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Nonaspirin Nonsteroidal Anti-inflammatory Drugs and Hemorrhagic Stroke Risk

The Acute Brain Bleeding Analysis Study

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Background and Purpose—The relationship between nonaspirin nonsteroidal anti-inflammatory drugs (NNSAIDs) and hemorrhagic stroke (HS) remains unclear. We examined the risk of HS associated with the use of NNSAIDs in Koreans.

Methods—We performed a nationwide, multicenter case-control study from 2002 to 2004. This study included 940 nontraumatic acute HS cases in patients aged 30 to 84 years, with an absence of a history of stroke or hemorrhage-prone brain lesions, alongside 940 community controls, matched to each case by age and sex. Pretrained interviewers obtained information on prescription drugs as well as over-the-counter drugs taken within 14 days before the onset of stroke. We adjusted potential confounders, including family histories of stroke, histories of hypertension, smoking, alcohol consumption, high salt intake, and laborious work hours. The adjusted ORs and their 95% CIs were calculated by conditional logistic regression.

Results—The proportion of NNSAIDs exposure within 14 days was 2.9% for HS patients and 2.0% for the controls. The adjusted odds ratios of stroke in NNSAIDs users compared with nonusers was 1.12 (95% CI, 0.77 to 1.65) for all HS, 1.03 (95% CI, 0.49 to 2.18) for subarachnoid hemorrhage, and 1.19 (95% CI, 0.76 to 1.87) for intracerebral hemorrhage.

Conclusions—No increased risk of HS either subarachnoid hemorrhage or intracerebral hemorrhage was found among NNSAIDs users. (*Stroke*. 2008;39:845-849.)

Key Words: anti-inflammatory agents ■ case-control studies ■ hemorrhagic ■ nonsteroidal ■ stroke

Substantial concerns exist over aspirin or cyclooxygenase (COX)-2 selective nonsteroidal anti-inflammatory drugs and their relations to cardiovascular diseases. However, the impact of nonaspirin nonsteroidal anti-inflammatory drugs (NNSAIDs) on hemorrhagic stroke (HS) has received little attention despite the widespread use of this therapeutic treatment for pain, fever, and inflammation within the general population.

Most NNSAIDs inhibit both COX-1 and COX-2.¹ Like NNSAIDs, aspirin acts as an inhibitor of COX; however, the inhibition of platelet COX-1 by aspirin results in anti-platelet effects associated with a reduction in thrombotic events.² This pharmacological mechanism might increase the risk of HS and decrease the risk of ischemic stroke. Both aspirin and NNSAIDs bind to the same active site on COX;² therefore, NNSAIDs could have a similar effect as aspirin on hemorrhagic stroke.^{3,4}

Until now, few epidemiological studies have focused on the risk of HS in subjects using NNSAIDs. These studies

showed no associations with the use of NNSAIDs and HS.⁴⁻⁶ However, they assessed the information of NNSAIDs exposure using self-reports⁵ or prescriptions databases to 1999.^{4,6} Accordingly, they failed to include over-the-counter (OTC) drugs^{4,6} and selective COX-2 NNSAIDs.⁴⁻⁶ Also, they used discharge diagnoses and proxy measures,⁶ and only prescription data for current and previous uses of other medications⁴ for adjusting confounders. For that reason, these studies could not adjust for the precise status of diseases, dietary habits, and physical activity. As we know, only 1 study has assessed both subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH),⁴ whereas the others only focused on the risk of ICH.^{5,6} Therefore, we performed a nationwide, multicenter, and matched case-control study in Korea to evaluate the association of NNSAIDs use and HS risk, including SAH and ICH.

Subjects and Methods

The Acute Brain Bleeding Analysis study is a nationwide multicenter matched case-control study designed to investigate the risk of HS

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attributable to phenylpropanolamine contained in cold remedies in Korea.⁷ The cases recruited for this study came from 33 hospitals, including 10 centers scattered regionally and covering considerable areas of South Korea from 2002 to 2004. This study was approved by the Institutional Review Board of every participating hospital and all study participants provided written informed consent to participate.

Identification of Cases

HS was defined as either SAH or ICH. The diagnosis of SAH was based on clinical symptoms via either a brain image (CT, MRI) or evidence of xanthochromia on a lumbar puncture. ICH was diagnosed based on clinical symptoms and the detection of blood in the brain parenchyma or ventricles by CT or MRI. Eligible criteria for the patients included age ranges of 30 to 84 years, absence of a history of stroke or hemorrhage-prone brain lesions, no causal relationship to trauma, and the ability to communicate and complete an interview within 30 days after the onset of the stroke.

Selection of Controls

One community control was matched to each case for sex and age within 5 years. The controls were recruited from siblings, friends, or neighbors of the case subject, in descending order of preference. The eligible criteria for the controls included absence of a history of stroke, absence of dementia or other neurological diseases, and the ability to communicate and complete an interview within 30 days after the onset of the stroke in the matched case.

Data Collection

Trained nurse interviewers administered structured questionnaires, which were evaluated for feasibility by an expert panel, to all participants. To avoid interviewer bias, the interviewers and subjects were kept blind to the hypothesis of this study. They were informed that the aim of this study was to investigate the effect of lifestyles and medications on the risk of HS.

The date showing the initial symptoms of HS were used as the index date for the cases. Each control was questioned based on the index date of their matched case. The information on the following risk factors was obtained from the interview for both cases and controls: age, sex, weight, height, level of education, occupation, smoking status, alcohol consumption, physical activity, duration of work, sleep habits, eating habits, family history of stroke, history of hypertension, diabetes mellitus, hyperlipidemia, heart disease, upper respiratory tract infections within 1 month, and all medications taken on the index date or during the 14 days before the index date. Especially high salt intake was coded as "yes" if the subjects answered that they liked salty food. From the quantitative history of physical activity surveys, we obtained information on physical activity performed in the past 6 months. Physical activity for ≥ 7 hours per week was classified as the high amount group.

We ascertained the exposure history to medications before the index date for all prescribed or OTC drugs. We tried to obtain the prescriptions from all of the subjects. When prescriptions were unavailable or medications were purchased OTC without prescription, the subjects were asked to bring in the medication packages. If these packages were unavailable, we asked the subjects to provide the exact name of the drug and manufacturer and select their medications from a book containing photographs of the packages.

Definition of Drug Exposure

Exposure to NSAIDs was defined as being exposed to NSAIDs within 14 days before the index date. The time window of exposure to NSAIDs was defined as the interval from the last exposure date to that of the index date. We classified NSAIDs according to selectivity of COX. Nonselective NSAIDs include aceclofenac, acetaminophen, diclofenac, flufenamic acid, ibuprofen, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, pranoprofen, and zaltoprofen. COX-2 preferential and selective NSAIDs include celecoxib, lornoxicam, meloxicam, nimesulide, rofecoxib, and talniflumate.⁸

Statistical Analysis

Conditional logistic regression was used to calculate ORs and 95% CIs for HS among users and nonusers of NSAIDs. Initially, we compared demographic, clinical, and behavioral features of case and control subjects using the Pearson χ^2 test, Fisher exact test, or Student *t* test when appropriate. Variables whose probability values were <0.1 and clinically important were selected as potential adjusting variables. We then selected variables with statistically significant differences between exposed and unexposed persons ($P<0.1$) with clinical importance among them. Finally, the model included family histories of stroke, histories of hypertension, smoking, alcohol consumption, high salt intake, and laborious work hours as the adjusting variables. Stratified analyses were conducted by different exposure time windows, the classes of NSAID, and the type of HS. Different logistic models were used according to the HS subtype. We adjusted for family history of stroke, history of hypertension, high salt intake, and laborious work hours for both SAH and ICH, and added smoking for the SAH group, and alcohol consumption for the ICH group. The unadjusted and adjusted estimates were calculated for each subgroup. All analyses were performed with SAS version 9.1 (SAS Institute Inc).

Results

In total, 940 HS cases and 940 controls were recruited. Of these cases, 442 (40.7% males; age, 50.8 ± 10.6 years) had SAH and 498 (58.0% males; age, 57.1 ± 11.4 years) had ICH. Table 1 shows the characteristics of the cases and the controls according to hemorrhagic stroke subtype.

The cases and controls were generally similar with regard to baseline characteristics for both SAH and ICH groups, including age, sex, body mass index, history of diabetes mellitus, history of hyperlipidemia, history of cardiovascular disease, arthritis status, upper respiratory tract infections within 30 days before the index date, use or nonuse of aspirin, and use or nonuse of antiplatelets and anticoagulants. Compared with the control subjects, the case patients were more likely to report a family history of stroke, a history of hypertension, high salt intake, and laborious work of ≥ 7 hours per day ($P<0.1$) for both SAH and ICH groups. Subjects who were current smokers and current alcohol drinkers were more likely to have SAH and ICH, respectively.

Table 2 shows the association between NSAIDs and HS in all of the subjects according to exposure status. Twenty-seven patients (2.9%) with HS were NSAID users compared with 19 (2.0%) controls, giving a crude OR of 1.18 (95% CI, 0.80 to 1.73). The adjusted OR was 1.12 (95% CI, 0.77 to 1.65) after adjusting for potential confounders. The adjusted ORs for HS according to prescriptions for NSAIDs within 3 or 14 days before the index date were 1.04 (95% CI, 0.64 to 1.71) and 1.27 (95% CI, 0.70 to 2.30), respectively, compared with nonusers. The adjusted ORs for HS using NSAIDs were 1.21 (95% CI, 0.79 to 1.87) for nonselective NSAIDs and 0.89 (95% CI, 0.40 to 2.00) for preferential or selective COX-2 NSAIDs.

The results of the subgroup analyses according to type of HS are summarized in Table 3. The adjusted OR in subjects with SAH was 1.03 (95% CI, 0.49 to 2.18), and ICH was 1.19 (95% CI, 0.76 to 1.87), which showed no statistical significance. The ORs from the subjects after excluding all aspirin users (36 cases and 30 controls) and their matched cases or controls were shown to be consistent with the ORs from all of subjects (data not shown).

Table 1. Characteristics of Case Patients and Control Subjects According to Hemorrhagic Stroke Subtype

Characteristics	Subarachnoid Hemorrhage		<i>P</i> *	Intracerebral Hemorrhage		<i>P</i> *
	N (%) of Cases (n=442)	N (%) of Controls (n=442)		N (%) of Cases (n=498)	N (%) of Controls (n=498)	
Age (yr, mean±SD)¶	50.8±10.6	50.1±10.8	0.30	57.1±11.4	56.1±11.7	0.18
Male¶	180 (40.7)	180 (40.7)	1.00	289 (58.0)	289 (58.0)	1.00
Body mass index (kg/m ² , mean±SD)	23.5±2.9	23.5±2.7	0.69	23.7±3.2	23.5±2.9	0.38
Family history of stroke§	97 (21.9)	67 (15.2)	<0.01	127 (25.5)	85 (17.1)	<0.01
History of hypertension§	143 (32.4)	62 (14.0)	<0.01	299 (60.0)	98 (19.7)	<0.01
History of diabetes mellitus	22 (5.0)	16 (3.6)	0.32	47 (9.4)	42 (8.4)	0.58
History of hyperlipidemia	14 (3.2)	18 (4.1)	0.47	17 (3.4)	27 (5.4)	0.12
History of cardiovascular disease	13 (2.9)	8 (1.8)	0.27	14 (2.8)	18 (3.6)	0.47
History of arthritis	30 (6.8)	28 (6.3)	0.79	37 (7.4)	42 (8.4)	0.56
Upper respiratory tract infections within 30 days before index date	61 (13.8)	46 (10.4)	0.12	82 (16.5)	85 (17.1)	0.80
Prescription for aspirin†	7 (1.6)	10 (2.3)	0.46	29 (5.8)	20 (4.0)	0.19
Prescription for antiplatelets and anticoagulates‡	1 (0.2)	2 (0.5)	0.38	1 (0.2)	3 (0.6)	0.25
Smoking§			<0.01			0.22
Never smoked	253 (57.2)	291 (65.8)		259 (52.0)	250 (50.2)	
Former smoker	30 (6.8)	41 (9.3)		89 (17.9)	78 (15.7)	
Current smoker	158 (35.7)	107 (24.2)		149 (29.9)	165 (33.1)	
Unknown	1 (0.2)	3 (0.7)		1 (0.2)	5 (1.0)	
Alcohol drinking§			0.23			0.08
Never drank	189 (42.8)	199 (45.0)		177 (35.5)	212 (42.6)	
Former drinker	13 (2.9)	19 (4.3)		27 (5.4)	32 (6.4)	
Current drinker	238 (53.8)	218 (49.3)		291 (58.4)	250 (50.2)	
Unknown	2 (0.5)	6 (1.4)		3 (0.6)	4 (0.8)	
High salt intake§	159 (36.0)	129 (29.2)	0.03	219 (44.0)	161 (32.3)	<0.01
Laborious work hours ≥7 hours/day§	137 (31.0)	105 (23.8)	0.02	143 (28.7)	115 (23.1)	0.05

**P* calculated by Pearson χ^2 test, Fisher exact test, or Student *t* test, when appropriate.

†Prescription for aspirin was defined as being exposed to aspirin within 14 days before the index date.

‡Clopidogrel, cilostazol, dipyridamole, ticlopidine, triflusal, and warfarin.

§*P* of characteristic was <0.1 when all the cases were compared with all the controls.

¶Matching variables.

Discussion

The results of this matched case-control study show that NANSAlDs are not a risk factor for HS, either in SAH or ICH. The absence of an association was evident in all separate analyses with different exposure times and different classes of NANSAlDs.

This study supports the findings of previous epidemiological studies,^{4–6} suggesting that use of NANSAlDs is not associated with an increased risk of HS. Although the study by Saloheimo et al⁹ showed use of NANSAlDs was associated with an increased risk for ICH, the majority of NANSAlDs users concurrently used aspirin in mainly high doses (>1225 mg/wk), which led the researchers to conclude that the elevated risk associated with NANSAlDs use was primarily attributable to concurrent use with aspirin.¹⁰

Most of the beneficial and harmful effects of NANSAlDs are related to their inhibition of the COX-1 and COX-2.¹¹ Along with the inhibition of platelet COX-1 activity, there is a decrease in platelet aggregation, leading to reduced throm-

boembolic potential and a commensurate prolonged bleeding time.¹² The effect of aspirin on platelet COX-1 is irreversible, thus the inhibition of COX-1 by aspirin is sustained for ≈10 days, the average lifespan of platelets.^{2,12} Like aspirin, NANSAlDs bind rapidly to COX; however, this binding is reversible and, therefore, short-lived in relation to that of aspirin.² Consequently, the thrombotic effects of aspirin and NANSAlDs could reveal themselves differently in HS. However, whether the apparently absent antithrombotic effect of NANSAlDs is attributable to the incomplete inhibition of COX-1 or to the concomitant inhibition of COX-2 is unknown.⁴

This study has several strengths. First, it was a prospective, nationwide case-control study. All cases of HS were confirmed by CT, MRI, or by postmortem examination, so the diagnostic accuracy is high. Furthermore, the neurologists were blinded to the drug exposure information when they evaluated all of the potential cases, according to predefined criteria. Although most previous studies have only assessed

Table 2. Association Between NSAIDs and Risk of Hemorrhagic Stroke

	Cases (n=940)	Controls (n=940)	Unadjusted OR	95% CI	Adjusted OR*	95% CI
Variables						
Exposure to NSAIDs†						
No	913	921	1		1	
Yes	27	19	1.18	0.80–1.73	1.12	0.77–1.65
Time window of exposure to NSAIDs‡						
Never use	913	921	1		1	
4–14 days	11	4	1.47	0.81–2.67	1.27	0.70–2.30
≤3 days	16	15	1.04	0.63–1.70	1.04	0.64–1.71
Classes of NSAIDs						
Never use	913	921	1		1	
Nonselective NSAIDs§	21	12	1.28	0.83–1.97	1.21	0.79–1.87
Preferential or selective COX-2 NSAIDs¶	6	7	0.93	0.42–2.07	0.89	0.40–2.00

*Adjusted for a family history of stroke, history of hypertension, smoking, alcohol consumption, high salt intake, and laborious work hours.

†Exposure to NSAIDs was defined as being exposed to NSAIDs within 14 days before the index date.

‡Time window of exposure to NSAIDs was defined as the interval from the last exposure date to the index date.

§Acetofenac, acetamin, diclofenac, flufenamic acid, ibuprofen, ketoprofen, mefenamic acid, nabumetone, naproxen, piroxicam, pranoprofen, and zaltoprofen.

¶Celecoxib, rofecoxib, lornoxicam, meloxicam, nimesulide, and talniflumate.

the risk of ICH,^{5,6,9} we compared the ORs in the specific subgroups of HS, both ICH and SAH.

Furthermore, we collected drug exposure data directly from our study participants. This made it possible to record prescribed as well as nonprescribed OTC NSAIDs. Previous studies were limited in their obtainment of information on OTC NSAIDs,^{4,6} which means that the presumptive unexposed group may have included those actually exposed to NSAIDs. Such misclassification of users as nonusers of NSAIDs would tend to bias the estimates of NSAID effects toward the null.¹³ We minimized interviewer bias by blinding interviewers from the research hypothesis. In addition, before starting the Acute Brain Bleeding Analysis study, a pilot study was conducted to examine the feasibility to confirm items and the order of questionnaire.⁷

In our study, several risk factors, such as family histories of stroke, history of hypertension, smoking, alcohol consumption, high salt intake, and laborious work hours, associated with HS, were included in the multivariate analysis. Family history of stroke is a risk factor associated with HS.¹⁴ Hypertension is also a well-established independent risk factor for both ICH and SAH.^{15,16} With regard to salt intake and hypertension,

many well-designed cross-sectional and longitudinal observational studies have reported that salt intake may increase blood pressure or contribute to hypertension.^{17–20} Also, physical activity may modify hypertension for HS and directly lower stroke risk as well.²¹ Recent meta-analysis showed moderate and high levels of physical activity were associated with reduced risks of HS.^{21,22} Smoking and alcohol drinking are known risk factors for ICH and SAH.^{23–27} We adjusted all of these risk factors in our statistical analysis.

However, these results must be interpreted in light of some limitations. First, this study presented a lower rate of NSAIDs exposure than other studies.^{4–6} The problem could decrease the power of this study. This difference was caused by the definitions of current NSAIDs users. Some of the other studies labeled current NSAIDs users even if the subject's prescription lasted until the index date or ended within 30 days before the index date.^{4,6} However, we defined exposure to NSAIDs as being exposed to NSAIDs within 14 days before the index date. Second, we included patients who were hospitalized and had the mental capacity for responding to a direct interview to avoid information bias from proxy interviewers. In this regard, we included those

Table 3. Association Between NSAIDs and the Risk of Hemorrhagic Stroke According to Hemorrhagic Stroke Subtype

Type of Hemorrhagic Stroke	Cases	Controls	Unadjusted OR	95% CI	Adjusted OR	95% CI
Subarachnoid hemorrhage (n=442) (n=442)						
No exposure	435	434	1		1	
Exposure to NSAIDs‡	7	8	0.93	0.44–1.97	1.03*	0.49–2.18
Intracerebral hemorrhage (n=498) (n=498)						
No exposure	478	487	1		1	
Exposure to NSAIDs‡	20	11	1.30	0.83–2.04	1.19†	0.76–1.87

*Adjusted for family history of stroke, history of hypertension, smoking, high salt intake, and laborious work hours.

†Adjusted for family history of stroke, history of hypertension, alcohol consumption, high salt intake, and laborious work hours.

‡Exposure to NSAIDs was defined as being exposed to NSAIDs within 14 days before the index date.

patients with milder strokes but may have overlooked patients with severe neurological deficits or those who died before they had reached a hospital. Thus, the study participants were not representative of all HS patients. Therefore, our findings do not apply to all HS patients, particularly those having severe or fatal neurological statuses. Third, we collected our information about potential confounders and drug exposure after the onset of HS. This recall bias might have affected the results; therefore, to minimize this effect, we kept the interviewers and participants blind to the major hypothesis of this study. The information on OTC NANSAlDs use from pharmacies was collected by depending on the participants' memories. Packages of major NANSAlDs were used to aid subjects' recall of the brand names but failed to cover all of the NANSAlDs in the market. However, we included many kinds of frequently used OTC NANSAlDs packages and the effect of missing OTC drugs used is likely small within our study. In conclusion, we found the use of NANSAlDs does not increase the risk of HS, either SAH or ICH.

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None.

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