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Clinical Research

Hyperthermia is not an independent predictor of greater mortality in patients with primary intracerebral hemorrhage

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background:
Our goal was to identify independent early predictors of 30-day mortality in patients with medically treated primary intracerebral hemorrhage (PICH), and to assess the prognostic significance of hyperthermia in these cases.

Material/Methods:
We prospectively studied 152 patients with supratentorial PICH confirmed by CT on admission. We recorded gender, age, severity of neurological deficit on admission (Scandinavian Stroke Scale), level of consciousness at admission and one day later, and maximum body temperature for the first three days after onset. Hematoma size and midline shift were assessed by CT scans. Outcome was measured by either mortality or Barthel Index functional status 30 days after stroke.

Results:
59 patients (38.8%) died within 30 days. Patients who died had greater neurological deficit on admission and higher maximum temperature within the first 24 hours after admission, and were more likely to have impaired consciousness on admission and after 24 hours, as well as large hematoma and midline shift (P<0.05 for all differences). However, statistically only severity of neurological deficit was an independent predictor of 30-day mortality. The functional status of survivors who had hyperthermia was much worse than those who were normothermic on Day 1.

Conclusions:
The severity of neurological deficit predicts greater 30-day mortality in patients with primary intracerebral hemorrhage. Patients with hyperthermia on the first day of hospitalization have greater 30-day mortality and worse functional status 30 days after stroke, but increased body temperature is not an independent predictor of 30-day mortality after PICH.

key words:
intracerebral hemorrhage • neurological deficit • hyperthermia • prognosis

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BACKGROUND

Primary intracerebral haemorrhage (PICH) receives much less attention than ischemic stroke, despite its high morbidity and mortality (32–52% of patients die within 30 days after the onset of symptoms) [1,2]. No specific treatment has been shown to improve outcome after PICH [3], except for surgical relief of large cerebellar hematomas [4]. If future randomized trials are to bring any conclusive results, the early indicators of poor prognosis should be taken into account in stratifying the patients included in these trials.

The recognized and well established clinical predictors of poor prognosis after PICH include severe neurological deficit on admission [2], decreased level of consciousness on admission, and older age [5,6]. Additional information can be obtained from computer tomography (CT), where large hematoma volume [1,7], hydrocephalus [7], and extension of the hemorrhage to the ventricular system [2,6] have all been shown to predict increased mortality after PICH. Some genetic factors, e.g. the presence of APOE ε4 allele, may also contribute to an increased mortality rate [8].

Increased body temperature shortly after ischemic stroke independently predicts poorer outcome [9], but the significance of hyperthermia after PICH is far from being unequivocally demonstrated. Schwarz et al. [6] showed that increased body temperature lasting longer than 72 hours after PICH is correlated with greater mortality. On the other hand, increased body temperature did not predict worse outcome in a cohort of 72 patients with hemorrhagic stroke studied by Wang et al. [10]. To date, the body of evidence is too small to draw conclusions and plan future interventions. Therefore we designed this study to establish early predictors of 30-day mortality in medically treated patients with PICH, and to assess the influence of early hyperthermia on the outcome of these patients.

MATERIAL AND METHODS

We prospectively studied consecutive patients admitted to the stroke unit of our department with a diagnosis of hemorrhagic stroke. The inclusion criteria consisted of a diagnosis of PICH and admission to the stroke unit within 24 hours after the onset of symptoms. The clinical diagnosis of stroke was made according to the WHO criteria [11], and a CT of the head was performed at admission in each case to confirm the diagnosis of hemorrhagic stroke. We excluded patients with brainstem or cerebellar PICH, and those with primary intraventricular hemorrhage. Patients with hemorrhage secondary to head trauma or with subarachnoid hemorrhage were also excluded. During four consecutive years 186 patients with PICH were admitted to the stroke unit within 24 hours after the onset of symptoms. Within this group, 20 patients had PICH to the cerebellum and 14 had PICH to the brainstem. After these patients were excluded, ultimately 152 patients were included in the study. Each patient was treated symptomatically according to the recommendations of the authorities in the

field [12] and the guidelines of the American Stroke Association [3]. The patients were followed up for 30 days, and outcome was assessed primarily by 30-day all-cause mortality. The functional status of patients who survived 30 days after PICH was assessed by the Barthel Index [13].

The study complied with the principles of the Helsinki Declaration.

The investigators recorded the age and gender of the patients. Any history of hypertension or antihypertensive therapy was recorded if found. Previous or current cigarette smoking and/or alcohol abuse were established according to information provided by the patients or their relatives. The severity of neurological deficit was assessed by means of the Scandinavian Stroke Scale (SSS) [14] at admission and 24 hours later (i.e. on Day 1). This scale has a scale of 0–58 points, where a score of 58 points indicates no deficit; a lower SSS score thus reflects a greater neurological deficit. The level of consciousness was assessed as an item on the SSS and graded as normal (6 points on the corresponding SSS item) or decreased (< 6 points) on admission and 24 hours later. Body temperature was measured on admission and then every four hours on Days 1, 2 and 3, using an infrared aural thermometer (ThermoScan Pro1, Braun, Germany), which registers the temperature of the tympanic membrane. Body temperature was expressed both as a continuous variable (degrees Celsius) and as a dichotomous variable, i.e. hyperthermia (>37.5°C) or normothermia (≤37.5°C). The highest temperature recorded each day was used in further analysis. If hyperthermia was found during the first day of hospitalization, body temperature was lowered with paracetamol (orally or rectally) or metamizole (parenterally). CT scans of the head obtained at admission were assessed to establish the size of hematoma and the presence of midline shift. The opinion of an experienced neuroradiologist was sought in each case. A hematoma was defined as large if its largest diameter was at least 15 mm.

Statistical analysis

According to their distribution, variables are expressed either as mean ± standard deviation (SD) or as a median with interquartile range (q1-q3). The significance of the differences between qualitative data was analyzed using the χ^2 test or Fisher exact test. Student's t-test was used to assess differences between the normally distributed variables (e.g. age) and the Mann-Whitney U-test was used for other variables (e.g body temperature or SSS score). Correlations between variables were assessed using Spearman rank correlation coefficients (r_s). Potential independent predictors of 30-day mortality were analyzed by logistic regression modeling. The appropriateness of the logistic regression model was confirmed by the Hosmer-Lemerschow test. Age and neurological deficit were entered into the model as continuous variables. Male sex, hyperthermia, presence of large hematoma in CT and presence of midline shift on CT were entered as dichotomous variables (present/absent).

Table 1. Variables differentiating survivors and those who died within 30 days after intracerebral hemorrhage.

Variable	Deceased (n=59)	Survivors (n=93)	P-value
Men	42.4%	54.8%	n.s.*
Age (years, mean±SD)	66.6±12.8	62.6±13.9	n.s.**
Body temperature on day 1 (degrees Celsius, median, q1-q3)	37.5 (36.8–38.1)	37.0 (36.6–37.5)	<0.005***
Hyperthermia on day 1	49.1%	21.5%	<0.005*
Decreased level of consciousness on admission	88.1%	48.4%	<0.0001*
Decreased level of consciousness on Day 1	89.8%	43%	<0.0001*
Neurological deficit on admission (SSS score, median, q1-q3)	6 (2–12)	28 (18–38)	<0.0001***
Neurological deficit on Day 1 (SSS score, median, q1-q3)	4 (0–12)	29 (18–39)	<0.0001***
Large hematoma on CT at admission	45.8%	15%	<0.0001*

SD– standard deviation; q1-q3– interquartile range; SSS– Scandinavian Stroke Scale;

*χ^2 test; **Student's t-test; ***Mann-Whitney U-test

Table 2. Characteristics of patients with ventricular extension of the hemorrhage (n=24) and a comparison with the other studied patients with primary intracerebral hemorrhage.

Variable	Patients with intraventricular extension of the hemorrhage (n=24)	Patients without intraventricular extension of the hemorrhage (n=128)	P-value
Men	41.7%	51.6%	n.s.*
Age (years, mean±SD)	61.9±17.0	64.6±12.9	n.s.**
Body temperature on day 1 (degrees Celsius, median, q1-q3)	37.4 (36.7–38.1)	37.1 (36.6–37.7)	n.s.**
Hyperthermia on day 1	45.8%	29.7%	n.s.*
Decreased level of consciousness at admission	75.0%	61.7%	n.s.*
Decreased level of consciousness on Day 1	79.2%	57.8%	<0.05*
Neurological deficit on admission (SSS score, median, q1-q3)	10 (4–19)	22 (8–35)	<0.01**
Neurological deficit on Day 1 (SSS score, median, q1-q3)	7 (2–19)	22 (6–35)	<0.01**
30-day mortality	58.3%	35.1%	n.s.*

SD– standard deviation; q1-q3– interquartile range; SSS– Scandinavian Stroke Scale;

*χ^2 test; **Mann-Whitney U-test

All the analyses were performed using commercial statistical software (Statistical Package for Social Sciences, SPSS, v. 8.0). A P value of less than 0.05 was considered significant.

RESULTS

One hundred and fifty-two patients took part in the study. The mean age of the participants was 64.2±13.6 years, and 76 (50%) were men. The median SSS score was 21 (7–34) on admission and 19 (4–35) 24 hours later. Hypertension was present in 75.6% of the patients, 19.7% were smokers (current or previous), and 9.2% revealed a history of alcohol abuse. There was no difference regarding the presence of these risk factors between survivors and those who eventually died from PICH. Fifty-nine patients (38.8%) died within one month after stroke. Of these, 14 (24%) died within 3 days after the onset of symptoms, and 25 (42%) died within 5 days.

Hyperthermia on Day 1 was found in 49 patients (32.2%). The highest body temperature recorded on Day 1 correlated significantly with the severity of neurological deficit on Day 1 (r=–0.32; P<0.001, Spearman's rank correlation coefficient). Those patients who had an elevated body temperature on Day 1 were treated with antipyretics, but 24 of them continued to show fever during Day 2 and/or Day 3. The 30-day case-fatality rate was similar in patients who responded to antipyretics and those who had protracted fever (52% vs. 66.7%, respectively; P = n.s., χ^2 test).

The variables that significantly differentiated survivors and those who died within 30 days after PICH are shown in Table 1.

Extension of the hemorrhage into the lateral ventricles was found in 24 patients (15.8%). The detailed characteristics of this subgroup and a comparison with other patients is given in Table 2. The case-fatality rate in hyperthermic patients with intraventricular extension was high (81.8%), but similar to other hyperthermic patients (52.6%; P = n.s., χ^2 test).

When we analyzed the subgroup of patients who survived at least five days after PICH (n=127) separately, similar variables differentiating survivors and those who subsequently died within 30 days were identified. The only notable exceptions were maximum body temperature on Day 1 and the presence of hyperthermia on Day

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Table 3. Variables differentiating survivors and the deceased within 30 days in the subgroup of patients who survived 5 days after the onset of PICH (n=127).

Variable	Patients who survived 5 days and subsequently died within 30 days (n=34)	Patients who survived 30 days (n=93)	P-value
Men	44.1%	54.8%	
Age (years±SD)	69.6±13.0	62.6±13.9	
Max body temperature on day 1 (centigrades; median, q1-q3)	37.3 (36.6–37.7)	37.0 (36.6–37.5)	<0.05**
Hyperthermia on day 1	38.2%	21.5%	n.s.***
Neurological deficit on admission (SSS score; median, q1-q3)	10 (4–22)	28 (18–38)	n.s.*
Neurological deficit on day 1 (SSS score; median, q1-q3)	8 (4–22)	29 (18–39)	<0.001***
Decreased consciousness on admission	79.4%	48.4%	<0.001***
Decreased consciousness on day 1	82.3%	43%	<0.05***
Midline shift on CT on admission	38.2%	17.2%	<0.05*
Large haematoma on CT	38.2%	15%	n.s.*

SD – standard deviation; q1-q3 – interquartile range; SSS – Scandinavian Stroke Scale;   <0.05*

*χ^2 test; **Student's t-test; ***Mann-Whitney U-test

Table 4. Logistic regression model, showing the significance of selected variables as independent predictors of 30-day mortality after intracerebral hemorrhage.

Variable	β	Standard error	Wald statistics	P-value	OR	95% CI for OR
Neurological deficit on admission	−0.076	0.019	16.491	0.001	0.927	0.89–0.96
Age	0.032	0.017	3.494	0.062	1.033	0.99–1.07
Midline shift on CT	0.863	0.471	3.355	0.067	2.371	0.94–5.97
Hyperthermia on day 1	0.712	0.434	2.693	0.101	2.038	0.87–4.77
Large hematoma on CT	0.386	0.479	0.651	0.42	1.472	0.58–3.76
Male sex	−0.044	0.428	0.011	0.918	0.957	0.41–2.21

OR – odds ratio; CI – confidence interval

1. Both were similar in those who died and in survivors (Table 3).

Logistic regression analysis revealed that the neurological deficit at admission was the one and only independent predictor of death within 30 days after the onset of PICH. The detailed logistic regression equation is shown in Table 4.

The functional status of patients who survived 30 days after PICH and had hyperthermia (n=20) was much worse than those who were normothermic on Day 1. The median Barthel Index in these groups was 20 (0–75) and 70 (25–100), respectively (P<0.001; Mann-Whitney U-test). 52% of the survivors who were normothermic on Day 1 had a Barthel Index ≥80, compared to 25% of the survivors who had hyperthermia on Day 1 (P<0.05; Fisher exact test).

DISCUSSION

Our study confirmed the significance of severe neurological deficit as an independent predictor of death within 30 days after PICH. Patients with hyperthermia on the first day of hospitalization were at increased risk of death within 30 days after the onset of symptoms, and if they survived, they had worse functional status 30 days after stroke. Nevertheless, increased body temperature correlated significantly with the severity of neurological deficit, and did not predict death independently in multivariate analysis.

The 30-day mortality rate recorded in this study is consistent with previous studies. Franke et al. [15] reported a 43% case-fatality rate within one month after PICH, and the community-based study by Bamford et al. [16] yielded an even higher 30-day fatality rate (52%).

The mortality rate in our study was probably affected by several confounders. The hospital-based design of the study and the inclusion of patients admitted within 24 hours after the onset may have increased the case-fatality rate (patients with milder symptoms and signs may be admitted after 24 hours, or may not be admitted to the stroke unit at all). On the other hand, patients with hemorrhage within the posterior fossa were excluded, and this is the group with clearly the worst prognosis [17].

Neurological deficit, which reflects the volume of the brain damaged by the hematoma, has consistently been reported in previous studies on this topic to be a predictor of poorer outcome after PICH [2,15]. Thus, the predictive role of hematoma size in our study disappeared

after controlling for neurological deficit. Diminished consciousness on admission was also much more frequent in those who eventually died (88.1% vs. 48.4%). One should take into account the fact that the level of consciousness is also assessed as an item on SSS; thus it was not included in the logistic regression analysis, in order to avoid the bias of inter-correlation. Similar close correlation between the level of consciousness and the presence of midline shift has already been established [18]. Therefore, the size of the hematoma and the presence of midline shift do not add any independent information regarding prognosis, if the severity of neurological deficit is included in the logistic regression model.

In the pre-CT era, the presence of fever shortly after the onset of stroke was reported more frequently in patients who had hemorrhagic stroke, as confirmed by subsequent autopsy [19]. To date, studies on fever after hemorrhagic stroke have been rare, and their results are inconsistent. Schwarz et al. [6] found an independent association between protracted fever in patients who survived the first three days after PICH and poorer outcome. Wang et al. [10] analyzed 72 patients with hemorrhagic stroke as a subgroup of subjects with acute stroke, and reported significantly higher admission body temperature in patients with hemorrhagic stroke, but body temperature did not predict one-year mortality in that study.

The occurrence of fever in patients with PICH can be explained by the presence of systemic infection, as its incidence increases shortly after stroke. Systematic analysis of the origin of fever after PICH lay beyond the scope of this study. We performed routine examinations (x-ray of the chest, urinalysis, white blood cell count, urine and blood cultures) to establish the potential source of infection. It has previously been shown that the presence of fever shortly after ischemic stroke worsens outcome independently of concomitant infections [20], suggesting a central origin of hyperthermia in the majority of cases. Anecdotal reports have related hyperthermia to direct damage of the hypothalamus by the hematoma, or to the presence of blood within the ventricles [21].

Extension of the hemorrhage into the ventricular system was associated with greater neurological deficit and worse outcome in our patients. This reflects more severe disease, as previously demonstrated [22]. The frequency of hyperthermia in this subgroup of patients was higher than in other patients, as previously reported by Schwartz and colleagues [6]. The mortality among hyperthermic patients with ventricular extension of the hemorrhage was high (>80%), but similar to the normothermic patients. On the other hand, the lack of difference may result from the small number of subjects, and we do not consider this finding to be definitive.

Half of the PICH-related mortalities involve patients who die within two days after the onset of symptoms because of direct damage of the brain [2,23]. Patients who survive for longer than 72 hours are prone to complications caused by brain edema. The most important determinants of the extent of brain edema at this stage of the disease are the inflammatory reaction and ischemia within the territory surrounding the hematoma [24,25]. Therefore hyperthermia could be a major predictor of death in patients with PICH who survive the first two or three days, i.e. in those who did not develop herniation as a consequence of mass effect of the hematoma. We analyzed separately a subgroup of patients who survived at least five days after PICH. Contrary to our hypothesis, maximum body temperature on Day 1 did not differentiate survivors and those who subsequently died within 30 days. The percentage of hyperthermic patients was also similar in these groups. Thus patient age and the impact of neurological deficit on developing complications of immobility (pneumonia, deep venous thrombosis and pulmonary embolism) may affect the delayed mortality in these patients.

We focused mainly on body temperature in the first twenty-four hours after admission. Patients who had fever during the first day of hospitalization were treated pharmacologically to decrease body temperature. Therefore, we considered it less reliable to analyze body temperature specifically on subsequent days. The bias caused by our interventions and by increasing probability of systemic infections with concomitant fever would make the interpretation of the findings difficult. Moreover, the 30-day mortality in patients who responded to antipyretics and in those with protracted fever was similar. Again, this finding should be interpreted carefully, because of relatively small subgroup of such patients.

The results of recent studies have further complicated our understanding of the significance of induced hypothermia for outcome after brain damage. Mild hypothermia has been shown to improve neurological outcome in patients after cardiac arrest [26], but a large trial on hypothermia in traumatic brain injuries failed to show any benefit [27]. Our study adds some new evidence against the prognostic significance of fever in hemorrhagic stroke. We can only speculate that the occurrence of fever has important implications in specific types of PICH, and the power of studies that do not discern various patterns of hemorrhage is too small to detect subtle differences. We therefore believe that further studies are needed to elucidate the mechanism of hyperthermia in PICH and to explain the discrepancy between ischemic and hemorrhagic stroke regarding the significance of this variable as a predictor of worse outcome in these two clinical entities. Until these data are available, it seems reasonable to maintain normothermia in all acute stroke patients.

CONCLUSIONS

The severity of neurological deficit predicts greater 30-day mortality in patients with primary intracerebral hemorrhage. Patients with hyperthermia on the first day of hospitalization have greater 30-day mortality and worse functional status 30 days after stroke, but increased body temperature is not an independent predictor of 30-day mortality after PICH.

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