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Severe traumatic head injury in adults: Which patients are at risk of early hyperthermia?

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Abstract *Objective:* Prevention of secondary insults, such as hyperthermia, is a major goal after traumatic brain injury. The aim of our study was to identify risk factors for early hyperthermia in severe head-injured patients. *Design:* Retrospective cohort study. *Setting:* A 17-bed multidisciplinary ICU of a 700-bed teaching hospital. *Patients:* A total of 101 adult patients admitted from January 1999 to December 2001 requiring continuous monitoring of intracranial pressure according to international guidelines. *Measurement and results:* Forty-four patients experienced early hyperthermia (at least one episode of body temperature >38.5°C within the first 2 days). On univariate analysis five variables were associated with early hyperthermia: sex; body temperature; white blood cell count on admission; prophylactic use of acetaminophen; and diabetes insipidus within 2 days. On multivariate analysis, white blood cell count >14.5×10^9/l on admission (odds ratio, 7.1; 95% confidence interval, 2.4–20.5; *p*=0.001) and a body temperature on admission >36°C (odds ratio, 6.7; 95% confidence interval, 2.3-20.1) were strong risk factors of early hyperthermia. Prophylactic use of acetaminophen was negatively associated with early hyperthermia (odds ratio, 0.1; 95% confidence interval, 0.02–0.4). Patients who experienced early hyperthermia were less prone to have good recovery (GOS=5; *p*=0.03). More patients with severe or moderate disability (GOS=3 or 4) experienced early hyperthermia (*p*=0.01). *Conclusion:* We identified a subgroup of patients at high risk of early hyperthermia, which is common in severe head-injured patients. These results could have clinical implications for prevention of hyperthermia after traumatic brain injury in adults.

Keywords Traumatic brain injury · Hyperthermia · Leukocytosis · Diabetes insipidus · Outcome

Introduction

Hyperthermia is a common issue in neurological intensive care unit (ICU) and is associated with a poor neurological outcome in stroke and spontaneous subarachnoid hemorrhage [1, 2, 3, 4, 5]. In a study including 390 stroke patients, Reith et al. found that for each 1°C increase in body temperature on admission, the relative risk of poor outcome rose by 2.2 [3]. Although less studied, hyperthermia following traumatic brain injury (TBI) is also known to increase morbidity and mortality [6, 7].

Pathophysiological links between hyperthermia and outcome following brain injuries are not clear. Experimental studies have shown that brain injury is worsened when hyperthermia (even 1 or 2°C) is superimposed to an ischemic (focal or global) lesion [8, 9, 10, 11], which is common after severe TBI [12]. Both human and animal studies have shown that the extent of cerebral damage is related to the timing of hyperthermia onset with a poorer outcome when hyperthermia occurs soon after injury [13, 14, 15].

Pathogenesis of hyperthermia in head trauma patients is related to several causes and mechanisms including: (a) inflammatory cascade due to tissue attrition; (b) catecholergic stimulation; (c) direct damage to cerebral centers of thermoregulation; or (d) infection.

The aim of our study was to identify risk factors of early hyperthermia (within two days) and related consequences of this event on outcome in a population of severe adult TBI patients.

Materials and methods

Study population and design

According to French legislation, no informed consent is needed to use data for an epidemiological study. We performed a retrospective observational cohort study on prospectively collected data in consecutive severe head trauma patients admitted to a 17-bed surgical ICU of a French teaching hospital (Hôpital Beaujon, Clichy, France). The inclusion criteria were an age higher than 18 years and a head trauma requiring an intracranial pressure (ICP) monitoring. The study period began in January 1999 and ended in December 2001. Indication for ICP monitoring was in agreement with international guidelines for head trauma: (a) Glasgow coma scale score (GCS) <8 after cardiopulmonary resuscitation with an abnormal admission cranial computed tomography (CT) scan; (b) GCS <8 with a normal CT scan with two or more of the following features noted on admission: age over 40 years, unilateral or bilateral motor deficit, systolic blood pressure (SBP) <90 mmHg; and (c) moderate head injury in case of traumatic mass lesions with a decreasing level of consciousness [16]. Exclusion criterion was death within the first 2 days.

Patient management

The initial management of these patients was performed on the scene of the accident by a medical team. This prehospital management included GCS determination and sedation, intubation, and ventilation when needed. Patient care (including the prehospital period) was delivered according to recommendations of the French society of anesthesiology and critical care on initial management of the severely head-injured patients [17]. A metallic survival blanket was used for all patients during transport to hospital. After determination of GCS score as well as intentional sedation with fentanyl and midazolam was used for all patients. Cerebral perfusion pressure (CPP) was maintained above 70 mm Hg with vasopressor (norepinephrine), if necessary. Refractory intracranial hypertension was treated by barbiturate (Thiopental). No intentional hypothermia was used. Management of hyperthermia, antibiotherapy, and prophylactic use of acetaminophen were left to discretion of physician in charge of the patient. The ICP was measured with an intraparenchymal probe (Codman, Johnson and Johnson Company, Raynham, Mass.). Blood and urine cultures were performed systematically when the body temperature was higher than 38.5°C. Ventilator-associated pneumonia was suspected when several criteria were associated with hyperthermia: new and/or progressive pulmonary infiltrate on chest X-ray and one of the following criteria: leukocytosis ($\geq$12,000/mm^3) or leukopenia ($\leq$4000/mm^3) and purulent tracheobronchial secretions. Ventilator-associated pneumonia was then confirmed with an invasive method using a fiberoptic bronchoscope by protected specimen brush growing $\geq$10^3 colony forming unit (CFU)/ml [18]. The final decision concerning presence or absence of infection was made by the physician in charge of the patient. When possible, nutritional support was performed by enteral nutrition started within the first 48 h via orogastric tube by a mixture containing glucose 50%, lipid 35%, and protein 15% (Sondalis, Nestle). No patient received intravenous glucose infusion within the first 48 h.

Data collection

The following data were gathered:

1. Gender, GCS score on scene, cause of injury, findings on initial cranial CT scan, associated injuries, Simplified Acute Physiology Score (SAPS) II, Injury Severity Score (ISS)
2. Body temperature, white blood cell count (WBC), and glycemia on admission
3. Highest and mean temperature, highest and mean ICP, lower and mean CPP, early arterial hypotension, occurrence of diabetes insipidus, seizures, and neurosurgery within the first 2 days.
4. Use of barbiturates, myorelaxant agent, vasoconstrictor, acetaminophen, and total dose of acetaminophen within the first 2 days.
5. Length of ventilation, length of ICU stay, and the five-point Glasgow Outcome Scale (GOS) 6 months after injury [19].

Definitions

Early hyperthermia was defined by at least one measurement of body temperature higher than 38.5°C within the first 2 days. Body temperature was measured using an infrared tympanic thermometer (Genius 3000A, Sherwood Medical, St. Louis, Mo.) every 3 h. Initial GCS was reported by attending physicians on arrival on scene after cardiopulmonary resuscitation. Early arterial hypotension was defined as any episode of systolic blood pressure below 90 mmHg during the first 24 h of care. Early diabetes insipidus episode was defined by the association of polyuria with urinary gravity <1.005, absence of glycosuria, and natremia >145 mmol/l (normal value between 135 and 145 mmol/l) within the first 2 days. Associated traumatic lesions were diagnosed on body CT scan performed in all patients on arrival.

Use of acetaminophen was considered as prophylactic if infused before body temperature has reached 38.5°C. Acetaminophen was administered intravenously (Pro-Dafalgan, Laboratoires UPSA, Rueil-Malmaison, France) in a 30-min period diluted with 100 ml of saline serum with a maximum dose of 4 g a day. Each infused vial contained 2 g of propacetamol (yielding 1 g of acetaminophen).

Evaluation of the five-point GOS was performed by a neurosurgeon blinded to occurrence of early hyperthermia.

Statistical analyses

All results are expressed as mean±standard deviation or as a ratio of total patients. Qualitative variables were compared using chi-square test or Fisher's exact test (two sided) when needed. Continuous variables were compared using Student's t test. A multivariate analysis was performed to determine risk factors of early hyperthermia using a logistic regression taking variables with a $p \leq 0.05$ into account after univariate analysis. Threshold values were specified before statistical study. Data are presented in Table 1 including coefficient of the explanatory variable and the associated standard error, odds ratio, 95% confidence interval of the odds ratio, and p value (quoted with the Wald χ^2 test). Explanatory variables were assessed for colinearity and tested for interaction.

Table 1 Demographic and clinical characteristics. *SAPS* simplified acute physiology score, *ISS* injury severity score, *WBC* white blood cell count, *EH* early hyperthermia, *n.s.* not significant

	Patients with EH (*n*=44)	Patients without EH (*n*=57)	*p* value
Age (years)	33±14	34±16	n.s.
Female	2 (4.5)	16 (28)	0.002
Multiple trauma patients	34 (77)	40 (70)	n.s.
Abdominal trauma	5 (11)	10 (18)	n.s.
Bone/pelvis trauma	14 (32)	18 (32)	n.s.
Lung trauma	25 (57)	34 (60)	n.s.
Glasgow coma score on scene	6±2	7±2	n.s.
SAPS 2 score on admission	37±11	38±12	n.s.
ISS score on admission	34±8	36±10	n.s.
Seizure	3 (7)	4 (7)	n.s.
WBC >14.5×10^9/l on admission	34 (77)	26 (46)	0.001
Glycemia (mmol/l)	7.1±2.5	6.7±2.1	n.s.
Admission temperature (°C)	37±1.2	35.9±1.2	<0.0001
Admission temperature >36°C	36 (82)	27 (47)	0.0004
Early arterial hypotension	22 (50)	25 (44)	n.s.
Diabetes insipidus	5 (11)	20 (35)	0.006
Diffuse edema	20 (45)	37 (65)	n.s.
Petechial lesions	8 (18)	11 (19)	n.s.
Intracerebral hematoma(s)	32 (73)	37 (65)	n.s.
Subarachnoid hemorrhage	22 (50)	19 (33)	n.s.
Urgent neurosurgery	10 (23)	15 (26)	n.s.
Muscle relaxant use	4 (9)	11 (19)	n.s.
Prophylactic use of acetaminophen	3 (7)	18 (32)	0.002
Barbiturate therapy	6 (14)	8 (14)	n.s.

Table 2 Clinical events and outcome associated with early hyperthermia (EH). *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *ICU* intensive care unit

	Patients with EH (*n*=44)	Patients without EH (*n*=57)	*p* value
Higher ICP in first 48 h (mmHg)	25±9	26±12	n.s.
Mean ICP in first 48 h (mmHg)	17±6	17±7	n.s.
Intracranial hypertension	21 (48)	29 (51)	n.s.
Lower CPP in first 48 h (mmHg)	52±8	52±11	n.s.
Mean CPP in first 48 h (mmHg)	68±9	69±8	n.s.
Vasoconstrictor use	38 (86)	50 (88)	n.s.
Length of stay (days)	24±14	22±14	n.s.
Length of ventilation (days)	20±11	19±10	n.s.
Glasgow coma score on ICU discharge	13±2	14±2	n.s.
Glasgow coma score <13 on ICU release	22 (50)	22 (39)	n.s.
Death in ICU	8 (18)	14 (25)	n.s.
Glasgow outcome scale (6 months)			
Good	4 (9)	15 (26)	0.03
Moderate/severe	31 (70)	26 (46)	0.01
Vegetative/dead	9 (21)	16 (28)	n.s.

Statistical analysis was performed using Statview 5.0 Software (SAS institute, Cary, N.C.) and JMP 3.0 Software (SAS institute, Cary, N.C.).

Results

One hundred seven head trauma patients fulfilling the inclusion criteria were admitted during the 2-year study period. Six patients died in the first 2 days. The remaining 101 patients had a mean age of 33±15 years, were mainly male, and 74 were multiple trauma patients. Cause of injury was: motor vehicle crash (*n*=21); motorcycle accident (*n*=27); fall (*n*=16); pedestrian accident (*n*=33); and assault (*n*=4). They had a mean SAPS 2 score of 38±11, an ISS score of 35±9, a mean GCS on admission of 7±2, and 25 patients underwent urgent neurosurgery. Mean body temperature on admission was 36.4±1.3°C. Sixty patients had a WBC >14.5×10^9/l on admission. Length of stay was 23±14 days and 22 patients died in ICU. Cranial CT scan findings were: diffuse edema (*n*=57); petechial lesions (*n*=19); intracerebral hematoma (*n*=69); and subarachnoid hemorrhage (*n*=41). Clinical events in the first 2 days and outcome are listed in Table 2.

Table 3 Multivariate logistic regression analysis of risk factors of early hyperthermia. *SE* standard error, *CI* confidence interval

Variable	Coefficient[a]	SE	Odds ratio	95% CI	*p* value
Admission temperature >36°C	1.91	0.56	6.7	2.3–20.1	0.0006
WBC >14.5×10⁹/l on admission	1.96	0.55	7.1	2.4–20.5	0.0003
Prophylactic use of acataminophen	−2.37	0.76	0.1	0.02–0.4	0.002

Early hyperthermia was defined as the dependent variable coded as "present or absent" with 44 early hyperthermias in 101 observations
p value is quoted with the Wald χ^2 test
[a] Coefficient of the explanatory variable

Forty-four patients experienced early hyperthermia. Mean temperature within the first 2 days was 36.8±1.0°C. Forty-nine patients received acetaminophen: 21 for prevention of hyperthermia and 29 for treatment of hyperthermia. Mean dose of acetaminophen used in prevention was 3.5±1.5 g within first 2 days.

On univariate analysis, three variables were positively associated with the occurrence of early hyperthermia: sex; WBC on admission; and admission body temperature >36°C. Conversely, prophylactic use of acetaminophen and early occurrence of central diabetes insipidus were negatively associated with occurrence of early hyperthermia (see Table 1 for details).

On multivariate analysis three independent variables remained associated with the occurrence of early hyperthermia. WBC >14.5×10⁹/l on admission and temperature >36°C on admission were positively associated with early hyperthermia. Prophylactic use of acetaminophen was negatively associated with early hyperthermia (see Table 3 for details). We found no colinearity as well as no interaction between independent variables.

Long-term outcome showed that patients who experienced early hyperthermia were less prone to have good recovery (GOS=5; *p*=0.03). More patients with severe or moderate disability (GOS=3 or 4) experienced early hyperthermia (*p*=0.01). Number of patients dead or vegetative were not different between patients with or without occurrence of early hyperthermia. These results are listed in Table 2. No episode of early hyperthermia was related to infection.

Discussion

In this study, several risk factors of early hyperthermia following TBI were identified. A WBC>14.5×10⁹/l and a body temperature >36°C on admission were strongly associated with the occurrence of at least one episode of hyperthermia within 2 days. Conversely, prophylactic use of acetaminophen was negatively associated with occurrence of early hyperthermia.

An association between post-traumatic leukocytosis and early hyperthermia after TBI has been previously reported by Natale et al. in a pediatric population [20]. Post-traumatic leukocytosis seems to correlate with cerebral damage and outcome after TBI [21]. Hyperthermia and leukocytosis are linked by common explanatory mechanisms including catecholaminergic discharge and inflammatory response. Brain trauma is associated with a dramatic adrenergic discharge inducing several biological and clinical specific consequences such as hypokaliemia, leukocytosis, or hemodynamic response. This sympathetic response is closely related to the severity of initial brain injury [22]; hence, releasing of neutrophils store by catecholamine could account for a major part in post-traumatic leukocytosis [21]. Brain trauma induces an acute local and systemic inflammatory cascade through the activation of immune cells with release of pyrogenic cytokines such as IL-1, IL-6, or TNF [23, 24, 25] following by a compensatory anti-inflammatory response [26]; however, overactivity of sympathetic tone may interact with the inflammatory response following cerebral lesions by enhancing production of anti-inflammatory cytokines such as IL-10 [27]. We may infer that links between early high WBC and hyperthermia are part of a complex mechanism of adrenergic and inflammatory response in which hyperthermia and leukocytosis are only prominent and visible signs.

In our study, normal temperature on arrival in ICU was associated with early hyperthermia. Several studies have shown that hypothermia is associated with poor outcome in multiple trauma patients [28, 29]; however, this concerns deep hypothermia (<33°C). The natural evolution of temperature in a trauma patient is to decrease in a cold environment [30]. Prehospital care tends to attenuate body heat loss by exposing the trauma patient to a warm environment. The relationship found between temperature on admission and early hyperthermia in our study could be due to the fact that major determinant of early hyperthermia (i.e., inflammatory cascade and catecholergic response) could occur very early in the course of post-trauma period.

At the time of the study there were no guidelines for prevention or treatment of hyperthermia after TBI. The rationale for the use of antipyretic agents in severe head trauma is to limit neurological consequences of hyperthermia. Hyperthermia worsens ischemic lesions, enhances brain swelling by increasing vascular permeability [31], and increases CO_2 production with rise of intracranial pressure. Acetaminophen was the drug used in our ICU to treat and/or prevent hyperthermia. Acetaminophen is widely used in ICU for pain relief or fever treatment

and is considered safe providing that the daily dose does not exceed 4 g. We found that acetaminophen infused before patients reach a temperature >38.5°C was a negative independent risk factor of early hyperthermia. Since there was no protocol for its use, no definitive conclusion can be drawn from our results.

On univariate analysis, occurrence of central diabetes insipidus was negatively associated with early hyperthermia. Two assumptions can be formulated to explain this association: firstly, patients with diabetes insipidus receive more fluid to compensate water loss, which can decrease body temperature. Secondly, central diabetes insipidus is due to either intracranial hypertension or direct post-pituitary injury. Thermoregulator centers are located close to this region and their function could be impaired in patients with occurrence of diabetes insipidus; however, when thermoregulator centers are impaired, it is usually hyperthermia which occurs [32]. In our study, initial cranial CT scan did not reveal any direct hypothalamic injury knowing that magnetic resonance imaging is a better tool to detect such lesions.

The incidence of early hyperthermia was higher in patients with intermediate outcome (GOS 3 or 4) than those who had a good recovery (GOS 5). Interpretation of these results are difficult because severity of lesion and hyperthermia can be considered as either causes or consequences because (a) severe cerebral lesion may be the cause of early hyperthermia, or (b) hyperthermia may aggravate cerebral lesion and then be associated with a worse outcome. Occurrence of early hyperthermia was not associated with a worse early outcome and long-term bad outcome (persistent vegetative state and dead). These results may also suggest that less severe lesions are prone to worsen with hyperthermia and more severe lesions are insensitive to the aggravation consequences of hyperthermia due to the fact that primary injury account for a major part of prognosis; however, our study was not designed to answer the question of the impact of early hyperthermia on neurological recovery, and therefore, drawing conclusions based on our results should be done cautiously.

In our study we did not find any association between the type of cerebral lesions found on initial CT scan and early hyperthermia. A recent study on risk factors of hyperthermia in a neurological intensive care has found a strong association between spontaneous subarachnoid hemorrhage and fever during ICU hospitalization [33]. This discrepancy can be explained in two ways: 1. Despite common characteristics, such as time course of vasospasm, traumatic and spontaneous (aneurysmal) subarachnoid hemorrhage have different pathophysiological mechanisms and clinical course [34, 35]. 2. We only studied hyperthermia occurring within 2 days after trauma. Concerning the other initial cerebral lesions, Natale et al. showed an association between two types of lesion (i.e., cerebral edema axonal and diffuse axonal injury) and early hyperthermia [20]. In this study, no logistic regression analysis was performed to confirm the above associations found in univariate analysis. Moreover, we studied adult patients, whereas Natale et al. [20] studied pediatric patients. Consequences of intracerebral lesions might be different depending on age. In a recent study by Thompson et al., two other types of cerebral lesions (i.e., diffuse axonal injury and frontal injury of any type) were associated with neurogenic fever, a possible sequela after severe head injury [36]. In this study, early hyperthermia was not predictive of neurogenic fever confirming that these two entities were distinct with probably different pathophysiological mechanisms.

Hyperthermia is a challenging (and costly) condition in intensive care and is often considered as a surrogate marker of infection; however, a recent study showed that at least half of fever episodes in ICU course's patient were not due to septic conditions [37]. In our study no episode of early hyperthermia was related to bacteriological infection. As a consequence, maintaining normothermia with phamacological or physical interventions should not expose to misdiagnosis of infection in the first 2 days following head trauma.

Our findings may have implications for clinical practice. Until now, studies on intentional mild hypothermia have failed to show an improvement of outcome in traumatic brain injured patients [38]; however, hyperthermia is commonly considered and treated as a secondary major insult in this population. We suggest that head trauma adult patient presenting a body temperature >36°C and/or a WBC>14.5×10^9/l on admission should undergo careful management of temperature. Prophylactic treatment using acetaminophen could be of interest in these patients knowing that this treatment will not affect root causes of hyperthermia.

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