Ambient Temperature and Severity of Intracerebral Haemorrhage: The INTERACT1 Study

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Key Words

Intracerebral haemorrhage · Ambient temperature · Haematoma volume · NIHSS score · Glasgow Coma Scale score · Clinical trials · INTERACT

Abstract

Background: Intracerebral haemorrhage (ICH) rates increase in winter months. We aimed to determine associations of ambient temperature with clinical severity and haematoma size in acute ICH among Chinese participants in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT1). **Methods:** INTERACT1 was a randomised controlled trial of early intensive blood pressure lowering in 404 patients with acute ICH. Among 304 (79%) Chinese participants, data on ambient temperature (average, minimum, maximum and range) on the day of ICH onset obtained from the China Meteorological Data Sharing Service System were linked to measures of clinical severity: elevated National Institute of Health Stroke Scale score (>10), low Glasgow Coma Scale score (<14), and haematoma parameters at the time of presentation. Clinical outcomes were evaluated in logistic regression models, and haematoma volume (log transformed, with and without intraventricular haemorrhage, IVH) was evaluated in multivariable regression models. **Results:** No significant associations were evident between tempera-

ture parameters and clinical parameters and haematoma volume (with and without IVH), even after adjustment for key prognostic factors. **Conclusions:** No relationship was evident between ambient temperature and severity in acute ICH.

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Introduction

Global climate change has elicited concerns over adverse effects on human health. Observational studies across the world are consistent in indicating an association between weather and rates of intracerebral haemorrhage (ICH) [1–3] due to various mechanisms including cold weather-induced blood pressure (BP) elevation [4, 5] and changes in blood coagulation [6], which can also result in larger haematomas and subsequent poorer clinical outcomes [7]. Few studies have investigated the association between ambient temperature and severity of ICH. We examined the relationship between diurnal ambient temperature and severity of ICH – defined by scores on the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) – and haematoma volumes of Chinese participants in the pilot phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT1).

Methods

The design of the INTERACT1 study has been described in detail elsewhere [8–11]. Briefly, 404 patients with computerized tomographic (CT) confirmed ICH, elevated systolic BP (150–220 mm Hg) and capacity to commence BP lowering within 6 h of onset were recruited in Australia, China and South Korea during 2005–2007. Exclusion criteria included a contraindication to intensive BP lowering, an ischaemic stroke within 30 days, a GCS score of 3–5, and significant pre-stroke disability or mental illness. Trial participants were randomly assigned to intensive lowering of BP (target systolic BP <140 mm Hg) or guideline-based management of BP (target <180 mm Hg) using routinely available intravenous agents. For patients allocated to the intensive treatment group, the treatment goal of 140 mm Hg was to be achieved within 1 h and maintained for the next 7 days. The study protocol was approved by the ethics committee at each participating site and written informed consent was obtained from each patient or their legal surrogate. After exclusion of 80 patients without information on ambient temperature in their city on the day of ICH onset, a total of 304 (79%) of all 384 Chinese participants were included in these analyses.

Information on daily ambient temperature (average, minimum, maximum and range) in each city was obtained from China Meteorological Data Sharing Service System. The accuracy and reliability of the weather data from this system has been previously evaluated [12]. Temperature parameters on the day of onset of the ICH event were linked with the data of each patient [13], which included measures of clinical severity according to scores on the NIHSS (scores >10 defined as severe) [14] and GCS (scores <14 defined as low) [15] at baseline. CT scans were performed using standardised techniques and haematoma volume was calculated independently by two trained neurologists (intraclass correlation coefficient = 0.97) using MISTar version 3.2 (Apollo Medical Imaging Technology). CT brain imaging outcomes were haematoma volume with and without intraventricular haemorrhage (IVH) at baseline.

With the current sample size of 304 patients, the present study had 80% power (2-sided $\alpha = 0.05$) to detect 42% or more increase in the risks of high NIHSS score (i.e. odds ratio of 1.42) per 1 SD increase in temperature parameters. The baseline characteristics of included patients were compared with those of excluded patients using Wilcoxon or χ^2 tests. Associations of ambient temperature on clinical severity (high NIHSS and low GCS scores) were estimated using logistic regression models and adjusted for confounders selected based on the literature and clinical knowledge including age, sex, city of residence, systolic BP, time from onset to first CT scan, and the location and volume haematoma at baseline. Effects of ambient temperature on the NIHSS scores as a dependent variable with 6 levels (0–4, 5–7, 8–11, 12–15, 16–19, 20) and the GCS scores as a dependent variable with 5 levels (3–9, 10–12, 13, 14, 15) were also calculated using ordinal logistic regression models. The association of ambient temperature and the imaging outcomes (haematoma volume with/without IVH) was evaluated using a simple linear regression model, and adjusted regression analysis was also conducted. Haematoma volume was log transformed in order to remove skewness. Data are reported with the standard level of significance ($p < 0.05$) and with 95% confidence intervals (CI). All analyses were performed using SAS software version 9.3 (Cary, N.C., USA).

Table 1. Baseline characteristics of included and excluded Chinese participants

	Included patients (n = 304)	Excluded patients (n = 80)	p value
Median time from ICH onset to randomisation, h:min	3:43 (2:53–4:49)	3:39 (2:55–5:04)	0.07
Age, years	62±12	63±14	0.82
Male	196 (65%)	53 (66%)	0.77
Medical history			
Hypertension	224 (74%)	63 (79%)	0.35
Previous ICH	36 (12%)	8 (10%)	0.65
Ischaemic stroke	32 (11%)	11 (14%)	0.42
Acute coronary event	5 (2%)	7 (9%)	0.00
Diabetes mellitus	25 (8%)	7 (9%)	0.88
Drug use			
Antihypertensive therapy	127 (42%)	35 (44%)	0.75
Antiplatelet therapy	18 (6%)	5 (6%)	0.91
Warfarin anticoagulation	1 (0%)	1 (1%)	0.31
Clinical features			
SBP, mm Hg	181±18	178±18	0.19
DBP, mm Hg	103±13	103±18	0.36
Heart rate, bpm	79±14	77±14	0.1
Median NIHSS score ¹	10 (5–15)	11 (6–17)	0.25
NIHSS score ≥14	95 (31%)	27 (34%)	0.67
Median GCS score ²	14 (13–15)	14 (11–15)	0.16
GCS score <9	31 (10%)	14 (18%)	0.07
Location of haematoma			
Lobar	24 (8%)	0 (0%)	0.17
Deep	252 (83%)	21 (95%)	0.12
Brainstem	12 (4%)	0 (0%)	0.34
Cerebellum	13 (4%)	1 (5%)	0.95
Baseline haematoma volume, ml	9 (5–12)	9 (5–12)	0.77

Data are number (with percentage), mean ± SD or median (with IQR). SBP = Systolic blood pressure; DBP = diastolic blood pressure.

¹ NIHSS scores can range from 0 (healthy) to 42 (coma with quadriplegia).

² GCS scores can range from 3 (deep coma) to 15 (healthy).

Results

The baseline characteristics of the included and excluded Chinese participants were broadly similar except for those included to have less history of an acute coronary event (table 1). The effects of ambient temperature on clinical severity of ICH are shown in table 2. There were no significant associations between temperature parameters and high NIHSS score or low GCS score in multivariable logistic regression analyses (all $p > 0.2$). Likewise, no clear associations of temperature parameters

Fig. 1. a–d Effects of ambient temperature on baseline volume of haematoma: simple regression analysis.

Table 2. Effect of ambient temperature on severity of ICH at presentation

Severe stroke at presentation	Univariable			Multivariable		
	odds ratio ¹		p value	odds ratio ¹		p value
High NIHSS score (>10)						
Mean temperature	1.056	(0.947–1.177)	0.33	1.096	(0.933–1.289)	0.27
Maximum temperature	1.063	(0.954–1.184)	0.27	1.100	(0.943–1.283)	0.23
Minimum temperature	1.051	(0.947–1.167)	0.35	1.076	(0.912–1.268)	0.38
Temperature range	1.051	(0.811–1.362)	0.71	1.209	(0.828–1.764)	0.33
Low GCS score (<14) at presentation						
Mean temperature	1.067	(0.952–1.196)	0.26	1.039	(0.895–1.206)	0.62
Maximum temperature	1.068	(0.954–1.195)	0.26	1.049	(0.911–1.208)	0.51
Minimum temperature	1.067	(0.956–1.191)	0.25	1.031	(0.887–1.199)	0.69
Temperature range	0.981	(0.747–1.288)	0.89	1.133	(0.803–1.6)	0.48

Values in parentheses are 95% CI. Multivariable: adjusted for patient age, sex, city of residence, systolic blood pressure, time from onset to first CT scan, location of haematoma (lobar vs. non-lobar), and log-transformed baseline haematoma volume.

¹ Per 5°C increase in temperature.

Fig. 2. a–d Effects of ambient temperature on baseline volume of haematoma and IVH: simple regression analysis.

with NIHSS and GCS scores were observed in ordinal logistic regression analyses (all $p > 0.09$; online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000358304). Crude and adjusted regression analyses demonstrated no clear associations between daily ambient temperature and haematoma volume with/without IVH (fig. 1, 2; table 3).

Discussion

These analyses from INTERACT1 indicate no appreciable associations of diurnal temperature parameters with clinical severity based on NIHSS and GCS scores,

nor of haematoma volume (with and without IVH) in patients with acute ICH at the time of presentation to hospital.

Few studies have reported upon ambient temperature and severity of ICH. The findings obtained from the present analyses are consistent with the results of the Northern Finland study, which demonstrate similar median haematoma volume and GCS score upon hospital admission during both the warm and cold period [16]. However, seasonal variation in case fatality for ICH (higher in the summer compared to other seasons) among 90 ICH patients in Northern Portugal has been suggested [17]. The discrepancy with our analyses may relate to differences in patient population and methodology.

Table 3. Effect of ambient temperature on baseline haematoma volume in multivariable regression analysis

Outcome	Parameter estimate	Standard error	p value
Haematoma volume ¹			
Mean temperature	0.0109	0.0307	0.72
Maximum temperature	0.0176	0.0291	0.55
Minimum temperature	0.0051	0.0311	0.87
Temperature range	0.0755	0.0694	0.28
Haematoma volume plus IVH ¹			
Mean temperature	0.0077	0.0329	0.82
Maximum temperature	0.0143	0.0311	0.65
Minimum temperature	0.0006	0.0332	0.99
Temperature range	0.0787	0.0742	0.29

Model adjusted for patient age, sex, city of residence, history of intracerebral haemorrhage, antithrombotic medications, systolic blood pressure, time from onset to first CT scan, and location of haematoma (lobar vs. non-lobar). Parameter estimate and standard error: per 5°C increase in temperature.

¹ log transformation operation performed.

Key strengths of INTERACT1 include the relatively large sample size of patients with early and rigorous evaluations of clinical and imaging findings after acute ICH. Despite being the largest study conducted to investigate the relationship between ambient temperature and ICH

severity, the sample size may still have been under-powered to detect modest associations with ambient temperature. Another limitation was the lack of individual-level environmental (indoor or outdoor) temperature at the exact time of ICH onset. Because the present evaluation was restricted to Chinese people with relatively small haematoma, our findings may not be applicable to other populations and those with large haematomas. Moreover, other possible confounding factors such as the presence of viral infections and use of vasoconstricting medications prior to hospital admission were not available in the present analysis.

In summary, there was no appreciable association between ambient temperature and severity of ICH upon hospital presentation.

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Disclosure Statement

The authors declare no conflict of interest.

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