Caffeine-Containing Medicines Increase the Risk of Hemorrhagic Stroke

Seung-Mi Lee, PhD*; Nam-Kyong Choi, PhD*; Byung-Chul Lee, MD, PhD; Ki-Hyun Cho, MD, PhD; Byung-Woo Yoon, MD, PhD; Byung-Joo Park, MD, PhD

Background and Purpose—Research on the relationship between caffeine-containing medicines (CCMs) and the risk of hemorrhagic stroke (HS) is sparse. The aim of this study is to evaluate the association between CCMs and the risk of HS.

Methods—We performed a multicenter case–control study in South Korea, from 2002 to 2004. A total of 940 patients with nontraumatic acute HS, aged 30 to 84 years without a history of stroke, 940 community, and 940 hospital controls, age and sex matched to each case, were included. We obtained information on all medications taken in the 14 days before the date (index date) and time of stroke onset (zero-time) for case subjects or matched zero-time for control subjects. Exposure to CCMs was defined by use on the index date before zero-time or during the preceding 3 days. The adjusted odds ratios and their 95% confidence intervals (CIs) were estimated by conditional logistic regression.

Results—The adjusted odds ratio for the association between the use of CCM and risk for HS was 2.23 (95% CI, 1.41–3.69) for all HS, 2.24 (95% CI, 1.08–4.66) for subarachnoid hemorrhage, and 2.49 (95% CI, 1.29–4.80) for intracerebral hemorrhage. Stratified by daily coffee intake, adjusted odds ratio of CCMs for HS was 2.95 (95% CI, 1.45–5.98) for those who did not drink coffee on a daily basis.

Conclusions—These results suggest that use of CCMs is associated with increased risk of HS, both subarachnoid hemorrhage and intracerebral hemorrhage. (Stroke. 2013;44:2139-2143.)

Key Words: caffeine ■ case-control studies ■ cerebral hemorrhage ■ subarachnoid hemorrhage

Caffeine is the most widely consumed central nervous system stimulant in the world.1 Caffeine is present in a variety of foods and beverages, as well as some medicines. Many cold remedies, pain relievers, and fatigue restoratives include caffeine for its antihypnotic effects or to enhance the main effects of these drugs.2 Although consumers frequently self-medicate with these medicines, few consumers are aware of the presence of caffeine as an ingredient.

There have been many studies devoted to caffeine in an attempt to determine its effects. Because the primary source of caffeine for many people is coffee, most caffeine studies have focused on the relationship between coffee consumption and the risk of disease. Although still controversial, increasing evidence supports the hypothesis that coffee consumption does not increase the risk of hemorrhagic stroke (HS).3–7 In addition, a recent meta-analysis reported that moderate coffee consumption may be weakly inversely associated with risk of all types of stroke.5 A few studies have addressed tea consumption, which might reduce the risk of ischemic stroke.9,10 The association of caffeine in pharmaceutical products and aneurysmal subarachnoid hemorrhage (SAH) or intracerebral hemorrhage (ICH) warrants further study.11,12 Therefore, a nationwide, multicenter, matched case–control study was performed to evaluate the association between caffeine-containing medicines (CCMs) and the risk of HS, including SAH and ICH in those aged 30 to 84 years.

Methods

Study Design and Setting

The multicenter, matched case–control study data collected for the acute brain bleeding analysis were used.13 Patients who had experienced a HS, and who were aged 30 to 84 years and able to complete an interview, were recruited sequentially from 33 hospitals in Korea between 2002 and 2004. This study was approved by the Seoul National University Hospital/Seoul National University College of Medicine institutional review board, and all study participants provided written informed consent to participate.

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2,710 patients aged 25 years or more and hospitalized with hemorrhagic stroke were screened. 416 patients* were excluded because: 306 had a history of stroke, 106 were less than 30 years or more than 84 years, 56 had a history of brain lesion to increase risk for hemorrhagic stroke, and 13 had a brain hemorrhage caused by trauma.

2,294 patients were eligible for this study except the ability to communicate & complete interview. 1298 patients* did not complete the interview because; 1,081 were not able to communicate within 30 days after stroke, 150 refused to participate in this study, 31 were discharged before the arrangement of interview, 5 were diagnosed as no hemorrhagic stroke, 3 were older than 84 years old at the day of interview and 67 withdrew consent during interview.

996 patients completed the interview. 968 were matched to hospital control. 943 were matched to community control. 940 patients were completely matched to 1880 control subjects without violation.

**Identification of Cases**

We screened all of the patients with HS admitted to the participating hospitals. HS was defined as either SAH or ICH. The diagnosis of SAH was based on clinical symptoms plus either a brain image (computed tomography [CT], MRI) or evidence of xanthochromia on a lumbar puncture. ICH was diagnosed on the basis of clinical symptoms and detection of blood in the brain parenchyma or ventricles by CT or MRI. Study eligibility criteria included ages ranging from 30 to 84 years, absence of a history of stroke or hemorrhage-prone brain lesions, no causal relationship of the stroke to trauma, and the ability to communicate and complete an interview within 30 days after the onset of the stroke. For each patient, we identified the zero-time as the calendar day (ie, index date) and the time of day that marked the onset of symptoms that were plausibly related to hemorrhage and that caused the patient to seek medical attention.14 We defined the zero-time after considering the symptoms of hemorrhage, including paralysis, vertigo, disorders of memory, epilepsy, numbness, diplopia, impaired vision, dysphagia, disorders of consciousness, dysarthria, sentinel headache, dysuria, syncope, aphasia, nausea, vomiting, and motor ataxia. The neurologist at participating hospitals reviewed each case and established the zero-time. All of the collected medical and image information was then sent to the central coordinating center according to the standard operating procedure agreed in advance. A second and final check on eligibility and reconfirmation of the diagnoses were completed by 1 neurologist at central coordinating center who was kept unaware of medication exposures. Any ambiguities were resolved by consensus with the neurologist at participating hospitals. The purpose of the multilevel review was to ensure uniform standards for documentation and eligibility across all participating hospitals. According to the process, missing clinical data were obtained. Finally, among the 2294 patients who were eligible for this study, a total of 5 patients were excluded after adjudication, who were not actually cases of HS.

**Selection of Controls**

Each case was matched to 2 controls (hospital and community) by age (±5 years) and sex. Hospital controls were selected among patients who were hospitalized in the same institution for diseases other than stroke, but who were not in the hospital when the stroke of the matched case occurred and had been hospitalized after the date of the stroke event. The eligible hospital controls were screened from the order communication system or electronic medical record system in each participating hospital using a daily update of the list of cases. If there were multiple subjects, the hospital controls were preferably selected among the hospitalized patients from otolaryngology, orthopedic, ophthalmology, neurology, and neurosurgery departments. The closest subject to the patient with respect to date of birth was the first chosen from the list of eligible controls. After confirming the interview availability by considering the subject’s conditions with an attending physician of the subject, the potential control was asked to sign a consent form to participate in the study.

The eligibility criteria for the community controls included absence of a history of stroke, absence of dementia or other neuropsychological diseases, and the ability to communicate. The community control was recruited from siblings, friends, or neighbors of the patient, in whom the patient perceived the person to be close and involved in the care of the patient.
Table 2. Association of CCMs and CFMs With the Risk of HS

<table>
<thead>
<tr>
<th>Type of Medicines</th>
<th>Cases n=940 (%)</th>
<th>Controls n=1880 (%)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCMs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>894 (95.1)</td>
<td>1836 (97.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Exposure to</td>
<td>46 (4.9)</td>
<td>44 (2.3)</td>
<td>2.21 (1.44–3.41)</td>
<td>2.28 (1.41–3.69)</td>
</tr>
<tr>
<td>CFMs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>916 (97.4)</td>
<td>1830 (97.3)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Exposure to</td>
<td>25 (2.7)</td>
<td>50 (2.7)</td>
<td>0.98 (0.61–1.58)</td>
<td>0.71 (0.39–1.28)</td>
</tr>
</tbody>
</table>

CCM indicates caffeine-containing medicines; CFMs, caffeine-free medicines; HS, hemorrhagic stroke; CI, confidence interval; and OR, odds ratio.

*ORs and 95% CIs were calculated by conditional logistic regression, adjusted for age, a family history of stroke, a history of hypertension, a history of diabetes mellitus, upper respiratory tract infection within 30 days from zero-time, high salt intake, current smoking, daily tea intake, and phenylpropanolamine intake on the index day before zero-time or during the preceding 3 days.

descending order of preference. The recruited patients offered names and contact information of potential controls in order (eg, first: sibling 1, second: sibling 2, third: friend 1, fourth: neighbor 1, fifth: neighbor 2, and sixth: neighbor 3). Therefore, the sequence of potential controls was established by the case. Trained nurse interviewers called the suggested potential controls according to the order. We selected the controls in sequence when they met the inclusion criteria and received consent to participate in the study.

Every interview with control subject had to be completed within 30 days after zero-time of the matched case and within 7 days when the matched case’s interview was completed.

Data Collection
Structured questionnaires evaluated for feasibility by an expert panel were administered by trained nurse interviewers to all participants. Each case and their matched controls were questioned on the basis of zero-time of the matched case. To avoid interviewer bias, the interviewers and subjects were kept blind to the hypothesis of this study. They were informed that the objective of this study was to investigate the effect of lifestyles and medications on the risk of HS. Information with regard to the following basic characteristics was obtained from the interview for both cases and controls: age, sex, height, weight, socioeconomic factors, lifestyle factors, medical history, family history of stroke, and all medications taken in the 14 days before zero-time. Dietary habits were examined according to intake of spicy or high salt food stuffs. Participants were asked to indicate how many cups of coffee or tea per day or per week they had consumed during the past year. The questionnaire did not inquire about the type of coffee consumed because consumption of decaffeinated coffee in the Korean population was very low. We obtained information on physical activity performed in the past 6 months from the quantitative history of physical activity surveys. We ascertained a history of exposure to medication for all prescribed and nonprescribed drugs and collected information related to drug brand names, generic names, indications, the first date of administration, dose, and duration.13

Definition of Caffeine-Containing Medicines
A list was made of all the CCMs marketed in Korea during the study period. The brand name, indication, and caffeine content per dose were collected for these medications (Table 1 in the online-only Data Supplement). To compare the risk of CCMs with caffeine-free medicines (CFMs), drugs with the same indication as CCMs (pain relievers, cold remedies, and fatigue restoratives) were included as CFMs. The exposure windows of CCMs and CFMs were defined as the index day before zero-time and the preceding 3 calendar days (eg, if zero-time was 15:00 [24-hour clock] on July 10, the exposure window was from 0:00 [12 midnight] on July 7 to 15:00 on July 10). We defined a 3-day exposure window on the basis of pharmacokinetic effect of caffeine,13 considering previous study results.11,12

Statistical Analysis
We compared demographic, clinical, and behavioral features of the case and control subjects using Pearson χ² test, Fisher exact test, or the Student t test where appropriate. Variables whose P values were <0.1 and with clinical importance were selected as potential confounding 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 age, family history of stroke, history of hypertension, history of diabetes mellitus, upper respiratory tract infection within 30 days from zero-time, high salt intake, current smoking, daily tea intake, and phenylpropanolamine intake on the index day before zero-time or during the preceding 3 days as the adjusting variables. Odds ratios (ORs) and 95% confidence intervals (CIs) of HS associated with CCMs and CFMs were estimated using a conditional logistic regression model. Subgroup analysis was conducted with the different types of HS and control groups.

We calculated the individual caffeine dose per day from medication, and tested trends against daily dose amounts. The CCM dose per day was calculated as follows: CCM dose/d (mg)=the caffeine content per dosage (mg)/the number of dosages per intake×the number of intake per day.

The risk of HS according to the daily intake of caffeine from medication was estimated. The daily intake dose of caffeine from CCMs was split into 2 groups at 35 mg/d which was the median daily intake dose of caffeine in the CCM-exposed control subjects. Additional stratified analyses were performed by the amount of coffee intake, using unconditional logistic regression. The amount of daily coffee intake was categorized into 3 groups: <1 cup, ≥1 cup and <3 cups, and ≥3 cups. All analyses were performed with Statistical Analysis System version 9.2 (SAS Institute, Inc).

Results
A total of 2710 patients with hemorrhagic stroke were screened for their eligibility. Among them, 416 patients were excluded at the time of screening. In addition, 1294 patients were excluded because of not completing the interview. Among 996 patients enrolled and interviewed, 56 were matched to no control subjects or matched to only 1 control subject (Figure 1).

In total, 940 HS patients were matched to 1880 control subjects. Of the cases, 442 (59.0% women; mean age±SD, 50.8±10.6 years) had a SAH and 498 (42.2% women; mean age, 57.1±11.3 years) had an ICH. The cases and controls were generally similar with regard to baseline characteristics, including age, sex, body mass index, history of diabetes mellitus, history of heart disease, and daily coffee intake (Table 1).

A total of 46 patients (4.9%) with HS were CCM users, compared with 44 (2.3%) of the controls, providing a crude OR of 2.21 (95% CI, 1.44–3.41). The adjusted odds ratio (aOR) of CCMs for HS was 2.28 (95% CI, 1.41–3.69), after adjusting for potential confounders, compared with nonusers. However, the aOR of CFMs was 0.71 (95% CI, 0.39–1.28; Table 2). The aOR for subjects with SAH was 2.24 (95% CI, 1.08–4.66), and ICH was 2.49 (95% CI, 1.29–4.80). The results of the subgroup analysis according to type of control are summarized in Table 3. The aOR for subjects with hospital control was 2.14 (95% CI, 1.20–3.83), and community control was 2.64 (95% CI, 1.36–5.12).

Table 4 shows the risk of HS according to daily intake of caffeine from medications. We did not observe a quantitatively significant trend in the association between daily dose of caffeine and risk for hemorrhagic stroke. According to daily coffee intake per group, aORs of CCMs for HS were 2.95 (95% CI, 1.45–5.98) for <1 cup, 1.59 (95% CI, 0.78–3.23) for ≥1 cup and <3 cups, and 1.63 (95% CI, 0.51–5.26) for ≥3 cups (Table 5).
The results of this case–control study indicate that the use of CCMs was associated with an increased risk of HS, both SAH and ICH. Few studies have addressed the association between caffeine and risk of HS. In a recent, small clinical trial, caffeine caused nearly identical blood pressure elevation in men and women, and women responded to caffeine with an increase in cardiac output. In addition, the interaction between caffeine and other ingredients within medications may further increase the risk of HS. Some researchers have reported that taking caffeine with phenylpropanolamine raises the blood pressure and the level of caffeine in the plasma because phenylpropanolamine increases caffeine absorption and inhibits its removal. Taking caffeine with Mahuang, which includes ephedrine or pseudoephedrine, has been reported to induce arrhythmias, high blood pressure, and intracranial hemorrhage, by increasing sympathomimetic action. Cold remedies or appetite suppressants containing phenylpropanolamine have also been suggested to increase the risk of HS.

In the stratified analysis according to coffee intake, the group that did not drink coffee daily had a significantly higher risk of HS compared with those who frequently drank coffee. The finding of a higher OR among persons with a lower daily intake of caffeine makes sense because users develop tachyphylaxis to caffeine. Those who did not drink coffee daily made up 44% of both the case and control groups. Therefore, our estimates of ORs do not seem to have been affected by coffee consumption itself.

This study has several strengths. First, the diagnostic accuracy was high because all cases of HS were confirmed by CT or MRI brain image. No SAH patients presented with a normal CT scan but positive LP finding. Furthermore, the neurologists were blinded to the drug exposure information when they evaluated potential cases according to predefined criteria. Second, we collected drug exposure data directly from our study participants. Most of the CCMs are available at pharmacies without a prescription, whereas only a few needs a physician’s prescription; therefore, we were able to collect information on prescribed and nonprescribed CCMs.

However, our results must be interpreted in the context of the following study limitations. First, there was no choice but to use personal interviews to obtain information on whether subjects took CCMs. Therefore, we included patients who were hospitalized and had the mental capacity to respond to a direct interview to avoid information bias from proxy interviewers. For this reason, we included those patients who experienced milder strokes, and in doing so excluded patients with severe neurological deficits or those who died before they had reached a hospital. Thus, the study participants did not represent the whole spectrum of HS patients; and, therefore, our findings do not apply to all HS patients, especially those with severe or fatal neurological status.

In the selection of nonpopulation-based controls from sources, such as hospital admissions or discharges, the same primary care provider, friends, or relatives, risks the possibility that the selection may be related to some of the factors under study. In our study, consistency among results across a series of control groups suggests that bias by control selection may not be a substantial weakness of this study. Second, we collected our information on potential confounders and drug exposure after the onset of HS. Recall bias at this point may have affected the results; therefore, to minimize this possibility, we kept the interviewers and participants blind to the major study hypothesis. The information on the use of nonprescription medication from pharmacies depended on the participants’ memories.
to confirm the association.

Although these results are suggestive, further analysis should be performed to confirm the association.

Third, temporal-precedence bias might have affected our study. The bias refers to a systematic error in which an exposure is counted, although the exposure occurs after the onset of the disease under study, often in response to disease symptoms. Therefore, reverse causality occurs when the probability of the outcome is causally related to the exposure being studied. The most common scenario for use of CCMs was for treatment of headache, which is often a presenting and important symptom of brain hemorrhage. Moreover, CCMs are used as self-medicating drugs to relieve pain or cold symptoms, or to recover from fatigue. Individuals who frequently experience colds or fatigue may be in a relatively unhealthy condition. Although this study cannot assuredly be performed to confirm the association.

Conclusions

Results from this nationwide multicenter case–control study suggest that caffeine in pharmaceutical products may increase the risk of HS, including both SAH and ICH. The increased risk was especially evident in the rarely drinks coffee group. Although these results are suggestive, further analysis should be performed to confirm the association.

Disclosures

None.

References

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Caffeine Containing Medicines Increase the Risk of Hemorrhagic Stroke

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Supplemental Methods

Selection of Controls

The ABBA study was originally designed to investigate the risk of HS in relation to PPA exposure in decongestants used as cold remedies. Thus, those departments’ patients were considered as optimal hospital control groups that were not related to the use of cold remedies to address the primary research question. Accordingly, a majority of the hospital controls were selected from neurology (34.8%), orthopedic (30.4%), neurosurgery (5.7%), and otolaryngology departments (5.5%).1,2

Community controls were selected from siblings, friends, or neighbors of each case in descending order of preference. The community controls were selected from among siblings (8.4%), friends (11.4%), and neighbors (78.6%).

Data Collection

We ascertained an exposure history to medication before the index date for all prescribed and non-prescribed drugs and collected information related to drug brand names, generic names, indications, and the first date of administration, dose, and duration. We also tried to obtain the doctor’s prescriptions from all study subjects. When prescriptions were unavailable or medications were purchased without prescriptions, 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 set of real samples of drugs and a sample book of photographs of drug packages. If the subjects could not select their products from the sample book, we asked their pharmacists by
telephone. We particularly included most of the pain relievers and cold remedies, regardless of caffeine content. Only patients who had verified exposures to medication were counted in the analysis.

**Definition of Caffeine Containing Medicines**

Most of the CCMs contained certain active ingredients according to their indication. The pain relieving, cold remedy, and fatigue restorative CCMs contained acetaminophen, sympathomimetic agents, and taurine, respectively. Therefore, to improve comparability, the CFMs for cold remediation were defined as drugs containing sympathomimetic agents without caffeine; those for treating fatigue were defined as drugs containing taurine without caffeine; and those for pain relief were defined as drugs containing acetaminophen without caffeine.

**Supplemental Results**

Compared to the control subjects, case patients were more likely to have a family history of stroke, a history of hypertension, an upper respiratory infection within 30 days prior to the index date, be current smokers, current alcohol drinkers, frequent spicy food intake, have a high salt intake, work ≥ eight hours a day, and perform laborious work ≥ seven hours a day; however, they were less likely to have a history of hyperlipidemia and daily tea intake (Table I).

**Supplemental Discussion**

Recall bias at this point may have affected the results; therefore, to minimize this
possibility, we kept the interviewers and participants blind to the major study hypothesis. The information on use of non-prescription medication from pharmacies depended on the participants’ memories. Packages of major non-prescription drugs were used to aid recall of brand names, but failed to cover all drugs, including CCMs, on the market. However, we included the packages of many frequently used non-prescription drugs, and the effect of participant use of missing drugs is likely negligible within our study.

The selection of non-population-based controls from sources such as hospital admissions or discharges, the same primary care provider, friends or relatives, risks the possibility that the selection may be related to some of the factors under study. However, population-based controls are often identified by telephone surveys using random digit dialing (RDD) sampling methods, which are now experiencing serious problems with response rates. A recent alternative approach involved selecting controls from frames such as driver license lists that contain valuable demographic information for use in matching. Moreover, the screening costs can be particularly high when the controls are selected by a face-to-face interview survey based on an area probability sample design. To that end, some researchers have suggested choosing more than one control group and in such studies, controls can be selected from non-hospitalized persons living in the community or from hospitalized patients admitted for diseases other than that for which the cases were admitted. In this study, in-depth face-to-face interviews had to be performed within the time period. Therefore, we were forced to choose between hospital controls and those from among friends or relatives. When performing secondary analysis, extra care should be taken to note whether the results are consistent across control groups.
Supplemental References

5. Ibrahim MA, Spitzer WO. The case control study: the problem and the prospect. J Chronic Dis. 1979;32:139-144.
**Supplemental Table I.** The list of caffeine containing medicines that the study subjects took within three days from the index date.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Indication</th>
<th>Formula</th>
<th>Caffeine content (mg/unit)</th>
<th>Maximum daily dose (mg/day)</th>
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<td>Codemil</td>
<td>Cold</td>
<td>Tablet</td>
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