was higher in hypertensive subjects than in normotensive subjects compared to non-smokers (AOR, 1.98; 95% CI, 1.01 to 3.85: $p< 0.05$).

Conclusions : Our findings suggest that smoking is an independent risk factor for ischemic stroke in Korea. *(Korean J of Oriental Med 2003;24(4):19-24)*

Key Words: smoking, stroke, risk, Korea

Introduction

Smoking is an independent risk factor for stroke[1-5]. It may contribute to stroke by inducing the aggregation of platelets[6] and formation of atheroma[7], reducing cerebral blood flow[8], and increasing fibrinogen[9].

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Smoking increases the relative risk of stroke about three-fold[2]. The risk is dependent upon the amount of smoking, is consistent for all subtypes of stroke[3]. The relative risk of stroke is equally high among male and female smokers[2,5]. Evidence is accumulating about passive exposure to environmental smoke as a risk factor for atherogenesis[4]. The mechanisms by which smoking causes stroke remain uncertain, but are probably multifactorial and primarily atherogenic[2].

However, the association between the amount of smoking and ischemic stroke remains uncertain in Korea. Therefore, we assessed the risk of smoking and

present a predictive model composed of the conventional risk factors and smoking for ischemic stroke in Korean people.

Subjects and Methods

1. Study population

This was a hospital based case-control study. The study population was composed of 308 ischemic stroke patients suffering small artery occlusion and large artery atherothrombosis within 1 year after onset, and 348 control subjects matched by age and sex. The subjects were enrolled from patients who were over 40 years old and visited the departments of neurology and oriental internal medicine in Ewha Womans University Dongdaemoon Hospital and Pundang CHA hospital from January 2002 to June 2003. The diagnosis of ischemic stroke was made when neurological deficits were accompanied by corresponding abnormal computed tomography (CT) or magnetic resonance imaging (MRI) findings of the brain. Patients with cerebral hemorrhage were excluded in advance. Another exclusion criteria included cardiogenic embolism and other etiologic subtypes of ischemic stroke. The selection was done on the basis of clinical examination, echocardiogram, cerebral angiogram, transcranial Doppler, or brain imaging study.

The control subjects were randomly selected from those who visited the same department during the same period, stratified by 5-year age group and sex. The exclusion criterion for control subjects was a clinical history of cerebrovascular disease and present neurological abnormalities.

The diagnosis of hypertension, diabetes mellitus or hyperlipidemia at enrollment was done at the time of visiting out patient clinic. Relevant information on the past medical history and the amount of smoked cigarettes was obtained from all of the study subjects. Informed consent was obtained from each subject after a full explanation of the study.

To assess the association between the risk of stroke and the consumption of cigarettes, we divided the subjects into 4 categories according to the amount of cigarettes consumed[2,5]: non-smokers who never smoked, light smokers who smoked 1 to 15 packs/year, medium smokers who smoked 16 to 30 packs/year, and heavy smokers who smoked 31 or more packs/year. Ex-smokers, who smoked previously but had quit, were very few (5 cases), so we excluded them from our study.

2. Statistical Analysis

To estimate the odds ratio of ischemic stroke associated with a particular medical history and smoking, we calculated adjusted odds ratio (AOR) and 95 percent confidence intervals (95% CI) by multivariate logistic regression analysis. For the predictive model, we considered the duration of risk factors as the independent variables. The logistic equation we set up is $\log (P/1-P) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta n X n$, where the X' s are independent variables, the β' s are regression coefficients, and the P is the probability of stroke occurrence. This is a popular method to build a predictive model, which has a familiar interpretation. The statistical package used for multivariate logistic regression was SPSS for Windows, version 11.0 (SPSS Inc., Chicago, IL).

Results

The baseline characteristics of the ischemic stroke patients (n=308) and control subjects (n=348) are shown in Table 1. Stroke patients showed significantly higher prevalence of hypertension, diabetes mellitus, and smoking than the controls. To evaluate the effects of confounding factors, we calculated the OR adjusted

Table 1. Basic Characteristics of Ischemic Stroke Patients and Controls.

	Controls n = 348	Patients n = 308	OR*	95% CI	*p***
Age (mean ± SD)	60.6 ± 10.6	61.8 ± 9.9	1.01	0.99 - 1.03	0.134
Male (%)	164 (47)	149(48)	1.05	0.77 - 1.43	0.749
Hypertension (%)	107(31)	213(69)	5.55	3.88 - 7.93	<0.001
DM (%)	47(14)	86(28)	2.16	1.40 - 3.32	<0.001
Hyperlipidemia (%)	85(24)	96(31)	0.92	0.62 - 1.36	0.123
Smoking (%)	87(25)	108(35)	2.19	1.50 - 3.20	0.003

*: crude odds ratio

**: chi-square test for the categorical data, and two-sample *t*-test for the continuous data

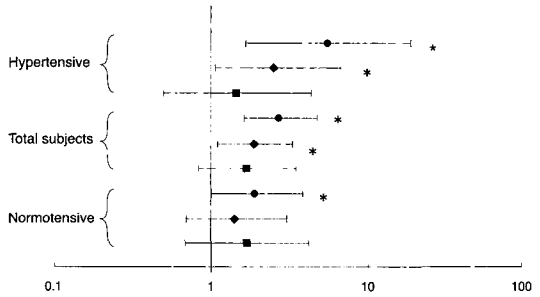

Fig. 1. The relative risk assessment according to the consumption of smoking and hypertension.
The total subjects represent the summed cases including hypertensive and normotensive subjects. Horizontal bars represent 95% confidence intervals on a log scale; ● for the heavy smokers, ◆ for the medium smokers, and ■ for the light smokers indicates the adjusted odds ratio.
*: The significant relative risk.

for hypertension, diabetes mellitus, and hyperlipidemia. These were dichotomous values, absent or present. The adjusted OR for ischemic stroke was significant in subjects with hypertension, diabetes mellitus, and smoking. When compared to non-smokers, the OR for ischemic stroke was not significant in the light smokers (AOR 1.71, 95% CI 0.84 to 3.51, $p> 0.05$) adjusted for hypertension, diabetes mellitus, and hyperlipidemia. However, the OR was significant in the medium smokers (AOR 1.92, 95% CI 1.11 to 3.33, $p< 0.05$) and heavy smokers (AOR 2.80, 95% CI 1.64 to 4.78, $p< 0.05$).

Then, we divided the subjects into hypertensive and normotensive groups. Only the OR was non-significant in the light smokers with hypertension (AOR 1.48, 95% CI 0.50 to 4.43, $p> 0.05$). In the normotensive group, the OR was significant just in the heavy smokers (AOR 1.98, 95% CI 1.01 to 3.85, $p< 0.05$).

By logistic regression, we determined the β coefficient, standard error, and p-value for each factor. The independent variables were continuous values, such as the duration of hypertension, diabetes mellitus, hyperlipidemia, and packs/year of smoking.

All of them had a significant β coefficient except hyperlipidemia. Then, we used backward methods to eliminate the effect of a non-significant confounding factor, hyperlipidemia. Finally, we established a logistic equation: $\log (P/1\text{-}P) = 0.048 \times$ (duration of hypertension) + $0.074 \times$ (duration of diabetes mellitus) + $0.016 \times$ (packs/year of smoking) -0.473. The P in the above equation means the probability of stroke occurrence.

Discussion

Since young age stroke has underlying conditions such as aneurysms, arteriovenous malformations, or genetic variants[10-12], we enrolled ischemic stroke patients and age- and sex-matched control subjects over 40 years old. Smoking is associated with atherosclerosis or microangiopathy, so we recruited for small vessel disease and large artery infarction, excluding cardiogenic embolism and other etiologic subtypes.

In the prevalence rate analysis by chi-square test, hypertension, diabetes mellitus, and smoking were

significantly more common in the stroke subjects than in the controls. Many reports said that hyperlipidemia is a risk factor for stroke, but there were not a few reports showing negative results[13]. In our study, hyperlipidemia is not an independent risk factor for stroke. We think that our negative result might be because the clinics from which the study subjects were enrolled have many cases of hyperlipidemia. The OR of diabetes mellitus was similar to the previous reports[14,15].

However, the adjusted OR of hypertension (AOR 5.55, 95% CI 3.88 to 7.93, $p< 0.05$) was higher compared with the previous reports[16-18]. This may be due to the Koreans' poor adherence to anti-hypertensive drugs. Many Koreans are not fully aware of the importance of blood pressure control, so the hazard of hypertension tends to be higher in Korea[19]. In our study, the overall adjusted OR of smoking (AOR 2.19, 95% CI 1.50 to 3.20, $p< 0.05$) was similar to that in Australia[20] and New Zealand[21], lower than in Norway[22], Germany, and America[23], and higher than in Japan[17].

These findings showed an interesting aspect that the risks of smoking in Asia-Oceania were lower than those in the western countries of America and Europe. The reason for this regional disparity could be due to the differences in natural and social environments, but further investigation is needed.

According to cigarette consumption, the medium and heavy smokers showed significant associations with stroke, whereas no significant association was found for the light smokers. In addition, heavy smokers had a higher OR than medium and light smokers. The risk of stroke increased as the number of cigarettes smoked increased, which is in line with previous reports[23-27].

To evaluate the effect of smoking combined with hypertension, we classified the subjects into hypertensive and normotensive groups and calculated the OR of smoking in each group. Only the heavy smokers were significantly associated with stroke in the normotensive group. On the contrary, in the hypertensive group, the medium and heavy smokers had higher OR than in the summed cases including hypertensives and normotensives. Especially, the hypertensive heavy smokers showed a fivefold increase in risk compared with those who never smoked. Thus, the effect of hypertension and smoking in combination could be more harmful, and the same results can be seen in other reports[28-30].

When we used the medication periods and packs/year of smoking as independent variables in logistic regression, we could get a logistic odds equation composed of three significant risk factors, hypertension, diabetes mellitus, and smoking: $\log (P/1\text{-}P) = 0.048 \times$ (medication period of hypertension) $+ 0.074 \times$ (medication period of diabetes mellitus) $+ 0.016 \times$ (packs/year of smoking) - 0.473. The P in the above equation means the probability of stroke occurrence. By using the above regression coefficients, the OR of each factor could be obtained through exponentiation ($e\beta$).

Therefore, we found that the risk of having stroke would increase about 1.6 fold per every ten-year of hypertension, 2.1 fold by diabetes mellitus, and 1.1 fold by smoking. Of note, the β coefficient of hypertension was lower than that of diabetes mellitus, while hypertension showed higher risk than diabetes mellitus in the above prevalence rate analysis. This discrepancy between the prevalence rateanalysis and regression analysis may be due to the relative short medication periods of hypertensives, because of Koreans' preference to alternative medicine. Not a few Koreans prefer controlling their blood pressure with alternative medicine at first, so hypertensive medication is likely to start late[19].

Of course, our study has two points at issue. First, there might be a so-called recall bias, a possibility that the subjects could not remember the medication period exactly. Second, the medication periods might not

reflect the actual duration of the diseases by some chance, since the independent variables we used were chronic diseases. In this study, however, we assessed the risk of smoking and presented a predictive model for the first time in Korea, though this predictive model should be confirmed by further clinical trials.

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