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The Effect of Winter Temperature on Patients with Ischemic Stroke

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Background: The incidence of ischemic stroke increases in winter. This study aimed to explore the effect of winter temperatures on the risk factors, etiology, coagulation, and degree of neurological impairment in patients with ischemic stroke using temperature and rainfall data from the Guangzhou Meteorological Bureau during the winter months of December, January, and February.

Material/Methods: We divided 112 patients with ischemic stroke into low-temperature and non-low-temperature groups. The low-temperature group experienced an average daily winter temperature of <13°C for five consecutive days within the 14 days before hospital admission and an average temperature of <13°C on admission. The non-low-temperature group experienced an average daily temperature of >13°C in the 14 days before hospital admission and an average daily temperature of >13°C on admission. Neurological deficits were scored and monitored using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) for disability in stroke. Blood pressure and coagulation indices of prothrombin time (PT) and thromboplastin time (TT) were recorded.

Results: Compared with the non-low-temperature group, the low-temperature group showed a significantly increased proportion of patients with hypertension and large artery atherosclerotic stroke, more prolonged PT, and higher NIHSS scores. However, TT was reduced in the low-temperature group ($P<0.05$).

Conclusions: When the average winter temperature was <13°C, the risk factors, etiology, coagulation factors, and degree of neurological impairment of patients with ischemic stroke were significantly different from patients with ischemic stroke during warmer temperature.

MeSH Keywords: Clinical Outcome • Prothrombin Time • Stroke • Temperature • Weather

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Background

Worldwide, hemorrhagic and ischemic stroke results in disability and high mortality. Ischemic stroke accounts for between 60–80% of all cases of stroke [1]. According to a World Health Organization (WHO) report, on average, one person in the United States dies of a stroke every four minutes [2]. In China, stroke has become the leading cause of death among urban residents, and the annual incidence of ischemic stroke is increasing by 8.7% [3]. Currently, risk factors for ischemic stroke include increased age, hypertension, diabetes, hyperlipidemia, coronary heart disease, atrial fibrillation, valvular heart disease, obesity, and lack of physical exercise [4]. Hypertension, defined as a blood pressure >140/90 mmHg, is the most important risk factor for ischemic stroke [5]. Epidemiological studies have shown that between 70–80% of patients with ischemic stroke have hypertension [6].

Clinically, prothrombin time (PT) and thromboplastin time (TT) indicate the function of the coagulation and fibrinolytic systems. The PT reflects the activity of exogenous coagulation factors I, II, V, VII, and X, and is the preferred indicator for detecting the effect of oral anticoagulants [7]. A decrease in the PT can be associated with a congenital increase in coagulation factor V, hypercoagulable states, thrombotic disease, and the use of oral contraceptives [8]. The TT is the time required for blood coagulation after the addition of standardized thrombin to the plasma and is mainly used to reflect the function of the fibrinolytic system. The TT is used as a screening test to monitor the function of the fibrinolytic system, and a reduced TT is common in patients with a hypercoagulable state [9].

The incidence of ischemic stroke is significantly increased in winter, especially when the temperature drops sharply in a cold period [10,11]. Currently, the pathogenesis of ischemic stroke remains unclear, but one of the causes may involve a cold-induced increase in blood pressure, hypercoagulation, and fibrinolysis. Currently, studies on the relationship between ischemic stroke and temperature have mainly been epidemiological studies and have not included studies on the effect of temperature. Therefore, this study aimed to explore the effect of winter temperatures on the risk factors, etiology, coagulation, and degree of neurological impairment in patients with ischemic stroke at the First Affiliated Hospital of Sun Yat-sen University using temperature and rainfall data from the Guangzhou Meteorological Bureau during the winter months of December, January, and February.

Material and Methods

Study inclusion and exclusion criteria and study groups

The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University. All patients included in the study provided consent to participate. The inclusion criteria included patients with a confirmed diagnosis of ischemic stroke in accordance with the Fourth National Conference on Cerebrovascular Diseases, 1995 [12], with focal neurological signs confirmed using cranial computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients were admitted to the hospital for no more than 14 days and completed all the required clinical examinations. Neurological deficits were scored and monitored using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) for disability in stroke.

Patients were excluded from the study if they had a NIHSS of ≤1, loss of consciousness, aphasia, or cognitive impairment, a previous history of stroke or transient cerebral ischemic attack (TIA), cerebral arteritis, aneurysm, or vascular malformation, acute angina or myocardial infarction, malignant tumor, chronic renal insufficiency, liver cirrhosis, blood disease, rheumatic disease, or other major systems diseases. Patients who were unwilling to cooperate with the study were excluded.

There were 112 patients with ischemic stroke who were divided into the low-temperature group and the non-low-temperature group. The low-temperature group experienced an average daily winter temperature of <13°C for five consecutive days within the 14 days before hospital admission and an average temperature of <13°C on admission. The non-low-temperature group experienced an average daily temperature of >13°C in the 14 days before hospital admission and an average daily temperature of >13°C on admission.

Meteorological data

Guangzhou Meteorological Bureau provides specific meteorological data for the nine years from December 1, 2006, to February 28, 2015, including the average daily temperature, maximum daily temperature, minimum daily temperature, the difference in daily temperature, precipitation at 20.00 hours, average pressure, average relative humidity, and the number of hours of sunshine. The extent to which the temperature decreased or increased from the previous day and two days was determined according to the differences between the average daily temperature, maximum daily temperature, and minimum daily temperature. Guangzhou is situated in a subtropical coastal area, with the Tropic of Cancer running through its central and southern zones. Based on analysis of the criteria for dividing seasons [13] with winter from December to March and the traditional Chinese winter of the three months of December, January, and February, this study assessed patients during the winter period of the months of December, January, and February.

Previous studies had shown that the incidence of ischemic stroke increased significantly in autumn and winter when the average daily temperature was <12.79°C [14]. A three-year study

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conducted between 1998 and 2000 that included 735 patients with ischemic stroke [15] showed that the incidence of stroke in winter and spring was significantly higher than in summer and autumn when the temperature was below the annual average of 12.8°C. Therefore, for this study, 13°C was chosen as the cutoff for defining low temperature, an average daily temperature <13°C was defined as low temperature and an average daily temperature >13°C was defined as a non-low-temperature.

Subtypes of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST)

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [16], the patients were classified into five types of ischemic stroke: large-artery atherosclerosis (LAA); cardioembolism (CE); small-vessel occlusion (SVO); stroke of other determined etiology (SOD); stroke of undetermined etiology (SUD). Patients with CE, SAO, SOD, SUD subtypes were combined into a non-large artery atherosclerosis (NLAA) group.

Patient assessment methods

The demographic and clinical history of the patients were obtained by reviewing the medical records. Data on the average daily temperature at the onset of ischemic stroke were collected from the meteorological data. The degree of neurological impairment was assessed using the NIHSS, and the modified Rankin Scale (mRS) for disability in stroke were used. The blood pressure of the patients was recorded within eight hours of hospital admission and measurement of coagulation factors thromboplastin time (TT) and prothrombin time (PT) were determined within 24 hours of hospital admission.

Statistical analysis

Data were analyzed using SPSS version 22.0 software. Meteorological data, the NIHSS, TT, and PT of each group did not conform to normal distribution. The median (M) and quartiles (P_{25}, P_{75}) were used to describe the risk factors and the TOAST classification. Meteorological information, NIHSS, TT, PT, and systolic and diastolic blood pressures were analyzed using the Mann–Whitney U test because these did not conform to normal distribution. Risk factors and TOAST classification were tested using the chi-squared (χ^2) test. A P-value <0.05 was considered to be statistically significant.

Results

Characteristics of the patients

Among the 112 patients with ischemic stroke who were admitted to the First Affiliated Hospital of Sun Yat-sen University between January 1, 2007, and February 28, 2015, 72 patients were men, and 40 were women (mean age, 63.59±11.72 years). They were divided into a low-temperature group (85 cases from 67 days) and a non-low-temperature group (27 cases from 23 days). The neurologists of our hospital scored the degree of neurological deficit within eight hours of admission according to the National Institutes of Health Stroke Scale (NIHSS). No significant differences were found in gender or age between the two groups (P>0.05).

Clinical and demographic findings

There were no significant differences in the medical history between the patients in the two study groups for hyperlipidemia, diabetes, coronary heart disease, and atrial fibrillation, and no difference in smoking or drinking behavior between the patients, indicating that the two groups of patients in this study were comparable (Table 1). Comparing the daily weather experienced by the different temperature groups, there was no statistical differences in daily temperature, temperature drop from the previous day, temperature drop from the previous two days, temperature rise from the previous day, temperature rise from the previous two days, the precipitation at 20.00 hours, the average air pressure, the average relative humidity, or the number of hours of sunshine. The results are shown in Table 2.

Risk factors, etiological types, coagulation factors, and degree of neurological impairment

According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [16], the patients were classified into five types of ischemic stroke: large-artery atherosclerosis (LAA); cardioembolism(CE); small-vessel occlusion (SVO); stroke of other determined etiology (SOD); stroke of undetermined etiology (SUD). The proportion of patients with hypertension in the low-temperature group was 65 (76.5%), which was greater than that in the non-low-temperature group, which was 14 (51.9%). The systolic blood pressure of 155 mmHg (140, 169) mmHg in the low-temperature group was higher than in the non-low-temperature group of 135 mmHg (120, 150) mmHg. The diastolic blood pressure of 89 mmHg (80, 96) mmHg in the low-temperature group was higher than in the non-low-temperature group of 80 mmHg (72, 82) mmHg. The proportion of cases of LAA in the low-temperature group was higher than that in the non-low-temperature group (P<0.05), and the proportion of modified Rankin Scale (mRS) scores for disability in stroke of 0–2 in the low-temperature group was 22 (25.9) compared with 22 (81.5) for the non-low-temperature group (P<0.05). The thromboplastin time (TT) in the low-temperature group was significantly lower than that in the non-low-temperature group (P<0.05). Compared with the non-low-temperature group, the prothrombin time (PT), NIHSS score, systolic

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Table 1. Comparison of the clinical information of the patients with ischemic stroke in the low-temperature group and the non-low-temperature group.

Parameters	Low-temperature group (n=85)	Non-low-temperature group (n=27)	P-value
Risk factor (n, %)			
Hypertension	65 (76.5)	14 (51.9)	0.02
Diabetes	29 (34.1)	8 (29.6)	0.67
Hyperlipidemia	25 (29.4)	7 (25.9)	0.73
Coronary heart disease	7 (8.2)	1 (3.7)	0.43
Atrial fibrillation	2 (2.4)	2 (7.4)	0.22
Smoking	29 (34.1)	14 (51.9)	0.10
Drinking	20 (23.5)	6 (22.2)	0.85
TOAST classification (n, %)			0.02
LAA	62 (72.9)	13 (48.1)	
NLAA	23 (27.1)	14 (51.9)	
mRS scores (n, %)			0.01
0–2	22 (25.9)	22 (81.5)	
3–5	63 (74.1)	5 (18.5)	

Data are expressed as number (%). LAA – large artery atherosclerosis; NLAA – non-large artery atherosclerosis; mRS – modified Rankin Scale; TOAST – Trial of Org 10172 in Acute Stroke Treatment classification [16].

Table 2. Comparison of the weather information for the low-temperature group and the non-low-temperature group of patients with ischemic stroke.

Parameters	Low-temperature group (n=85)	Non-low-temperature group (n=27)	P-value
Mean daily temperature on admission (°C) (P_{25}, P_{75})	11.00 (9.20, 12.10)	19.00 (16.70, 20.60)	<0.01
Mean daily temperature difference (°C) (P_{25}, P_{75})	8.40 (5.50, 12.55)	7.10 (4.90, 10.40)	0.23
Mean temperature drop difference with the previous day (°C) (P_{25}, P_{75})	8.70 (5.20, 11.50)	8.70 (4.70, 9.90)	0.25
Mean temperature drop difference with the previous two days (°C) (P_{25}, P_{75})	8.60 (4.90, 10.90)	8.20 (5.50, 10.00)	0.73
Mean temperature rise difference with the previous day (°C) (P_{25}, P_{75})	8.80 (5.40, 12.75)	7.20 (5.50, 8.60)	0.09
Mean temperature rise difference with the previous two days (°C) (P_{25}, P_{75})	8.40 (5.50, 12.55)	7.70 (6.40, 9.20)	0.21
Mean rainfall at 20: 00 hrs (0.1 mm) (P_{25}, P_{75})	0 (0, 16)	0 (0, 5)	0.82
Mean pressure (0.1 hPa) (P_{25}, P_{75})	10146 (10121, 10169)	10123 (10103, 10161)	0.07
Mean relative humidity (%) (P_{25}, P_{75})	68 (59, 80)	69 (60, 82)	0.59
Mean hours of sunshine (0.1 h) (P_{25}, P_{75})	29.0 (0.0, 81.5)	64.0 (9.0, 86.0)	0.07

Data are expressed as median (M) and quartiles (P_{25}, P_{75}). Temperature drop difference with the previous day=the previous day maximum temperature–present day minimum temperature. Temperature drop difference with the previous two days=the previous two day's maximum temperature–present day's minimum temperature. Temperature rise difference with the previous day=present day's maximum temperature–previous day's minimum temperature. Temperature rise difference with the previous two days=present day's maximum temperature–previous two day's minimum temperature.

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Table 3. Comparison of systolic blood pressure (mmHg), diastolic blood pressure (mmHg), National Institutes of Health Stroke Scale (NIHSS), thromboplastin time (TT), and prothrombin time (PT) for the low-temperature group and the non-low-temperature group of patients with ischemic stroke.

Parameters	Low-temperature group (n=85)		Non-low-temperature group (n=27)		P-value
Median systolic blood pressure (mmHg) (P_{25}, P_{75})	155	(140, 169)	135	(120, 150)	<0.01
Median diastolic blood pressure (mmHg) (P_{25}, P_{75})	89	(80, 96)	80	(70, 82)	<0.01
Median NIHSS score (P_{25}, P_{75})	6.0	(4.0, 10.5)	5.0	(2.5, 9.0)	0.04
Median TT (s) (P_{25}, P_{75})	17.3	(16.1, 18.3)	18.7	(17.6, 19.5)	<0.01
Median PT (g/L) (P_{25}, P_{75})	12.0	(11.4, 12.6)	11.3	(10.5, 12.1)	0.01

Data are expressed as median (M) and quartile (P_{25}, P_{75}); NIHSS – National Institutes of Health Stroke Scale; TT – thromboplastin time; PT – prothrombin time.

blood pressure, and diastolic blood pressure in the low-temperature group were significantly higher (P<0.05). These results are shown in Tables 1 and 3.

Discussion

Ischemic stroke, also known as cerebral infarction, is mainly caused by insufficient blood and oxygen supply to the brain, and the resulting damage to brain tissues results in structural and functional disorders as well as in neurological impairment. The incidence and mortality rates of ischemic stroke increase significantly in cold winter [17,18]. A three-year study conducted in the Biya River, Poland, included 1,173 patients with ischemic stroke and showed that the incidence increased significantly in December and was lowest in August and September [17]. In 2007, a review of the incidence of ischemic stroke and meteorological data in Shenzhen, China from 2003 to 2005 showed that cold was the main meteorological association in Shenzhen residents, and with the decrease in temperature, the incidence of ischemic stroke increased, especially among women and patients <65 years [20]. Ischemic stroke has been previously reported to be associated with low temperatures, and every 1°C fall in temperature below the average daily temperature was associated with a 3.9% increase in incidence [21].

The findings of the present study showed that, when compared with the non-low-temperature group, the low-temperature group showed significantly more severe neurological impairment (P<0.05). Also, low temperatures increased the incidence of stroke. However, the pathogenesis of the relationship between low temperature and ischemic stroke remains unclear, but it may be due to vasoconstriction and increased blood pressure vascular congestion and edema that results from the cold [22]. Long-term hypertension can lead to reduced blood coagulation and fibrinolysis and resulting in intravascular thrombosis [23]. Chronic hypertension is also a cause of cerebral artery atherosclerosis leading to ischemic stroke [24].

There is evidence that low temperature can lead to hypertension. A two-year observational study that included 57,375 people showed that blood pressure in January was significantly higher than that in July (P<0.05), and the average blood pressure increased by 6.9/2.9 mmHg with the decrease of ambient temperature by 10°C [25]. A study of blood pressure in 213 volunteers for three consecutive years showed that systolic blood pressure decreased by 0.4 mmHg and the diastolic blood pressure decreased by 0.28 mmHg for each temperature increase of 1°C when the ambient temperature was >10°C [26]. An animal study showed that blood pressure, heart rate, and blood viscosity of spontaneous hypertensive rats (SHR) increased after cold stimulation (P<0.05) [27].

The findings of the present study showed that the blood pressure of the low-temperature group was higher than that of the non-low-temperature group (P<0.05). [28] There are several possible explanations for these findings. Cold can lead to the upregulation of vasoconstriction-associated molecules, including adrenaline, noradrenaline, and renin, which induce peripheral vasoconstriction, increase peripheral vascular resistance, and increase blood pressure [28]. Also, cold can lead to decreased production of vasodilator molecules, including nitric oxide (NO), which results in increased blood pressure [28].

In 1993, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [16], identified five types of ischemic stroke, which were used to group the patients in this study as large-artery atherosclerosis (LAA). The TOAST subgroups included cardioembolism (CE); small-vessel occlusion (SVO); stroke of other determined etiology (SOD); stroke of undetermined etiology (SUD) [16]. The findings from a four-year retrospective study involving 442 patients with ischemic stroke

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with an average follow-up time of 3.2 years showed that the recurrence rate of stroke at 30 days was significantly different in the LAA group (P<0.001), who had the highest recurrence rate of 18.5% (95% CI, 9.4–27.5%) [29]. A study conducted between 2011 to 2014 showed that the proportion of LAA in patients with ischemic stroke was significantly greater than in other types of stroke (P<0.05), and the incidence of hypertension in patients with LAA was higher than that in other types of stroke [30]. Our results showed that the proportion of patients with LAA in the low-temperature group was significantly higher than that in the non-low-temperature group (P<0.05), which was consistent with previously published findings. It is possible that low temperature can induce the increase of red blood cells and platelets, promote the increase of blood viscosity, platelet adherence and activation, leading to thrombosis [31].

The prothrombin time (PT) not only reflects the activity of exogenous coagulation factors I, II, V, VII, and X but can also reflect the level and activity of prothrombin in the plasma [32,33]. PT is a screening test used to examine the function of the exogenous coagulation system and is also an important detection index for clinical anticoagulation therapy. Ischemic stroke is a thrombotic disease, and PT can be expected to be reduced at low temperatures. However, the increase in PT in patients with ischemic stroke may be explained by several mechanisms. First, during thrombosis, a large number of exogenous coagulation factors that included factors I, II, V, VII, and X are consumed and the rate of synthesis of blood coagulation factors is lower than the consumption in the liver. The plasma of patients with exogenous coagulation factors is therefore decreased, resulting in a prolonged PT. Second, there is a fibrinolytic system in the body that opposes the coagulation system, and after the formation of thrombus, the fibrinolytic system plays a protective role. Platelets can accumulate at sites of vascular disease, and the activity of the fibrinolytic system releases thrombin releasing into the blood that enhances coagulation activity and promotes thrombosis. In a previously published study of 120 patients with ischemic stroke that compared the blood coagulation indicators with 30 healthy people, the results showed that among the patients with ischemic stroke, the PT was significantly higher than that in the normal control group [34]. These previous findings were consistent with the results of the present study.

The thromboplastin time (TT) is a screening test that measures the time to convert fibrinogen to fibrin. The TT of patients with cerebral infarction was previously shown to be significantly reduced, and levels of fibrinogen were significantly increased (P<0.01) [35]. In the present study, the TT in the low-temperature group was significantly lower than that in the non-low-temperature group (P<0.05), and the degree of neurological impairment was significantly greater (P<0.05), indicating that TT could be used as an additional clinical index in ischemic stroke. Timely measurement of coagulation factors in patients with ischemic stroke is helpful in the early identification of a hypercoagulable state, to monitor active treatment, and may be a prognostic marker of disease severity.

Low temperatures can affect the coagulation and fibrinolysis systems and promote the formation of a hypercoagulable state. A previously published animal study [36] showed that low temperature could significantly reduce the TT in mice and increase platelet aggregation (P<0.05). Other animal experiments [37] have shown that low temperature can alter the regulation of the balance between coagulation and fibrinolysis. A change in the levels of the thrombin-antithrombin complex and the balance between fibrinolytic and antifibrinolytic factors may promote the occurrence of stroke. The results of this study showed that the TT in the low-temperature group was significantly reduced compared with the non-low-temperature group (P<0.05), which was consistent with the findings from previous studies.

This study had several limitations. First, the patient data in this study were obtained from a single center, the First Affiliated Hospital of Sun Yat-sen University, which may have introduced study bias. Second, this study measured coagulation factors in the patients on hospital admission but did not follow-up the changes in coagulation through the course of the disease. Therefore, the findings from this study require validation with large-scale multicenter controlled studies.

Conclusions

The aim of this study was to investigate the effect of winter temperatures on the risk factors, etiology, coagulation, and degree of neurological impairment in patients with ischemic stroke using temperature and rainfall data during the winter months of December, January, and February. The findings showed that when the average winter temperature was <13°C, the risk factors, etiology, coagulation factors, and degree of neurological impairment of patients with ischemic stroke were significantly different from patients with ischemic stroke during warmer temperature. Temperature is an important factor to consider in the management of patients with ischemic stroke, and low temperature should be considered as a risk factor associated with reduced prognosis.

Acknowledgments

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Conflict of interest

None.

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