Body Temperature and Mortality in Acute Cerebral Infarction

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Background and Objective: *In animal models, a rise in body temperature after cerebral ischemia consistently produces more extensive brain damage. In humans, however, the relationship between body temperature and stroke outcome has been far less extensively investigated, providing conflicting results. The objective of the present study is to determine whether body temperature recorded during the first 72 hours after admission is an independent predictor of mortality in acute cerebral infarction.*

Material and Method: *The medical records of patients admitted within 48 hours of onset of symptoms to Prasat Neurological Institute between 1 January 2002 and 31 December 2003, with a diagnosis of cerebral infarction, confirmed by CT or MRI of the brain were retrospectively studied. The relationship between the highest temperature recorded during the first 72 hours after admission and mortality during hospital stay was evaluated. Multiple logistic regression analysis included relevant confounders and potential predictors such as gender, age, hypertension, diabetes, smoking, previous stroke, ischemic heart disease, atrial fibrillation, consciousness and infections was performed.*

Results: *There were 332 patients included in the present study. During the first 72 hours after admission, 88 (26.5%) patients had fever (>37.5 C). The highest temperature recorded during the first 72 hours after admission was a significant predictor of in hospital mortality in the final multivariate logistic regression model. For each 1 C increase in body temperature the odd ratio of mortality rose by 3.95 (OR, 3.95; 95%CI, 1.84-8.45).*

Conclusion: *In the present study, the highest body temperature recorded during the first 72 hours after admission was shown to be a significant predictor of mortality in acute cerebral infarct patients.*

Keywords: *Body temperature, Cerebral infarction, Mortality, Prognostic factors*

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Stroke (cerebrovascular disease) is still a leading cause of death and disability in Thailand[1,2]. In Bangkok, in 1983, one community survey showed that the prevalence of stroke was 690/100,000 population[3] (aged over 20 years old). Another study in 1998 showed that the prevalence rate of stroke in the elderly in rural areas was 1.12 per cent[4]. In Thailand, cerebral infarction was found in about 70 per cent of all strokes[5].

In animal models, a rise in body temperature after cerebral ischemia consistently produced more extensive brain damage[6-9]. Even if hyperthermia occurs 24 hours after cerebral ischemia, neuronal damage is greater than in rodents with normal body temperature[10,11]. Futhermore, in several studies, hypothermia has been shown to be neuroprotective in experimental focal[12-17] and global cerebral ischemia[18]. In humans, however, the relationship between body temperature and stroke outcome has been far less extensively investigated, providing conflicting results[19-24]. To determine whether body temperature is directly related to outcome, one must take account of relevant confounder and predictive factors such as age, gender, cardiovascular risk factors, consciousness and infections. In many studies, this had not been done[20,24,25]. The objective of the present study was to determine whether body temperature recorded during the first 72 hours after admission is an independent predictor of mortality in cerebral infarction.

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Material and Method

The medical records of patients admitted within 48 hours of the onset of symptoms to Prasat Neurological Institute between 1 January 2002 and 31 December 2003, with a diagnosis of cerebral infarction, confirmed by CT or MRI of the brain were retrospectively studied. All medical records of these patients and collected data were reviewed by using a standard designed form.

Axillary temperature on the unaffected side was recorded twice daily, except for the day of admission by Terumo digital clinical thermometer model C202. Only the highest temperature recorded during the first 72 hours after admission was considered in the analysis of data. Mortality was defined as death during hospital stay.

The following prognostic factors were accounted for in the statistic analysis: gender, age, hypertension, diabetes mellitus, smoking, previous stroke, ischemic heart disease, atrial fibrillation, admission conscious level and infections. The classification of specific factors were as follows.

Hypertension: On antihypertensive treatment at the time of admission or hypertension diagnosed during hospital stay by repeated detection of blood pressure > 140/90 mmHg.

Diabetes mellitus: On antidiabetes treatment at the time of admission or fasting plasma glucose >120 mg/dl.

Smoking: Daily smoking of any kind of tobacco. Ex smokers were coded as non smokers.

Previous stroke: Stroke was defined according to the World Health Organization criteria[26]: Rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin.

Ischemic heart disease: A history of ischemic heart disease, or ischemic heart disease diagnosed during hospital stay.

Atrial fibrillation: If present on admission electrocardiogram.

Admission conscious level: It was classified into conscious, subconscious or unconscious, which were defined as follows; 1) conscious: alert, appropriate response to verbal commands; 2) subconscious: drowsy or stuporous; and 3) unconscious: coma or no eye opening to verbal stimuli.

Infections: If clinically present, or if discovered by radiologic examination of the chest or analysis of urine during the first 72 hours after admission.

Statistics analysis

Statistical analysis was done with the SPSS 11.5 for Windows. Continuous and categorical variables were expressed as mean and percentages respectively. Univariate analysis odd ratio (OR) and 95%CI for screened of variables was performed before multivariate analysis. Regarding categorical data, Chi-square or Fisher's exact test was used.

For mortality (death during hospital stay), multiple logistic regression models were fitted. Explanatory variables initially included in the model were those with a probability value < 0.1 from the univariate analysis. The variables with a probability value of Wald's test > 0.1 were removed from the model, and the log likelihood ratio test was performed each time to assess the fitness of the more parsimonious model. The significance level was set at 0.05. The statistical highest temperature recorded during the first 72 hours after admission was always retained in the model.

Results

Table 1 shows the basic characteristics of the 332 patients, and also a number of patients who had fever (> 37.5 C) and infections diagnosed during the first 72 hours after admission. The most common comorbidity was hypertension which was found in 212 (63.9%) patients. Fever was found in eighty eight patients (26.5%). Nineteen patients (5.7%) died during their stay in hospital. The probable causes of death were brain herniation (36.8%), myocardial infarction (15.8%), pneumonia (21.0%), sepsis (21.0%) and congestive heart failure (5.3%) respectively.

Table 1. Basic characteristics of the patients

1. Number of patients	332	
2. Gender (male)	209	(63.0%)
3. Age (years; mean, SD)	62	(11.4)
4. Hypertension	212	(63.9%)
5. Diabetes	126	(38.2%)
6. Smoking	121	(36.8%)
7. Previous stroke	90	(27.5%)
8. Ischemic heart disease	59	(19.0%)
9. Atrial fibrillation	16	(5.0%)
10. Subconscious or unconscious	31	(9.3%)
11. HTEM* (C; mean, SD)	37.4	(0.71)
12. Fever (>37.5 C) in the first 72 hours	88	(26.5%)
13. Infections	22	(6.6%)
13.1 Pneumonia	12	(3.6%)
13.2 Urinary tract infection	13	(3.9%)
13.3 Others	3	(0.9%)

* HTEM indicates highest temperature recorded during the first 72 hours after admission

Univariate analysis of samples in terms of mortality are shown in Table 2. Gender, ischemic heart disease, atrial fibrillation, consciousness, highest temperature recorded during the first 72 hours after admission (HTEM) and infections were significantly ($p < 0.05$) associated with mortality. HTEM was a significant predictor of in hospital mortality in the final multivariate logistic regression model (Table 3). For each 1 C increase in body temperature the odds ratio of mortality rose by 3.95 (OR, 3.95; 95%CI, 1.84-8.45). However, the admission conscious level (OR, 9.13; 95%CI, 2.33-35.81) and ischemic heart disease (OR, 6.89; 95%CI, 1.85-25.70) were also a strong predictor of mortality which is shown in Table 3.

Discussion

The results of the present study suggest that the highest body temperature recorded during the first 72 hours after admission is an independent predictor of mortality. For each 1 C increase in body temperature the odds ratio of mortality rose by 3.95 (OR, 3.95; 95%CI, 1.84-8.45). This finding is quite similar to the six previous studies that showed a possible association between body temperature and stroke mortality. In reprospective study of 177 patients with acute cerebral infarction, Castillo et al[27] found that the difference in body temperature between those who died within 6 months and those who survived was highly significant ($p < 0.001$). However, multivariate analysis was not used. Azzimondi et al[28] analysed the data of 183 patients and determined that high fever (maximum temperature recorded during the first 7 days, $\geq$ 37.9 C) was an independent factor for worse prognosis (OR, 3.4; 95%CI, 1.2-9.5). In both studies, the important potential confounder and predictive factors such as a major comorbid condition were not considered. Reith et al[29], in a consecutive study of 390 stroke patients, determined that admission body temperature was independently related to stroke mortality. For each 1 C increase in body temperature, the odds ratio of mortality rose by 1.8 (OR, 1.8; 95%CI, 1.1-2.8) which was less than the odds ratio (3.95) of this present study. However, Reith et al did not distinguish hemorrhagic from ischemic stroke. While this present study included only ischemic stroke. Castillo et al[30] studied the prognostic value of body temperature measured at different times during 72 hours after the onset of stroke on 260 patients with ischemic stroke. Mortality rate at 3 months was 1% in normothermic patients and 15.8% in hyperthermic patients ($p < 0.001$). Hyperthermia within the first 24 hours from stroke onset, but not afterwards was independently related to a larger volume (OR, 3.23; 95%CI, 1.63-6.43) and higher neurological deficit (OR, 3.06; 95%CI, 1.70-5.33). In a retro-

Table 2. Univariate analysis of samples in terms of mortality

Variable	Non death (n=313)	Death (n=19)	p value	OR	95% CI
1. Gender (male, %)	64.5	36.8	0.015	0.32	0.12-0.84
2. Age (years; mean)	62	62.7	0.791	-	-
3. Hypertension (%)	63.9	63.2	0.948	0.97	0.37-2.53
4. Diabetes (%)	38.1	38.9	0.949	1.03	0.39-2.74
5. Smoking (%)	37.6	22.2	0.188	0.47	0.15-1.47
6. Previous stroke (%)	26.2	50.0	0.053	2.82	1.08-7.34
7. Ischemic heart disease (%)	17.1	47.4	0.003	4.36	1.68-11.27
8. Atrial fibrillation (%)	4.0	21.1	0.010	6.42	1.85-22.30
9. Subconscious or unconscious (%)	5.8	68.4	< 0.001	35.51	12.08-104.36
10. HTEM* (C, mean)	37.3	38.7	< 0.001	-	-
11. Infections (%)	5.1	31.6	0.001	8.54	2.87-25.40

*HTEM indicates the highest temperature recorded during the first 72 hours after admission. Significance level was set at 0.05

Table 3. Multiple logistic regression analysis of mortality

Covariate	Coeff (b)	SE (b)	p value	OR	95%CI
HTEM*	1.37	0.39	<0.001	3.95	1.84-8.45
Consciousness	2.21	0.70	0.002	9.13	2.33-35.81
Ischaemic heart disease	1.93	0.67	0.004	6.89	1.85-25.70

*HTEM indicates the highest temperature recorded during the first 72 hours after admission

spective cohort of 509 patients with acute stroke, admission body temperature was classified as hypothermia (≤ 36.5 C), normothermia (> 36.5 C and ≤ 37.5 C) and hyperthermia (> 37.5 C), Wang et al[31] found that the odds ratio for in hospital mortality in hypothermic versus normothermic patients with ischemic stroke was 0.1 (95%CI, 0.02-0.5). A similar but nonsignificant trend for in hospital mortality was seen among patients with hemorrhagic stroke. Kammersgaard et al[32] studied 390 patients with acute stroke admitted within 6 hours from stroke onset and found that the mortality rate at 60 months after stroke was higher for patients with hyperthermia (p = 0.001). However, there are some conflicting studies. Sharma et al[21] studied 294 patients with acute stroke and determined that pyrexia (> 37.5 C) was not a significant predictor (OR, 0.91; 95%CI, 0.60-1.40) of mortality. Mortality was strongly related to dysphagia (OR, 4.10; 95%CI, 2.39-7.05) which was not included as covariate in this present study because the accurate data regarding dysphagia was not available due to limitation of the retrospective study.

The mechanism for poor outcome seen after hyperthermia remains speculative. The area of reversibly impaired neuronal function surrounding the infarct tissue, known as the ischemic penumbra, is thought to be the site where temperature dependent stroke progression occurs[19]. Several mechanisms have been postulated to explain this effect of hyperthermia. Neurotransmitters associated with poor cerebral infarct outcome, such as glutamate, γ-aminobutyric acid, and glycine, have been shown to increase during hyperthermia and to diminish with hypothermia[33]. The imbalance between energy supply and demand following cerebral ischemia is increased by hyperthermia, as the metabolic rate of the brain increases with the rise in temperature. Experimental studies performed on animal models of cerebral ischemia have shown that temperature manipulation related changes in the metabolic rate of the ischemic brain may contribute to the neuroprotective effect of hypothermia and to the neurotoxic effect of hyperthermia on the ischemic brain[34]. Ischemic induced blood brain barrier opening is remarkably sensitive to brain temperature. The mild extravasation of protein across the barrier observed after periods of normothermic global ischemia is attenuated by mild to moderate (30 C-33 C) intraischemic hypothermia but is markedly exaggerated by mild intraischemic hyperthermia (39 C)[33]. In relation to the stroke-induced inflammation reaction, hyperthermia allows maximum activation of leucocytes, promoting the cytotoxic function of inflammatory cells[34].

In conclusion, this present study suggests that the highest body temperature recorded during the first few days after admission is an independent predictor of in hospital mortality in acute cerebral infarct patients. For each 1 C increase in body temperature the odds ratio of in hospital mortality rose by 3.95 (OR, 3.95; 95%CI, 1.84-8.45). This result supports a lowering of fever, as previously recommended in almost all guidelines for medical therapy of stroke. Therapeutic hypothermia may have beneficial effects on stroke outcome. However, there is a long way to go before its clinical use can become routine.

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อุณหภูมิร่างกายและการเสียชีวิตในผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันในระยะเฉียบพลัน

สุชาติ หาญไชยพิบูลย์กุล

ความเป็นมาและวัตถุประสงค์: *ข้อมูลจากการทดลองในสัตว์พบว่าอุณหภูมิของร่างกายที่สูงขึ้นภายหลังการเกิดภาวะสมองขาดเลือดนั้นมีผลให้สมองมีความเสียหายมากขึ้น สำหรับในมนุษย์การศึกษาความสัมพันธ์ของอุณหภูมิของร่างกายกับความเสียหายของสมองและการเสียชีวิตยังมีไม่มากนัก และข้อมูลยังมีความขัดแย้งกันอยู่ วัตถุประสงค์ของการศึกษานี้เพื่อหาความสัมพันธ์ระหว่างอุณหภูมิของร่างกายในช่วง 72 ชั่วโมงแรกที่รับไว้ในสถาบันประสาทวิทยากับการเสียชีวิตในผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันในระยะเฉียบพลัน*

วิธีการ: *ทำการศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยโรคหลอดเลือดสมองตีบหรืออุดตันที่มารับการรักษาเป็นผู้ป่วยในของสถาบันประสาทวิทยาภายใน 48 ชั่วโมงหลังเกิดอาการ ในช่วง 1 มกราคม 2545 - 31 ธันวาคม 2546 โดยทุกรายได้รับการตรวจยืนยันด้วยเอกซเรย์คอมพิวเตอร์หรือเอกซเรย์แม่เหล็กไฟฟ้า บริเวณสมอง จากนั้นได้ทำการศึกษาหาความสัมพันธ์ระหว่างอุณหภูมิสูงสุดของร่างกายที่วัดได้ในช่วง 72 ชั่วโมงแรกของการรับไว้เป็นผู้ป่วยในกับการเสียชีวิตในสถาบันฯโดยใช้สถิติ Multiple logistic regression ทั้งนี้ได้พิจารณาควบคุมตัวแปรอื่น ๆ ที่อาจมีผลต่อการเสียชีวิตด้วย ซึ่งได้แก่ เพศ อายุ ความดันโลหิตสูง เบาหวาน การสูบบุหรี่ การเคยเป็นโรคหลอดเลือดสมองมาก่อน (previous stroke) โรคกล้ามเนื้อหัวใจขาดเลือด ภาวะหัวใจเต้นริก (atrial fibrillation) ระดับความรู้สึกตัว และการติดเชื้อ*

ผลการศึกษา: *รวบรวมผู้ป่วยได้ทั้งสิ้น 332 ราย ในช่วงเวลา72 ชั่วโมงแรกของการรับไว้เป็นผู้ป่วยในพบว่าผู้ป่วย 88 (26.5%) ราย มีไข้ (>37.5 C) อุณหภูมิสูงสุดของร่างกายที่วัดได้ในช่วง 72 ชั่วโมงแรกของการรับไว้เป็นผู้ป่วยในมีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการเสียชีวิตในสถาบันฯกล่าวคือในทุก 1 C ที่เพิ่มขึ้น odd ratio ของการเสียชีวิตจะเพิ่มขึ้น 3.95 เท่า (OR, 3.95; 95%CI, 1.84-8.45)*

สรุป: *จากการศึกษานี้พบว่าอุณหภูมิสูงสุดของร่างกายที่วัดได้ในช่วง 72 ชั่วโมงแรกของการรับไว้เป็นผู้ป่วยในมีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการเสียชีวิตในสถาบันฯของผู้ป่วยโรคหลอดเลือดสมองตีบ หรือ อุดตันในระยะเฉียบพลัน*