Triggering of Ischemic Stroke Onset by Decreased Temperature: A case-crossover study

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Abstract

Background and Purpose: Some studies suggest that low temperatures can affect mortality, especially deaths associated with circulatory and respiratory condition. The authors investigated the association between ischemic stroke onset and low temperatures in 545 patients over a 3-year period (January 1998 to December 2000) in Incheon, Korea.

Methods: We chose to use a case-crossover study design to assess the changes in the risk of ischemic stroke during a brief hazard period after exposure to a temperature change. For each subject, 1 case period was matched to 2 control periods exactly 1 week apart before and after the date and time of the onset of the ischemic stroke.

Results: Decreased ambient temperature was found to be associated with the risk of acute ischemic stroke. One day after being exposed to cold weather, we found a statistically significant increase of odds ratio to 2.38 (95% CI 1.33, 4.35) for the onset of an ischemic stroke for an interquartile range decrease in temperature. The elevated risk period was 24 to 54 hours after cold exposure. Risk estimates associated with decreased temperature were found to depend on the season, and to be greater in the winter than in the summer. We also found that women, the elderly, and those with hypertension, hypercholesterolemia, or no prior history of stroke are more susceptible to cold-induced ischemic stroke. We suggest that stroke incidence rises with falling temperature, and that even a moderate decrease can lead to a higher occurrence of ischemic stroke. We noted that the impact of cold on stroke incidence was greatest one day after the fall in temperature.

1. Introduction

The adverse health effects associated with cold weather include direct effects, such as hypothermia, and indirect effects, such as increased rates of pneumonia, influenza, and other respiratory illnesses (1). Previous studies also have suggested that low temperatures can affect mortality, and that they increase all cause-of-deaths (2-4). In particular, temperature was found to be significantly and negatively associated with cerebrovascular death after taking influenza into account (5). However, the impact of cold on stroke has not been studied intensely despite frequent mass media reports of anecdotal cases, especially in the winter. If cold is one of the major risk factors of stroke, timely warnings are very important so that susceptible people are able to protect themselves from developing this tragic disease.

We postulate that cold exposure is associated with an increased risk of ischemic stroke and that there is a time interval between the fall in temperature and the peak risk of stroke incidence. Keatinge (6) reported physiologic changes of blood after exposure to cold in a clinical experiment. He found that the increased blood viscosity and plasma fraction of platelets started after 1 hour after cold exposure and did not reach a peak even after 6 hours.

We used a case-crossover design to examine the association between falling temperature and stroke onset. Although our main objective was to determine the presence and magnitude of the association between temperature fall and stroke, we also focused on the delayed effect of temperature fall on the risk of stroke. In addition, we analyzed effect modifications caused by major risk factors of stroke such as hypertension and hypercholesterolemia on the relationship between temperature fall and stroke onset.
Our results show that stroke incidence rises with falling temperature, and that even a moderate decrease of temperature can lead to an increased risk of ischemic stroke. We noted that the impact of cold on stroke incidence becomes most important 1 day after the temperature fall, and report upon modification effects due to age, sex, hypertension, hypercholesterolemia, and a prior history of stroke upon the associations between temperature fall and stroke onset.

2. Methods

Study population
Between January 1998 and December 2000, 545 patients (316 men and 229 women) were interviewed at Inha University Hospital during their period of hospitalization. All of the ischemic stroke cases were diagnosed after an imaging study of the brain by MRI or CT. Regular meetings were held during the study period to insure that consistent interview and diagnostic procedures were used. Data were collected on standard demographic variables as well as risk factors of ischemic stroke. The interview identified the onset time, hospital visit time, and the stroke characteristics. The protocol was approved by the Institutional Review Board of Inha University Hospital, and informed consent was obtained from each patient or care-giver.

Study design
We used a case-crossover study design to assess the change in the risk of ischemic stroke during a brief hazard period after exposure to a temperature change. The important feature of this approach was that the control information for each patient was based on his or her past exposure experience (7,8). Because comparisons are made within-subject, all time-invariant confounders are inherently controlled for (9). The occurrence of neurologic symptoms was used as the marker of disease onset. Information on temperature, relative humidity, and barometric pressure was obtained from the National Meteorological Office.

Statistical Analysis
The analysis of a case-crossover study can be viewed as a stratified data analysis of 545 retrospective, self-matched follow-up studies, each with a sample size of one (10). The stratifying variable is the individual patient. We used the pair-matched analytic approach (conditional logistic regression) to contrast exposures (meteorological variables) for the case period with exposures for the control period. For each subject, 1 case period was matched to 2 control periods exactly 1 week apart before and after the date and time of the onset of the ischemic stroke. Thus, by matching the time of day and the day of the week for the case and the control periods, we controlled for potential confounders due to circadian pattern of stroke onset or day-of-week variations. Exposures to temperature, relative humidity, and barometric pressure were entered into the model as continuous variables. Results are expressed as odds ratios (OR) for an interquartile change in ambient temperature. Unadjusted and adjusted models for relative humidity and barometric pressure were constructed separately. We also evaluated the effect of daily and 3-hour average temperatures on the onset of the ischemic stroke. To explore the susceptibility of groups to the influence of temperature change, we analyzed each subgroup stratified by age, sex, prior stroke, hypertension, hypercholesterolemia, obesity, and smoking to determine if the effects of temperature change differ in these respects.

3. Results

The characteristics of the study population are shown in Table 1. Of the 545 patients, 115 (21.1%) reported that they had a prior history of stroke. 339 (62.2%) and 65 (11.9%) reported hypertension and hypercholesterolemia before stroke onset, respectively. 148 (27.2%) were obese and 217 (40.3%) were current smokers. The distributions of 3-hour and 24-hour average levels of meteorological variables for the period from January 1998 to December 2000 in Incheon are presented in Table 2.

Figures 1 shows results from the conditional logistic regression models, and the unadjusted and adjusted odds ratios between onset of stroke and 24-hour average temperature. Odds ratios are expressed for an interquartile range decrease in temperature (17.4 °C). One day after exposure to falling temperature, we found a statistically significant increase of odds ratio of 2.38 (95% CI 1.33, 4.35) for the onset of ischemic stroke. Exposures 2 days or more before the onset did not reach statistical significance. We also analyzed response to ambient temperature in more detail by considering 3-hour averages (Figure 2), and found a statistically significant association between stroke onset and decreased temperature during the period 24 to 54 hours before the onset of stroke. Table 3 shows seasonal differences in the association between ambient temperature and the risk of stroke onset. Statistically significant elevation of risk of stroke onset one day after a decreased temperature was observed in the winter compared to an insignificant elevation in the summer. After adjusting for relative humidity and barometric pressure, the association between temperature and stroke onset was sustained. We found that women, the elderly, and those who have hypertension, hypercholesterolemia, or no prior history of stroke were more susceptible to cold-induced ischemic stroke. Particulate and gaseous air pollutants, i.e., PM10, NO2, SO2, CO and ozone, did not show statistically significant associations with the stroke onset.
4. Discussion

This study shows that decreased ambient temperature is associated with a higher risk of acute ischemic stroke onset. The elevated risk period of ischemic stroke was 24 to 54 hours after exposure to a fall in temperature. In addition, risk estimates of decreased temperature varied depending on the season, and were greater in the winter than in the summer. Women, the elderly, and those with hypertension, hypercholesterolemia, or no prior history of stroke were more susceptible to cold-induced ischemic stroke. None of the air pollutants achieved statistical significance in this analysis.

The effect of temperature change on human health continues to draw public attention because of increased public awareness of climate change. Previous studies have demonstrated inconsistent results in terms of the relationship between ambient temperature and mortality, including stroke. After an analysis of the relationship between climate and mortality in 44 large US cities, Kalkstein concluded that the coldest winter days are not associated with mortality spikes (1). In contrast, Gorjanc reported that cold temperature contributed significantly to higher mortality rates for total deaths, and that stroke mortality tended to be higher during severe winter weather (11). However, these studies evaluated the effects of cold temperature on mortality rather than on stroke onset. Controversy over the possibility that patients already suffering ischemic stroke die early in a few days due to the impact of cold cannot be avoided by these studies. In this study, we provide clues for this mortality displacement issue by analyzing onset time rather than the date of death.

A community-based study on stroke reported a non-significant relationship between the incidence of ischemic stroke and temperature (12). The study explained that the previously reported winter excess of ischemic stroke could have been due to referral bias in hospital-based studies. To avoid the selection bias, which frequently occurs in hospital-based study, we used a case-crossover study design to evaluate the effects of temperature on stroke onset. Because the case-crossover design involves self-matching, there is no variability of individual risk factors for ischemic stroke within each stratum (13), and therefore, confounders are eliminated. Thus, the effects of cold temperature observed in this study were independent of characteristics that are stable over time in the individual. It has been previously noted that case-crossover design may introduce selection bias and confounding by time variant factors (9,14). However, some studies have indicated that bi-directional case-crossover designs can substantially control for temporal confoundings (15,16). We controlled for circadian rhythm and the day-of-week effect by matching the time of the onset with the periods one week prior and one week post onset of the ischemic stroke.

We found that the onset of ischemic stroke was found to be statistically associated with temperature fall. However, we did not get a statistically significant association between the air pollution level and ischemic stroke onset, although high air pollution is now considered a risk factor for stroke death (17). One possible explanation for this lack of significance is that cold temperature is associated with a much higher risk, scaled at around 2.4 than that of air pollution, scaled at less than 1.1 in the interquartile range change. In addition, because temperature and air pollutant levels are significantly related to each other, the effect of air pollution could easily have been removed by controlling for temperature in this analysis. To evaluate the effect of air pollution properly, it would be necessary to make the sample size much larger, which is probably not applicable with this case-crossover design.

Some studies confirm the biological plausibility of the relationship between cold temperature and ischemic stroke, by demonstrating demonstrating increased platelet counts, fibrinogen, and alpha-2-macroglobulin at low temperatures (6,11,18). These effects on blood coagulability and plasma viscosity could increase the susceptibility of individuals to acute stroke events.

We found a lag period of 24 to 54 hours between exposure to cold and the onset of stroke. The physiologic reason for this lag might be that it takes some time for the lower temperature to affect blood viscosity or coagulation. After the effective window period of 30 hours, the risk of cold on stroke decreased to become statistically non-significant. Bull and Morton also reported an interval of 3-4 days between a change in temperature and stroke death (19).

Risk estimates of temperature change depend on the season, and are greater in the winter than in the summer. The greater effect of temperature change in winter suggests that low temperatures as well as temperature changes are significantly associated with the onset of ischemic stroke. The possibility of increased stroke occurrence caused by outdoor exposure during winter places greater emphasis on the preventive aspects of stroke. A significant reduction of stroke-related health problems could be achieved by reducing the outdoor winter exposures of susceptible people.

For women, aged 65 years and older, and those with hypertension, hypercholesterolemia, or no prior history of stroke, a higher risk of cold-induced ischemic stroke was observed, while for obese individuals and smokers, the risk was lower than in non-obese and non-smoking individuals. Obese people are less affected by temperature fall even though obesity itself is an important risk factor of ischemic stroke. The insulating effect of fat is believed to make the obese less vulnerable to cold. It is not entirely clear why smokers are less affected by temperature fall than nonsmokers, but it is possible that there are fewer smokers among the premorbid who are more susceptible to cold change.
In conclusion, this study demonstrates an association between exposure to falling temperatures and ischemic stroke onset. In addition, the study provides evidence of a lag effect between temperature change and the risk of ischemic stroke. Our analysis indicates that the elderly, women, and those who have hypertension, hypercholesterolemia, or no prior history of stroke carry a greater risk of ischemic stroke onset due to exposure to falling temperatures.
Figure 1. Odds ratio for association between onset of stroke and 24-hour average temperature. Odds ratios and 95% CIs are for a decrease of 17.4 °C (one interquartile range).

Figure 2. Effective window period of cold change on the onset of ischemic stroke.
Odds ratios and 95% CIs are for a decrease of 17.4 °C (one interquartile range).
5. References


