Antihyperthermic treatment decreases perihematomal hypodensity

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Abstract

Objective

To investigate the effect on perihematomal hypodensity and outcome of a decrease in body temperature in the first 24 hours in patients with intracerebral hemorrhage (ICH).

Methods

In this retrospective study on a prospectively registered database, among the 1,100 patients, 795 met all the inclusion criteria. Temperature variations in the first 24 hours and perihematomal hypodensity (PHHD) were recorded. Patients ≥37.5°C were treated with antihyperthermic drugs for at least 48 hours. The main objective was to determine the association among temperature variation, PHHD, and outcome at 3 months.

Results

The decrease in temperature in the first 24 hours increased the possibility of good outcome 11-fold. Temperature decrease, lower PHHD volume, and a good outcome were observed in 31.8% of the patients who received antihyperthermic treatment.

Conclusion

The administration of early antihyperthermic treatment in patients with spontaneous ICH with a basal axillary temperature ≥37.5°C resulted in good outcome in a third of the treated patients.

Glossary

ANOVA = analysis of variance; **CI** = confidence interval; **ICH** = intracerebral hemorrhage; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PHHD** = perihematomal hypodensity.

Spontaneous (nontraumatic) intracerebral hemorrhage (ICH) constitutes around 10%–15% of strokes and is associated with poor outcome.[1] In the last decade, mortality due to ICH has decreased but, unlike ischemic stroke, both morbidity and dependence are increasing, probably due to the absence of effective treatments and to population aging.[2,3]

ICH growth during the first hours is a critical factor for neurologic deterioration and poor outcome, regardless of other factors that determine high mortality and poor outcome at the time of ICH, such as hematoma volume and intracranial hypertension with displacement of intracerebral structures.[4,5] The relation between ICH growth in the first hours and poor outcome was recently confirmed in an extensive meta-analysis.[6]

Clinical trials aimed at halting hematoma growth have failed to show efficacy so far[7] and new therapeutic targets are being sought, now focusing on other secondary mechanisms associated with brain damage, such as the perihematomal hypodensity (PHHD) volume.[8–10]

Hyperthermia has been associated with poor outcome in ICH[11] and with the increase of PHHD volume,[12] especially by hypertensive mechanisms.[13] Hypothermia has been proposed as a treatment for ICH that is associated with a decrease in PHHD. However, this kind of treatment is not recommended for patients with ICH due to the high morbidity and mortality, and more clinical trials are needed to verify its efficacy and safety.[14–17]

We analyzed the association between the clinical outcome at 3 months and the decrease in body temperature in the first 24 hours in patients with ICH. Then, we analyzed the association between the PHHD and the decrease in temperature, and finally tested the hypothesis of treating patients with ICH with antihyperthermic drugs for reducing PHHD and improving the clinical outcome.

Methods

Study design

This is a retrospective study performed on a prospective register of patients in a databank approved by the Galician Ethics Committee. Patients were treated in the emergency service of a single tertiary university hospital (University Clinical Hospital of Santiago de Compostela [Spain]) by trained health personnel and later admitted to the stroke unit and treated by neurologists specialized in cerebrovascular treatment according to a protocol based on Spanish and international clinical guidelines.[18,19]

Standard protocol approvals, registrations, and patient consents

This study was carried out in accordance with the Helsinki Declaration of the World Medical Association (2008) and approved by the Clinical Research Ethics Committee of Galicia. Informed consent was obtained from patients or their relatives at the time of inclusion in the registry, authorizing the anonymous use of data for further studies.

Inclusion and exclusion criteria

From January 2008 to December 2018, 1,100 patients with spontaneous ICH were included in the data bank. Exclusion criteria were the following: (1) latency time (from the onset of symptoms to hospital care) >24 hours (n = 185); (2) previous modified Rankin Scale (mRS) score >1 (n = 193); (3) known chronic inflammatory diseases (n = 26); (4) absence of at least 2 neuroimaging studies in the first week (n = 208); (5) isolated primary intraventricular hemorrhage (n = 23); (6) loss of follow-up (face-to-face or telephone) for 3 months (n = 174); (7) patients undergoing surgical removal of hematoma (n = 38). For the purpose of this study, 795 patients were considered valid.

Clinical and analytical variables

The variables analyzed in this study are shown in table 1 and table-e1 (doi.org/10.5061/dryad.np5hqbzps). In particular, axillary temperature was recorded upon admission and every 6 hours during the whole hospitalization time in the stroke unit. For this study, we used the maximum temperature obtained in the first 24 hours after admission to the stroke unit. As the main variable, we determined the difference between the axillary temperature at admission and the temperature at 24 hours (differences >0°C considered as increase and ≤0°C as decrease).

The intensity of the neurologic deficit was determined by the NIH Stroke Scale (NIHSS) upon admission and every 6 hours during the hospitalization in the stroke unit. For this study, the NIHSS was assessed at admission. The functional deficit was assessed by the mRS score at discharge and at 3 months ± 15 days. Both scales were evaluated by internationally certified neurologists, supervised by the same neurologist (M.R.-Y.).

Neuroimaging studies

All of the patients included in the study underwent at least 2 computerized CT scans: the first one on admission and the next one during the first 7 days. The volumes were determined using the ABC/2 method[20] until 2016 and afterwards through the automated planimetric method.[21] The PHHD volume was calculated by subtracting the hematoma volume from the total volume of the lesion (figure 1). ICH growth and PHHD volume were categorized as ≤6 mL vs >6

Table 1 Clinical variables, biochemical measures, and neuroimaging values by outcome groups at 3 months

	Good outcome (n = 348)	Poor outcome (n = 447)	p Value
Age, y	71.1 ± 12.8	76.9 ± 11.6	<0.0001
Women	41.7	45.9	0.250
Latency time, min	242.7 ± 207.8	231.7 ± 204.7	0.489
Previous modified Rankin Scale score	0 (0, 1)	1 (0, 1)	<0.0001
Arterial hypertension	66.7	66.4	0.504
Diabetes	19.3	23.3	0.192
Smoking	13.5	7.8	0.010
Alcoholism	16.1	14.5	0.952
Dyslipidemia	42.5	36.5	0.092
Ischemic heart disease	8.3	10.7	0.278
Atrial fibrillation	15.8	25.1	0.002
Heart failure	2.9	4.0	0.441
Previous stroke	17.3	18.8	0.514
Axillary temperature at admission, °C	36.5 ± 0.7	36.3 ± 0.9	<0.0001
Temperature at admission − at 24 hours, °C	0.48 ± 0.32	0.01 ± 0.38	<0.0001
Decrease in temperature in 24 hours	96.2	54.8	<0.0001
Antihyperthermic treatment	13.5	22.6	0.001
Basal glycemia, mg/dL	130.0 ± 45.4	146.6 ± 50.2	<0.0001
Leukocytes, ×10³/mL	7.1 ± 2.7	12.3 ± 6.8	0.001
Platelets, ×10³/mL	216.6 ± 83.7	191.2 ± 88.0	0.685
Fibrinogen, mg/dL	425.2 ± 90.1	453.3 ± 110.1	0.001
C-reactive protein, mg/L	4.3 ± 4.4	6.1 ± 5.8	<0.0001
Glycosylated hemoglobin, %	5.9 ± 0.8	5.9 ± 0.8	0.148
LDL cholesterol, mg/dL	115.2 ± 24.0	100.2 ± 23.9	0.105
HDL cholesterol, mg/dL	43.1 ± 14.4	39.1 ± 18.7	0.734
Triglycerides, mg/dL	102.7 ± 36.9	98.4 ± 49.0	0.806
Microalbuminuria, mg/24 h	18.8 ± 35.1	22.3 ± 33.6	0.403
Sedimentation rate, mm	29.1 ± 19.9	43.8 ± 31.6	0.004
ICH volume at admission, mL	20.9 ± 18.7	46.4 ± 40.9	<0.0001
Growth of the ICH, mL	12.1 ± 24.0	21.9 ± 35.6	<0.0001
Growth of the ICH ≥6 mL	23.6	46.8	<0.0001
PHHD volume, mL	7.6 ± 10.6	17.8 ± 21.7	<0.0001

Table 1 Clinical variables, biochemical measures, and neuroimaging values by outcome groups at 3 months *(continued)*

	Good outcome (n = 348)	Poor outcome (n = 447)	p Value
PHHD volume ≥6 mL	27.9	62.6	<0.0001
Leukoaraiosis	31.9	44.5	<0.0001
NIHSS at admission	9 (5, 13)	15 (11, 19)	<0.0001
Modified Rankin Scale score at 3 months	2 (0, 2)	5 (3, 6)	<0.0001
ICH topography			0.133
Deep hemisphere	54.3	46.8	
Lobar	38.8	45.2	
Cerebellar	4.9	4.0	
Brainstem	2.1	4.0	
Hemorrhagic contamination	14.9	25.3	<0.0001
ICH diagnosis			0.071
Hypertensive	51.4	45.0	
Amyloid	10.9	16.1	
Anticoagulants	12.4	21.5	
Other/indeterminate	25.3	17.4	

Abbreviations: HDL = high-density lipoprotein; ICH = intracerebral hemorrhage; LDL = low-density lipoprotein; NIHSS = NIH Stroke Scale; PHHD = perihematomal hypodensity.
Values are mean ± SD or %.

mL due to its sensitivity and specificity according to the literature.[6,22] All neuroimaging studies were reviewed by the same neuroradiologist (J.M.P.).

Intervention

Following the hospital protocol, all patients with a baseline temperature ≥37.5°C were treated with 1 g of paracetamol orally or 2 g of metamizole intravenously every 8 hours. The treatment was maintained for at least 48 hours, regardless of the recorded temperature. We considered a positive response to antihyperthermic treatment when the maximum temperature in the first 24 hours was lower than the temperature at admission. Patients were not subjected to other hypothermic procedures.

Outcome endpoints

The main objective of the study was to determine the association between the temperature decrease in the first 24 hours and the clinical outcome at 3 months (mRS categorized: ≤2 good outcome vs >2 poor outcome). Secondary objectives were (1) the association between the PHHD volume and the outcome at 3 months and (2) the influence of the antihyperthermic treatment on the PHHD volume and its repercussion on the outcome at 3 months.

Figure 1 Example of CT scan
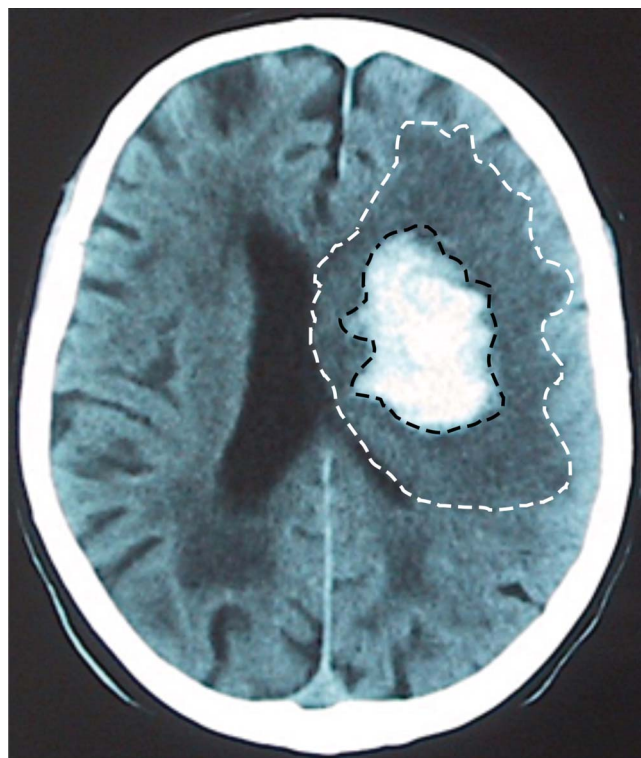
CT scan obtained during the first week after admission. The perihematomal hypodensity volume is calculated by subtracting the hematoma volume (region inside the black dashes) from the total volume of the lesion (white dashes).

Statistical method

First, an analysis was performed describing the sample. Frequencies and percentages were calculated for categorical variables, while the continuous variables were expressed by mean values ± SD or median values and interquartile range depending on their adjustment to normality. Kolmogorov-Smirnov test with Lilliefors correction was applied to assess normality. Analysis of variance (ANOVA) and χ^2 tests were performed to determine differences in the variables between the groups (patients with good outcome vs patients with poor outcome). Bivariate correlations were performed using Spearman coefficients. The logistic regression analysis was performed with the independent variables selected by their statistical significance in the bivariate analysis or by their clinical significance. These results were shown as odd ratios (ORs) with 95% confidence intervals (CIs). A p value <0.05 was considered to be statistically significant. All statistical analyses were conducted in SPSS 21.0 (IBM, Armonk, NY).

Data availability

All data are available within the text of the article. Further anonymized data could be made available to qualified investigators upon reasonable request.

Results

In this study, 795 patients with ICH were included and 305 were excluded. Some differences were found between the included and excluded groups. The included patients were older and more hypertensive and hyperlipemic, with more atrial fibrillation and higher basal temperature. Regarding the ICH diagnosis, there were more amyloid and anticoagulant cases and less indeterminate and primary intraventricular hemorrhages in the included group (7.5% vs 0%; $p < 0.0001$). The rest of the variables studied that could be determined in the excluded group were similar in the 2 groups. A description of the clinical and analytical variables of the included patients is provided in table e-1 (doi.org/10.5061/dryad.np5hqbzps).

Main objective: the effect of temperature decrease on the outcome at 3 months

An analysis was carried out to study the variables that influence the outcome at 3 months. At 3 months (±15 days), 348 patients (43.8%) presented good outcome while 447 (52.2%) showed poor outcome. The variables associated with the outcome are listed in table 1. Regarding body temperature, it can be seen that the temperature at admission was higher in patients with good outcome (36.5 ± 0.7°C vs 36.3 ± 0.9°C; $p < 0.0001$), although in both groups the average temperature was below 37°C. However, the decrease in temperature in the first 24 hours was significantly higher in patients with good outcome (0.48 ± 0.32 vs 0.01 ± 0.38; $p < 0.0001$) and the percentage of patients with temperature decrease was also higher in the good outcome group (96.2% vs 54.8%; $p < 0.0001$). In addition, we observed a relationship (ANOVA test; $p < 0.0001$) between variations in axillary temperature in the first 24 hours and the mRS values, with the patients with high temperature decrease being the ones with lower mRS (figure 2).
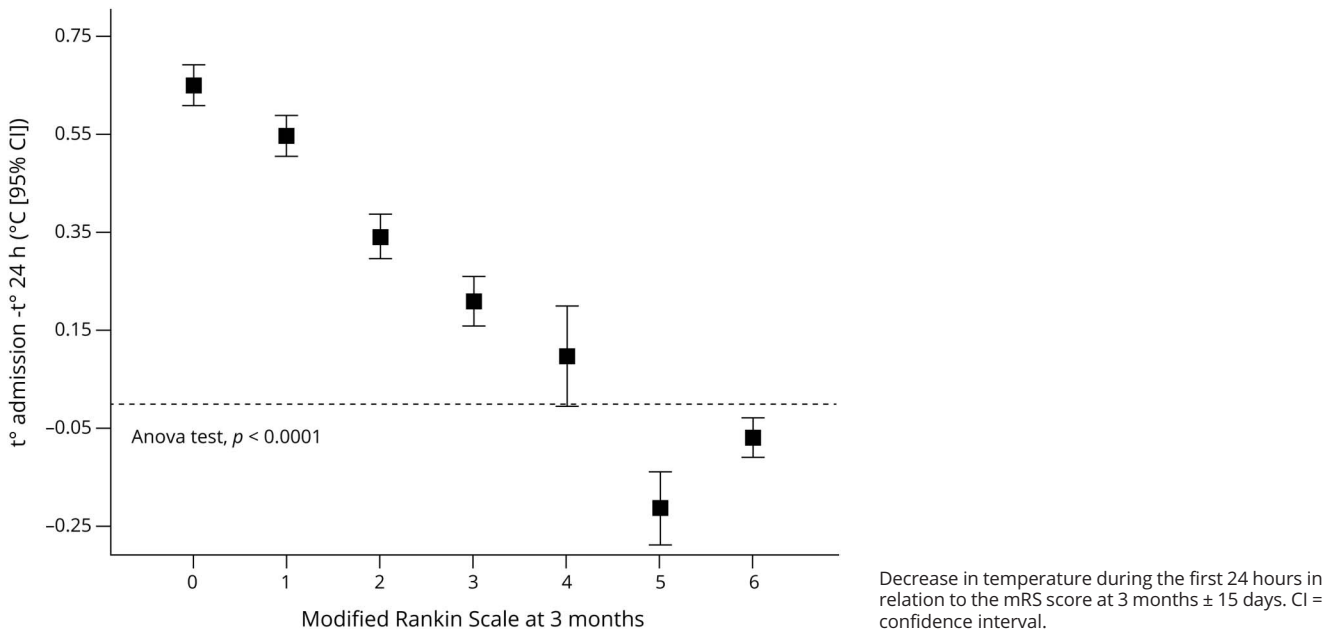
In the logistic regression model (table 2), the temperature decrease in the first 24 hours was independently associated with good outcome at 3 months (adjusted OR, 11.28; 95% CI, 4.69–27.01; $p < 0.0001$). Therefore, the decrease in temperature in the first 24 hours multiplies by 11 the possibility of good outcome, while the hematoma growth multiplies by 5 the possibility of poor outcome (adjusted OR, 5.55; 95% CI, 2.63–11.11; $p < 0.0001$).

Secondary objectives

Influence of PHHD volume on the outcome at 3 months

The average PHHD volume measured in the second CT neuroimage was 13.3 ± 18.20 mL in the whole sample; 373 patients presented a PHHD volume ≥6 mL and 418 patients <6 mL. PHHD volume was directly related to worse mRS scores at 3 months (figure 3). A descriptive analysis (table e-2; doi.org/10.5061/dryad.np5hqbzps) categorizing the patients according to the PHHD volume showed that good outcome is more frequent in the group of patients with

Figure 2 Temperature and modified Rankin Scale (mRS) score

Decrease in temperature during the first 24 hours in relation to the mRS score at 3 months ± 15 days. CI = confidence interval.

a PHHD volume <6 mL (72.1% vs 27.9%; $p < 0.0001$). Age, frequency of arterial hypertension, temperature at admission, leukocytes, fibrinogen, microalbuminuria, C-reactive protein, and sedimentation rate showed lower values in patients with a PHHD volume <6 mL. The ICH volume and the NIHSS at admission also showed lower values in patients with PHHD <6 mL.

The logistic regression analysis (table 2) showed that good outcome is 0.23 times more frequent in patients with a PHHD volume ≥6 mL (OR, 0.23; 95% CI, 0.17–0.31; $p < 0.0001$), although we did not observe an association between outcome and PHHD volume after adjusting with ICH growth.

Regarding temperature, PHHD volume was lower in patients with a decrease in temperature in the first 24 hours (figure 4). The temperature decrease in the first 24 hours was more frequent in patients with a PHHD volume <6 mL (91.6% vs 64.2%; $p < 0.0001$). In another adjusted logistic regression model (table e-3; doi.org/10.5061/dryad.np5hqbzps), the decrease in temperature was found to be 17 times more frequent in patients with a PHHD volume <6 mL (adjusted OR, 16.87; 95% CI, 3.75–75.84; $p < 0.0001$).

Influence of the antihyperthermic treatment on PHHD volume and its repercussion on the outcome at 3 months

Among the 795 patients included in the study, 148 received antihyperthermic treatment according to the hospital protocol (their clinical and biological variables are listed in table 3). Body temperature was reduced in 65 patients (43.9%), while in 83 (56.1%) the treatment did not cause a reduction of the

temperature. Interestingly, among the 647 patients who did not receive treatment, 529 showed a decrease in body temperature (84.6%).

The average decrease in temperature was significantly different in the 3 groups of patients: responders, nonresponders, and not treated with antihyperthermic drugs ($0.86 ± 0.45°C$ vs $−0.09 ± 0.25°C$ vs $0.21 ± 0.39°C$; $p < 0.0001$) (figure 5A); likewise, PHHD volume was lower in the group of patients with a positive response to treatment compared with patients who responded negatively and those with no treatment ($1.9 ± 2.8$ mL vs $36.6 ± 23.4$ mL vs $11.2 ± 15.8$ mL; $p < 0.0001$) (figure 5B).

A good outcome at 3 months was observed in 72.3% of responder patients to antihyperthermic drugs, while none of the patients with a negative response experienced good outcome at 3 months ($p < 0.0001$) (table e-4; doi.org/10.5061/dryad.np5hqbzps). The positive response to antihyperthermic treatment was also associated with good outcome as shown in the logistic regression analysis of table 2 (OR, 3.00; 95% CI, 1.71–5.28; $p < 0.0001$; adjusted OR, 1.67; 95% CI, 1.18–7.87; $p = 0.022$).

Discussion

Spontaneous ICH constitutes a progressive cause of mortality and morbidity that until now could be considered a therapeutically orphan disease. Neither the surgical approach nor procoagulant drugs has shown safety or efficacy.[7,23–25] Thus new therapeutic approaches have been explored focusing on more reachable objectives. In

Table 2 Multivariate analysis

Independent variables	OR not adjusted	95% CI	p Value	OR adjusted	95% CI	p Value
Decrease in temperature in 24 hours	20.78	12.78–33.77	<0.0001	11.28	4.69–27.01	<0.0001
PHHD volume ≥6 mL[a]	0.23	0.17–0.31	<0.0001	0.61	0.37–1.02	0.058
Positive antihyperthermic treatment	3.00	1.71–5.28	<0.0001	1.67	1.18–7.87	0.022
Growth of the ICH ≥6 mL	0.35	0.26–0.48	<0.0001	0.18	0.09–0.38	<0.0001
NIHSS at admission	0.79	0.76–0.81	<0.0001	0.83	0.78–0.87	<0.0001
Age	0.96	0.95–0.97	<0.0001	0.97	0.94–0.99	0.007
Glycemia	0.99	0.99–0.99	<0.0001	0.99	0.98–0.99	0.028
Axillary temperature at admission	0.58	0.49–0.68	<0.0001	1.14	0.80–1.62	0.464
ICH volume at admission	0.96	0.94–0.97	<0.0001	0.99	0.98–1.00	0.143
Previous modified Rankin Scale score	0.66	0.57–0.77	<0.0001	0.72	0.50–1.04	0.080
Smoking	1.61	1.10–2.37	0.014	1.27	0.54–3.03	0.583
Atrial fibrillation	0.51	0.37–0.71	<0.0001	0.82	0.43–1.532	0.527
Leukocytes	0.94	0.90–0.97	0.001	0.98	0.89–1.07	0.621
Fibrinogen	0.99	0.99–0.99	<0.0001	0.99	0.99–1.00	0.063
C-reactive protein	0.93	0.90–0.95	<0.0001	1.01	0.95–1.08	0.704
Sedimentation rate	0.99	0.98–0.99	<0.0001	0.99	0.98–1.01	0.732
Leukoaraiosis	0.58	0.45–0.75	<0.0001	0.80	0.39–1.63	0.545
Hemorrhagic contamination	0.44	0.33–0.61	<0.0001	0.63	0.35–1.14	0.124

Abbreviations: CI = confidence interval; ICH = intracerebral hemorrhage; NIHSS = NIH Stroke Scale; OR = odds ratio; PHHD = perihematomal hypodensity.
Dependent variable: good outcome at 3 months ± 15 days.
[a] Adjusted only for patients with growth of the ICH <6 mL.

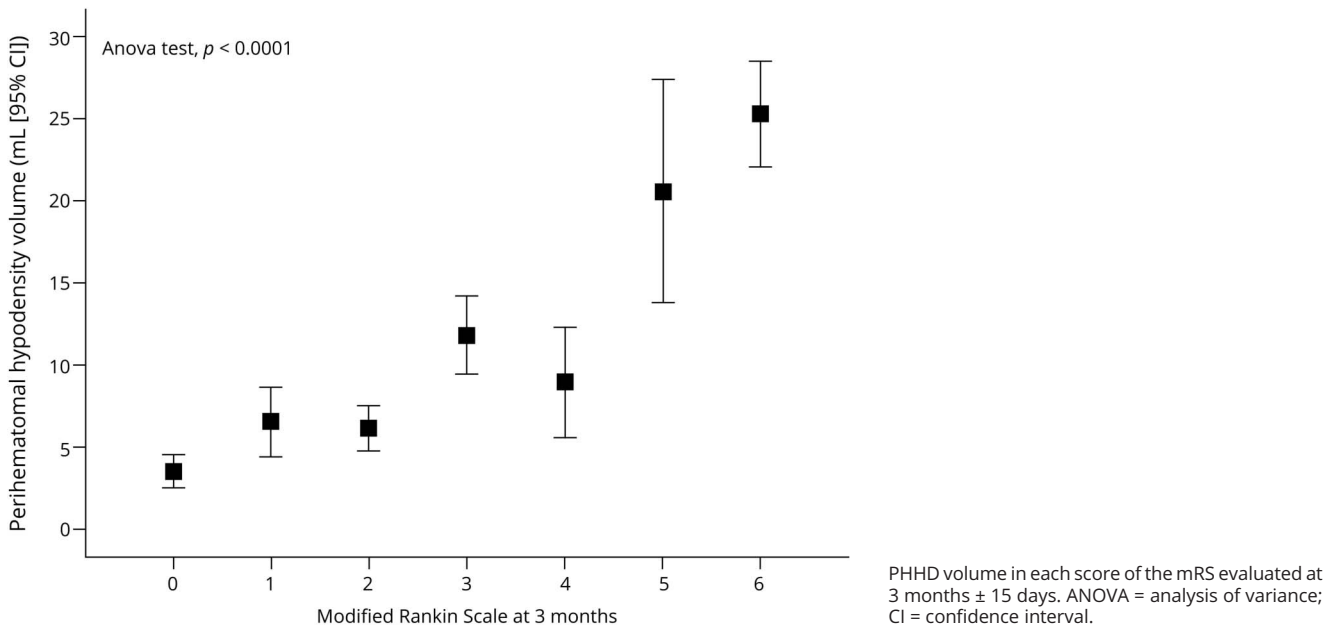recent years, PHHD has been identified as an attractive possibility.

PHHD mechanisms are complex and not completely understood, and therefore we prefer to use the descriptive name perihematomal hypodensity instead of perihematomal edema, frequently cited in the literature. Undoubtedly, many events of a large PHHD are associated with inflammatory mechanisms[26] and have been linked to the appearance of a cytotoxic edema in the first hours and with a vasogenic edema in later phases.[9,27,28] However, other mechanisms should not be ruled out, such as ischemic necrosis or neurotoxicity associated with coagulation mechanisms.[29,30] A novel and promising hypothesis associated the presence and progression of PHHD with the existence of spreading depressions and isoelectric spreading depolarizations, although its association with episodes of metabolic derangement and ischemic lesions remains speculative.[31] It has also been postulated that upregulated microRNA-23a-3p in patients with ICH promotes the apoptosis of cerebral vascular endothelial cells by downregulating ZO-1, thus participating in the formation of PHHD after ICH.[32]

The prognostic role of PHHD in ICH has been widely debated in the literature, with contradictory results.[10] The latest prospective studies showed a strong relationship between PHHD volume and higher mortality and morbidity.[8,9,33–36] This prognostic capacity is higher during the first 24 hours, progressively decreasing its value during the subacute phase of ICH.[9] Although the prognostic capacity of the PHHD volume over the clinical outcome was not the main objective of our study, we initially showed that PHHD volume was significantly higher in patients with a worse outcome at 3 months, and a PHHD volume <6 mL was 4 times more frequent in patients with a good outcome. However, the association between PHHD and clinical outcome was not observed after including other relevant variables in the model, such as ICH volume and temperature. Moreover, high levels of significant prognostic factors of poor outcome at 3 months (such as fibrinogen or temperature) were also found in patients with low volumes of PHHD, pointing out the weak association between PHHD and clinical outcome.

PHHD has been the target of different treatments for ICH.[15,16] Corticosteroids could be effective in late phases in which vasogenic edema may predominate, however, they have not shown utility and cause a greater number of complications.[37] Similarly, hypertonic solutions did not affect the outcome at 3 months.[38]

Figure 3 Perihematomal hypodensity (PHHD) and modified Rankin Scale (mRS) score

PHHD volume in each score of the mRS evaluated at 3 months ± 15 days. ANOVA = analysis of variance; CI = confidence interval.

There is a clear relation between hyperthermia, even moderate, and a poor outcome of nontraumatic ICH.[11,39–42] In our experience, an axillary temperature at admission ≥37.5°C multiplies by 4 the risk of a poor outcome at 3 months.[11] Preclinical trials aiming for hypothermic temperatures of 35°C confirmed the association between hypothermia and a decrease in PHHD along with a better outcome,[17] with evidence that supports the translationality to human clinical practice,[43–45] especially if hypothermia is established early.[14] However, this therapeutic procedure is

Figure 4 Perihematomal hypodensity (PHHD) volume

Scatterplot of decrease in body temperature at 24 hours and the PHHD volume. The decrease in temperature is associated with a lower PHHD volume.
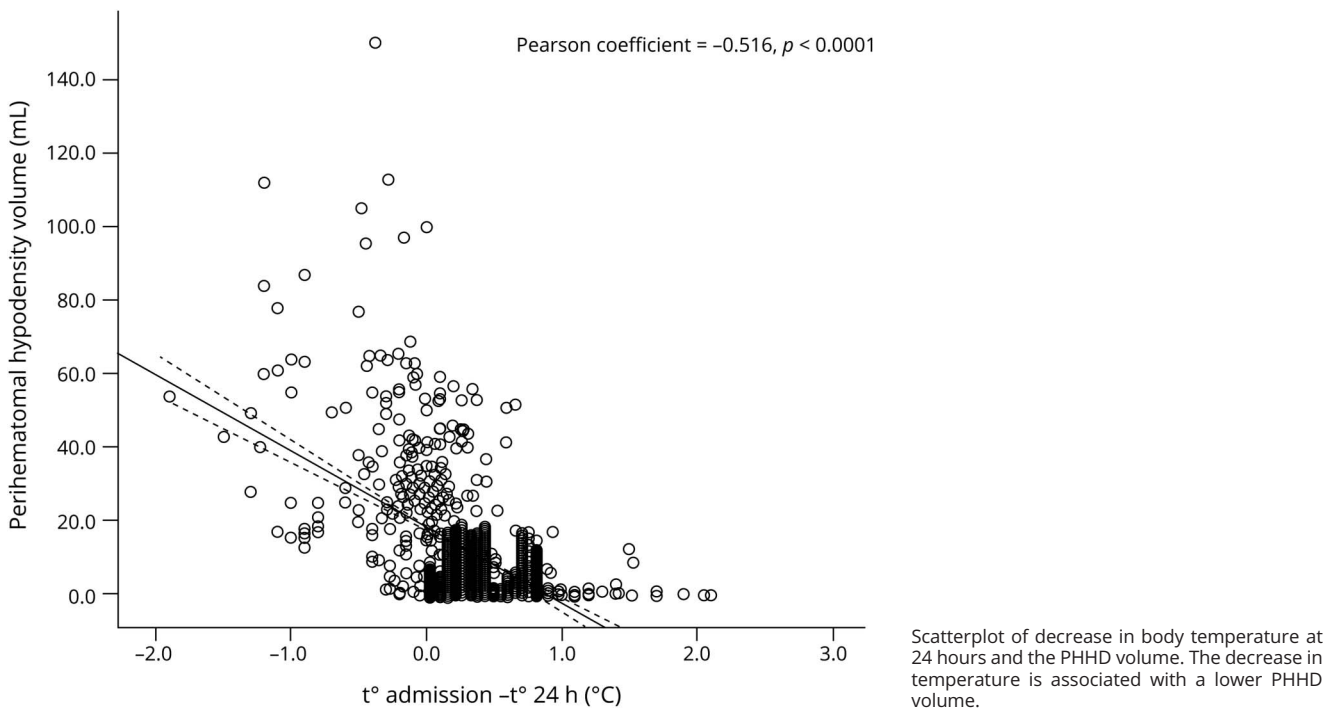
Table 3 Clinical variables, biochemical measures, and neuroimaging values categorized in patients with a negative and positive response to antihyperthermic treatment

	Antihyperthermic treatment		
	No (n = 647)	Yes (n = 148)	*p* Value
Age, y	73.3 ± 13.1	73.6 ± 13.4	0.738
Women	44.4	38.0	0.146
Latency time, min	231.7 ± 208.9	227.7 ± 187.6	0.840
Previous modified Rankin Scale score	1 (0, 1)	1 (0, 1)	0.599
Arterial hypertension	58.0	77.3	<0.0001
Diabetes	19.1	27.6	0.015
Smoking	10.6	11.7	0.681
Alcoholism	14.5	20.2	0.077
Dyslipidemia	36.1	40.5	0.291
Ischemic heart disease	8.4	9.8	0.547
Atrial fibrillation	19.0	12.9	0.062
Heart failure	3.4	4.3	0.5
Previous stroke	18.9	16.6	0.693
Axillary temperature at admission, °C	36.4 ± 0.6	38.0 ± 0.4	<0.0001
Temperature at admission − at 24 hours, °C	0.21 ± 0.39	0.29 ± 0.58	0.034
Decrease in temperature in 24 hours	76.1	58.9	<0.0001
Basal glycemia, mg/dL	137 ± 47	149.8 ± 53.1	0.0004
Leukocytes, ×10³/mL	8.5 ± 3.1	10.6 ± 3.8	<0.0001
Platelets, ×10³/mL	203 ± 77.6	200.5 ± 90.4	0.920
Fibrinogen, mg/dL	435.6 ± 100.7	475.9 ± 99.9	<0.0001
C-reactive protein, mg/L	4.2 ± 3.9	11.7 ± 6.9	<0.0001
Glycosylated hemoglobin	5.8 ± 0.9	5.9 ± 1.0	0.35
LDL cholesterol, mg/dL	110.9 ± 35.5	100.1 ± 31.8	0.014
HDL cholesterol, mg/dL	39.2 ± 18.3	35.5 ± 18.7	0.098
Triglycerides, mg/dL	103.9 ± 49.8	112.1 ± 56.9	0.152
Microalbuminuria, mg/24 h	15.3 ± 30.1	27.5 ± 27.5	0.008
Sedimentation rate, mm	22.6 ± 20.5	46.9 ± 25.9	<0.0001
ICH volume at admission, mL	36.9 ± 37.9	61.2 ± 54.1	<0.0001
Growth of the ICH, mL	11.1 ± 26.6	5.2 ± 14.4	0.009
Growth of the ICH ≥6 mL	39.1	25.7	0.002
PHHD volume, mL	11.2 ± 15.8	21.4 ± 24.6	<0.0001

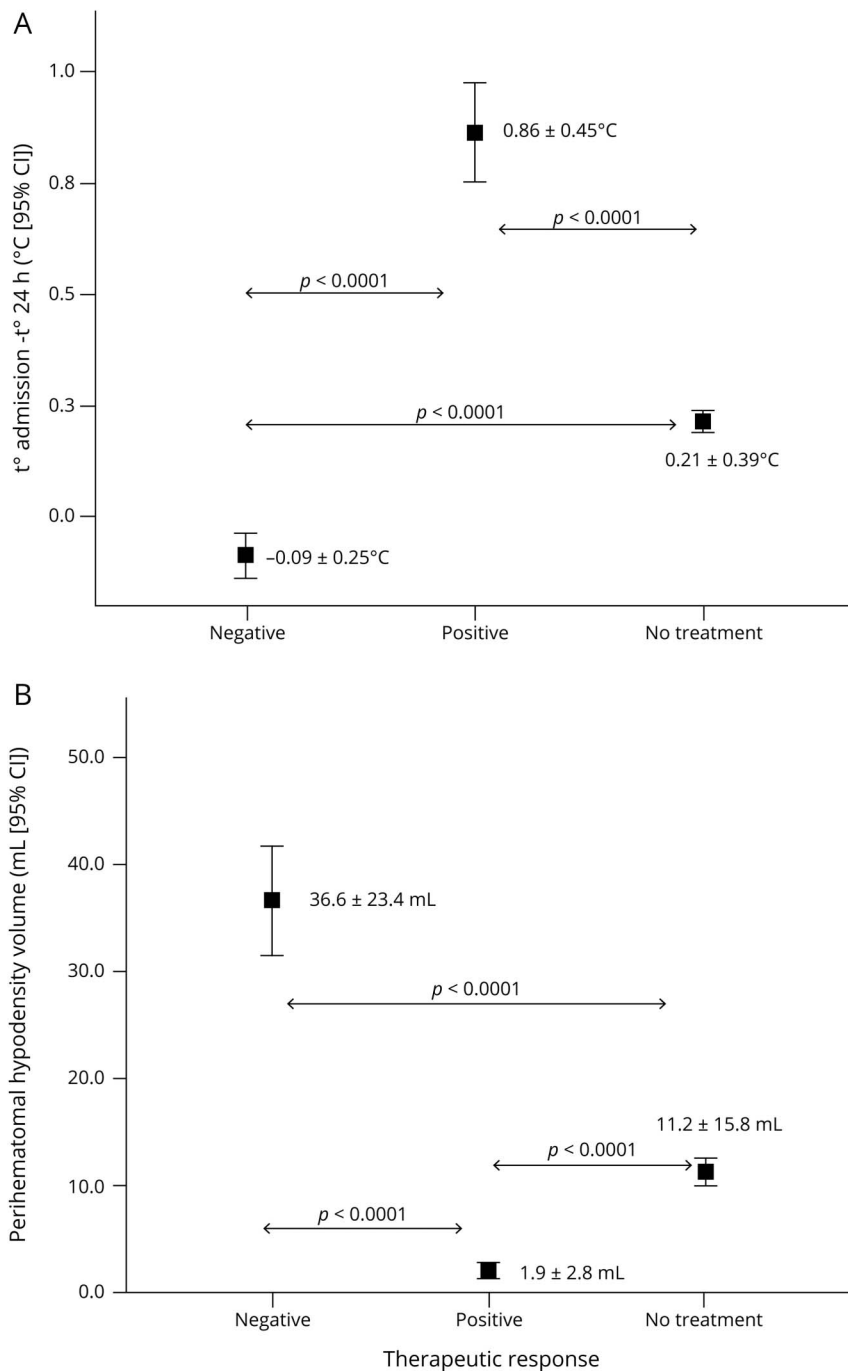|	Antihyperthermic treatment		
	No (n = 647)	Yes (n = 148)	*p* Value
PHHD volume ≥6 mL	54.1	45.9	0.083
Leukoaraiosis	31.3	30.7	0.927
NIHSS at admission	12 (7, 17)	17 (13, 21)	<0.0001
Modified Rankin Scale score at 3 months	3 (1, 6)	6 (2, 6)	<0.0001
Good outcome at 3 months	46.5	31.7	<0.0001
ICH topography			0.264
Deep hemisphere	49.7	55.0	
Lobar	41.8	38.2	
Cerebellar	5.0	2.8	
Brainstem	3.5	4.9	
Hemorrhagic contamination	20.8	24.5	0.301
ICH diagnosis			<0.0001
Hypertensive	42.6	65.0	
Amyloid	10.7	8.6	
Anticoagulants	15.4	7.4	
Other/indeterminate	31.4	19.0	

Abbreviations: HDL = high-density lipoprotein; ICH = intracerebral hemorrhage; LDL = low-density lipoprotein; NIHSS = NIH Stroke Scale; PHHD = perihematomal hypodensity.
Values are mean ± SD or %.

still not safe and has not been proven in clinical trials for patients with ICH.

Based on this evidence, in this study we aimed to investigate the efficacy of a moderate decrease in temperature (in our series, the change in temperature in the first 24 hours, with or without antihyperthermic treatment), since it is incorporated into the clinical practice guidelines for ischemic stroke management.[46,47] We have verified that a decrease in body temperature multiplied by 11 the association with a good outcome. The variation in body temperature is proportional to the changes in PHHD volume, and this association is independent of other variables.

A questionable aspect of our findings is the limited effectiveness of antihyperthermic treatment, since it only managed to reduce the temperature in fewer than half of the patients who presented an axillary temperature ≥37.5°C on admission. This is probably due to the multiple mechanisms that can condition the temperature increase in ICH, and the type of hemorrhage is

Figure 5 Therapeutic response

(A) Decrease in body temperature at 24 hours in the antihyperthermic treated group (without and with a therapeutic response) and the nontreated group. (B) Perihematomal hypodensity (PHHD) volume in the 3 groups according to the therapeutic response. CI = confidence interval.

undoubtedly one of these variables.[13] In our series, the therapeutic response was positive in only 31.1% of hypertensive ICH, in 42.9% of amyloid ICH, in 25.0% associated with antiplatelets/anticoagulants, and in 74.2% of indeterminate cases ($p < 0.0001$, data not shown in the Results). The overall benefit (determined as good outcome at 3 months) of patients who received antihyperthermic treatment was 31.8%.

Despite the fact that only 31.8% of patients who received antihyperthermic treatment benefited from a moderate

decrease in temperature, associated with a decrease in PHHD volume (paracetamol and metamizole do not have remarkable antiinflammatory effects raising other mechanisms), these results could encourage the consideration of a prospective and multicentric study, since the design of our study does not allow for the evaluation of a possible benefit of antihyperthermic treatment in normothermic patients.

Our study shows the weakness of its retrospective nature, such as the lack of a blind assignation of patients to

antihyperthermic treatments that could bias the sample. Nevertheless, the influence of the temperature variation over the different mRS has the same trend independent on the antihyperthermic treatment. Also, due to the retrospective nature of the study, we could rule out any inclusion bias.

The administration of early antihyperthermic treatment in patients with a spontaneous ICH with a basal axillary temperature ≥37.5°C is associated with a moderate decrease in temperature in the first 24 hours and with a better prognosis at 3 months in one-third of the treated patients.

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Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication history

Appendix Authors

Name	Location	Contribution
Pablo Hervella, PhD	Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain	Designed and conceptualized the study, analyzed the data, wrote the manuscript
Manuel Rodríguez-Yáñez, MD PhD	Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain	Major role in the acquisition of data, neuroimaging study, interpreted the data, revised the manuscript
José Manuel Pumar, MD, PhD	Clinical University Hospital, Santiago de Compostela, Spain	Major role in the acquisition of data, neuroimaging study, interpreted the data, revised the manuscript
Paulo Ávila, BSc	Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain	Acquired and interpreted the data, critical revision of the manuscript
Andrés da Silva-Candal, PhD	Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain	Acquired and interpreted the data, critical revision of the manuscript

Appendix (continued)

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