Keep the Brain Cool—Endovascular Cooling in Patients With Severe Traumatic Brain Injury: A Case Series Study

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Received, February 2, 2010.
Accepted, June 13, 2010.

BACKGROUND: As brain temperature is reported to be extensively higher than core body temperature in traumatic brain injury (TBI) patients, posttraumatic hyperthermia is of particular relevance in the injured brain.

OBJECTIVE: To study the influence of prophylactic normothermia on brain temperature and the temperature gradient between brain and core body in patients with severe TBI using an intravascular cooling system and to assess the relationship between brain temperature and intracranial pressure (ICP) under endovascular temperature control.

METHODS: Prospective case series study conducted in the neurologic intensive care unit of a tertiary care university hospital. Seven patients with severe TBI with a Glasgow Coma Scale score of 8 or less were consecutively enrolled. Prophylactic normothermia, defined as a target temperature of 36.5°C, was maintained using an intravascular cooling system. Simultaneous measurements of brain and urinary bladder temperature and ICP were taken over a 72-hour period.

RESULTS: The mean bladder temperature in normothermic patients was 36.3 ± 0.4°C, and the mean brain temperature was determined as 36.4 ± 0.5°C. The mean temperature difference between brain and bladder was 0.1°C. We found a significant direct correlation between brain and bladder temperature (r = 0.95). In 52.4% of all measurements, brain temperature was higher than core body temperature. The mean ICP was 18 ± 8 mm Hg.

CONCLUSION: Intravascular temperature management stabilizes both brain and body core temperature; prophylactic normothermia reduces the otherwise extreme increase of intracerebral temperature in patients with severe TBI. The intravascular cooling management proved to be an efficacious and feasible method to control brain temperature and to avoid hyperthermia in the injured brain. We could not find a statistically significant correlation between brain temperature and ICP.

KEY WORDS: Brain temperature, Intracranial pressure, Intravascular cooling, Prophylactic normothermia, Traumatic brain injury

Neurosurgery 68:867–873, 2011 DOI: 10.1227/NEU.0b013e318208f5fb www.neurosurgery-online.com

In severe traumatic brain injury (TBI), there is ample experimental and clinical evidence for secondary insults potentiating the neuronal damage caused by the initial impact; however, the exact pathophysiological mechanisms of secondary injury are not completely understood.[1-4] Secondary brain injury involves a number of temperature-dependent processes; most are thought to be aggravated by hyperthermia.[2,5-9] Increased brain temperature is known to enhance glutamate-induced excitotoxicity, disruption of the blood-brain barrier, inflammatory processes, and leukocyte migration after acute brain damage.[2,5,6,9-13] Hyperthermia is a common problem in neurocritical care patients, and in severely head-injured patients, elevations of core body temperature occur with a frequency of up to 73%.[14-17] In addition to its detrimental consequences on the injured brain, fever is a predictor of poor outcome

ABBREVIATIONS: cCT, cerebral computed tomography; **GCS,** Glasgow Coma Scale; **ICP,** intracranial pressure; **TBI,** traumatic brain injury

and increased length of intensive care unit (ICU) stay in the TBI population.[15,17-22]

As brain temperature has been reported to be extensively higher than core body temperature in TBI patients, posttraumatic hyperthermia is of particular relevance in the injured brain.[23-27] The temperature difference between brain and core body can reach up to 2°C after acute brain damage.[26] Therefore, increased brain temperature may remain undetected when measuring systemic temperature only, and even minor temperature elevations might have deleterious effects on the injured brain, thus leading to impaired outcome.

Phases of hyperthermia should be avoided to prevent an aggravation of secondary brain injury processes through hyperthermia.[28] Early-stage prophylactic temperature control is essential to avoid a temperature increase in neurocritical care patients at risk of the development of fever.[28,29] Data concerning the induction of therapeutic hypothermia in TBI patients are controversial. There is still no general recommendation for the use of hypothermia in this patient population, in part because of possible adverse effects such as cardiac arrhythmia, uncontrollable shivering, or thromboembolic or infectious complications.[25,28,30,31] Controlled normothermia, defined as maintaining core temperature within a physiological range between 36.0°C and 37.5°C, might be a feasible approach for the prevention of hyperthermia without increasing the number of adverse events associated with hypothermia.[28,32] Intravascular cooling techniques have been shown to be feasible and efficacious in maintaining core temperature within a narrow range.[28,33-37] In a prospective pilot study, we tested the efficacy and safety of long-term normothermia in neurocritical care patients using an intravascular cooling device (CoolGard; Alsius, Irvine, California).[32] Endovascular devices have been shown to be efficient methods for controlling and stabilizing core temperature without increasing the number of adverse events.[33,34,38] However, little is known about the influence of intravascular temperature management on brain temperature. This influence is of utmost interest because the injured brain, as in TBI patients, is the primary target for neuroprotection through normothermia.

The aim of this study was to assess the influence of intravascular temperature management on brain temperature while prophylactically maintaining normothermia. Furthermore, we wanted to investigate temperature gradient changes under intravascular cooling and interactions of brain temperature with intracranial pressure (ICP).

MATERIALS AND METHODS

Setting

This study was performed at the University Hospital Innsbruck, Austria, a 1500-bed tertiary care hospital with approximately 74,000 admissions per year. The hospital provides 6 specialty ICUs (medical, neurologic, neurosurgical, pediatric including neonatal, surgical, and trauma). The neurologic ICU (neuro-ICU) is a 10-bed neurocritical care unit admitting, on a nonelective basis, approximately 450 adults per year. Only patients diagnosed with isolated TBI are transferred to the neuro-ICU, polytraumatized patients are admitted to the surgical or trauma ICU. Severely head-injured patients requiring immediate craniotomy are admitted to the neurosurgical ICU. Patients with severe TBI admitted to our neuro-ICU were consecutively enrolled in this study.

Study Approval

The study was approved by the institutional review board at Innsbruck Medical University (protocol number UN3189). According to Austrian law, informed consent is to be obtained before enrollment in competent patients. However, from those patients who were incompetent at the time of enrollment, the informed consent was obtained after the patient regained competence.

Inclusion/Exclusion Criteria

Seven patients with severe TBI, ie, a Glasgow Coma Scale (GCS) score of 8 or less before intubation, were consecutively enrolled in our study. The diagnosis of severe TBI was established by cerebral computed tomography (cCT) on admission and based on the presence of pathological cCT scan findings such as contusions and traumatic subdural, epidural, or subarachnoid hemorrhage. Inclusion criteria included a diagnosis of severe TBI, GCS score of 8 or less before intubation, age of 18 years or older, as well as the need of a central venous line and ICP probe placement. Patients requiring immediate surgery (ie, expansive acute epidural/subdural hemorrhage) were admitted to the neurosurgical ICU and were not included in our study.

Patient Management

Our ICU management of patients with severe TBI adheres strictly to internationally accepted recommendations.[39] According to the guidelines of the Brain Trauma Foundation, a cerebral perfusion pressure more than 60 mm Hg was considered sufficient for adequate cerebral perfusion. Arterial blood pressure management included the application of norepinephrine or epinephrine and was adjusted according to cerebral perfusion pressure values. Arterial blood pressure was continuously measured using an arterial line with the adapted transducer positioned at the level of foramen of Monro. Following the latest guidelines, ICP monitoring is indicated in TBI patients with a GCS score of 3 to 8 and pathological cCT scan findings to ensure adequate cerebral perfusion. For ICP measurement, an intraparenchymal probe (Neurovent-Temp-P; Raumedic AG, Muenchberg, Germany) was placed in the right hemisphere. In patients with lesions (ie, contusions, traumatic subdural or epidural hemorrhage), at the routinely used insertion site, the probe was placed extralesionally in the contralateral hemisphere. The correct position of the ICP probe was verified on a cCT scan. ICP treatment was initiated at ICP values exceeding 20 mm Hg. Mild hyperventilation ($Paco_2$ 33-35 mm Hg [4.4-4.6 kPa]) and mannitol up to a daily dose of 150 g were used for the management of intracranial hypertension according to Brain Trauma Foundation guidelines.[39] Persistent hyperglycemia exceeding 180 mg/dL was treated with subcutaneous sliding-scale insulin every 3 to 6 hours. Insulin infusion was not routinely used unless subcutaneous treatment was unsuccessful or ketosis developed.

Cooling Procedure and Temperature Measurement

Normothermia was maintained using an intravascular cooling device (CoolGard 3000; Alsius); the technical details were described previously.[34,38] A cooling catheter (Cool Line; Alsius) was inserted in the subclavian vein, placed in the superior vena cava, and remained inserted

for at least 72 hours. A chest radiograph was obtained to verify the correct position of the central venous line. In severely head-injured patients, a central venous catheter is required for the management of fluid status and the administration of intravenous medication/nutrition. Since the Cool Line catheter also provides 3 "working lumina" for infusion, the placement of the cooling catheter is not additionally invasive for the patient. The target temperature was set at 36.5°C to maintain prophylactic normothermia as predefined in the study protocol. The core temperature was measured in the urinary bladder using a Foley catheter (Kendall Curity, Mansfield, Massachusetts) connected to the intravascular cooling device.

A combined pressure/temperature probe was inserted in the brain parenchyma for ICP and brain temperature measurement (Neurovent-Temp-P; Raumedic AG). The pressure/temperature probe was inserted in the right hemisphere according to a standardized neurosurgical procedure.

Data Collection and Statistical Analysis

Data were collected at 5-minute intervals over a period of 72 hours. Brain temperature and ICP values were recorded from a bedside monitor (Datex Ohmeda; Sanitas, Wals, Austria) and retrieved electronically. Bladder temperature recordings were obtained from the CoolGard device. Statistical analyses were performed using SPSS Version 15 software (SPSS, Chicago, Illinois). Results are given as means, averaged from the 5-minute data over the 72-hour sampling period. ICP values were logarithmically transformed to receive a normal distribution. In each patient, repeated measurements of brain and bladder temperature and ICP were taken. The Pearson correlation coefficient was calculated to express the relationship between brain temperature, bladder temperature, and ICP. However, *P* values are not shown because of multiple measurements per patient. To evaluate a possible time lag for ICP reactivity, a cross-correlation time series analysis was performed.

RESULTS

Patients' Characteristics

Seven patients with severe TBI were included in this case series study. The mean age was 55 ± 16 years, 6 patients (86%) were male and 1 was female. The demographic and clinical characteristics of the patients enrolled are listed in Table 1. All patients had severe isolated TBI with a GCS score of 8 or less at enrollment. The cCT scans on admission showed multiple intracranial pathologies in all patients including contusions, traumatic subarachnoid hemorrhage, and traumatic subdural and epidural hemorrhage. Two patients died during the neuro-ICU stay.

Brain and Bladder Temperature

The target temperature was set at 36.5°C. In 3 patients with intractable intracranial hypertension, ie, ICP values continuously exceeding 20 mm Hg, refractory to conventional intensive care management, the target temperature was lowered stepwise and set between 33.5°C and 36.0°C to achieve a decrease in ICP. Changes in core body temperature were induced gradually in steps of 0.5°C.

The body core temperature was represented by urinary bladder temperature. The urine output was within a normal range and accounted for >1 mL/kg/24 h in each patient. Table 2 shows the temperature characteristics for each patient. The mean temperature difference between the brain and bladder was 0.1°C (range, −2.0 to 2.3°C). The Pearson correlation coefficient for the relationship between brain temperature and bladder temperature in all patients was $r = 0.95$ (Figure 1). Brain temperature was higher than core temperature in 52.4% of all temperature measurements. In 19.7%, brain temperature and bladder temperature were equal. In 27.7% of all temperature recordings, bladder temperature exceeded brain temperature. Figure 2 shows exemplary courses of brain and core body temperature in 1 patient. The mean temperature difference between brain temperature and the target temperature of the endovascular cooling device was −0.05°C; for bladder and target temperature, the mean difference was calculated to be 0.1°C.

In patients with a target temperature of 36.5°C, the mean bladder temperature was 36.3 ± 0.4°C, and the average brain temperature was 36.4 ± 0.5°C, with a mean temperature

TABLE 1. Patient Characteristics[a]

Patient	Age at TBI, y	Sex	Radiological Diagnosis of Cerebral CT Scan on Admission	Initial GCS Score Before Intubation	ICP (Mean ± SD)	GOS
1	69	M	Multiple contusions	8	17 ± 5	3
2	65	M	Multiple contusions, tSAH, SDH	7	22 ± 7	3
3	67	M	Multiple contusions, tSAH	7	8 ± 5	3
4	50	F	SDH, multiple contusions	6	26 ± 8	1
5	21	M	EDH, multiple contusions	5	9 ± 4	4
6	58	M	tSAH, SDH, multiple contusions	7	21 ± 3	3
7	54	M	Subcranial fractures, ICH, cerebral venous sinus thrombosis	3	21 ± 2	1

[a]TBI, traumatic brain injury; CT, computed tomography; GCS, Glasgow Coma Scale; ICP intracranial pressure; SD, standard deviation; GOS, Glasgow Outcome Score (at time of neurologic intensive care unit discharge); tSAH, traumatic subarachnoid hemorrhage; SDH, subdural hemorrhage; EDH, epidural hemorrhage; ICH, intracerebral hemorrhage.

TABLE 2. Temperature Characteristics[a]

Patient	Target Temperature, °C	Bladder Temperature, °C (Mean ± SD)	Brain Temperature, °C (Mean ± SD)	Difference Between Brain and Bladder Temperature, °C	Brain Temperature–ICP Correlation Coefficient
1	36.5	36.1 ± 0.4	36.2 ± 0.3	0.1	−0.15
2	36.0-36.5	36.4 ± 0.4	36.0 ± 0.5	−0.4	−0.15
3	33.5-35.0	33.7 ± 0.5	34.0 ± 0.4	0.3	−0.56
4	36.5	36.4 ± 0.2	36.4 ± 0.1	0.0	−0.10
5	36.5	36.5 ± 0.2	36.9 ± 0.3	0.4	−0.10
6	36.5	36.1 ± 0.5	36.0 ± 0.4	−0.1	0.20
7	35.0-35.4	35.0 ± 0.1	35.0 ± 0.2	0.0	−0.29

[a]Temperature characteristics of 7 patients with traumatic brain injury. SD, standard deviation; ICP, intracranial pressure.

difference of 0.1°C. There was no difference between brain and bladder temperature in hypothermic patients.

To assess a possible time lag of brain temperature reactivity to intravascular cooling, a time series analysis was performed. The cross-correlation time series analysis revealed a strong relationship between brain and bladder temperature without a delay of brain temperature adaptation to target temperature.

Brain Temperature and ICP

The mean ICP in all patients was 18 mm Hg (range, −3 to 59 mm Hg). Because of heterogeneity of intracranial pathology and clinical characteristics as well as the induction of therapeutic hypothermia in some patients, the correlation between ICP and brain temperature was calculated for each individual patient (Table 2). The mean estimated correlation between brain temperature and ICP was $r = -0.17$ in all patients. Accordingly, the correlation coefficients for each patient expressing the relationship between brain temperature and ICP did not reveal a significant correlation. One patient in moribund status showed a significant negative correlation between the 2 parameters ($r = -0.56$).

We used a cross-correlation time series analysis to assess a possible time lag interval between temperature and ICP changes. However, we could not find any relationship between brain temperature and ICP because all correlations remained not statistically significant in our model.

DISCUSSION

In this prospective trial in patients with severe TBI, we aimed to assess the interactions between brain and core body temperature and ICP under the influence of an intravascular cooling device.

Brain and Core Body Temperature

Our findings show a mean temperature gradient between brain and bladder of only 0.1°C, brain temperature being higher than core temperature in more than 50% of all measurements. The

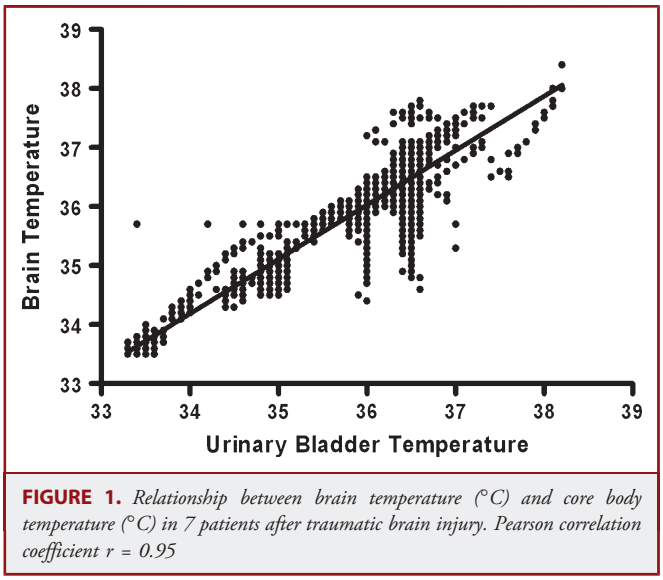

FIGURE 1. *Relationship between brain temperature (°C) and core body temperature (°C) in 7 patients after traumatic brain injury. Pearson correlation coefficient r = 0.95*

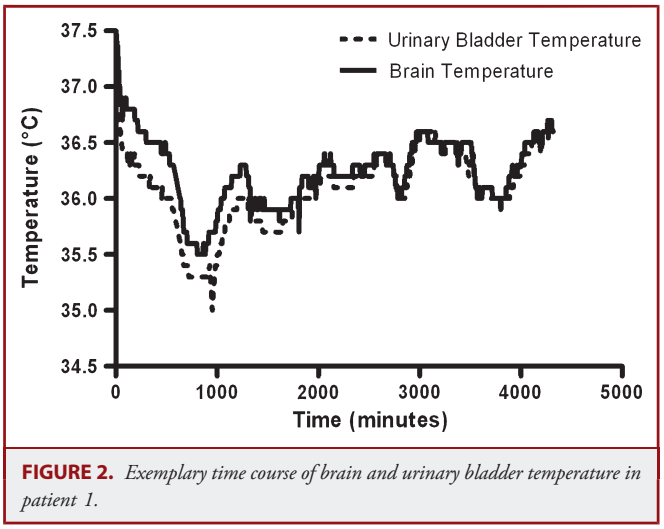

FIGURE 2. *Exemplary time course of brain and urinary bladder temperature in patient 1.*

temperature gradient between core body and brain varies widely and is described to range from −0.4°C to 2.1°C.[23,24,26,40] Recent literature findings about the temperature difference between brain and core body show smaller temperature gradients under conventional fever control in neurocritical care patients with various diagnoses.[25,41,42] There is only 1 retrospective trial describing brain and core temperature under the influence of intravascular temperature control. They found a smaller temperature difference in TBI patients under endovascular temperature control compared with a control group treated with conventional therapeutic temperature management.[35] In previous studies, highest temperature gradients were measured when core temperature exceeded or fell below the normothermic range.[24,26] A tight temperature control protocol might lessen the difference between brain and systemic temperature by adapting intracranial temperature to systemic temperature values. We found a significant correlation between the 2 temperature curves in the 7 TBI patients included in our study, indicating that intravascular cooling influences both brain and core temperature to the same extent. To assess whether changes of core and brain temperature occurred simultaneously, we performed a cross-correlation time series analysis. Results obtained from this statistical analysis demonstrated that the intravascular temperature management affected brain and core temperature simultaneously without a substantial time lag of brain temperature adaptation.

The difference between brain temperature and target temperature was 0.05°C in all patients. This very small deviation indicates that brain temperature can be effectively controlled and maintained by an intravascular cooling system. This is of utmost interest because the idea of neuroprotection through normothermia might only be achieved by influencing brain temperature through cooling the circulating blood. In our patient population, intravascular cooling could effectively prevent fever and strictly maintain normothermia in the injured brain.

Dysfunction in cerebrovascular autoregulation may lead to a decrease in cerebral blood flow. This is of particular interest in severely head-injured patients because cerebral traumatic damage is often associated with impaired cerebral perfusion.[43] Although assuming partly impaired cerebrovascular autoregulation in our patient population, lowering brain temperature through endovascular cooling was efficacious.

Brain Temperature and ICP

We found no significant correlation between ICP and brain temperature. Hypothermic patients did not have lower mean ICP values compared to patients with normothermic core temperature. However, both patients treated with induced hypothermia had sustained intracranial hypertension refractory to conventional intensive care management. The increasing ICP was then additionally counteracted by the induction of hypothermia, which was not successful. In 1 patient with intractable increased ICP, there was even a large negative correlation between brain temperature and ICP. In this case, the injury severity might have been reflected by the negative association between hypothermia and increasing ICP.

The relationship between brain temperature and ICP is discussed controversially.[25,27,41,44,45] Several authors report a reduction of ICP values in patients with induced therapeutic hypothermia/normothermia.[30,35,46] Rossi et al[25] describe an increase in ICP during episodes of brain hyperthermia. However, they could not find an absolute correlation between brain temperature and ICP. In a recently published prospective case-control study, a strong influence of prophylactic normothermia on intracranial hypertension was described.[35] This observation is in contrast to the findings of Huschak et al,[41] who studied 40 unselected neurosurgical patients and measured brain temperature and ICP at 5-minute intervals. They found no correlation and concluded that an increase in brain temperature could not predict the development of increasing ICP. An association between increased brain temperature and intracranial hypertension was found mainly during periods of hyperthermia.[17,25] The core temperature of our study population was strictly controlled according to our study protocol. Therefore, no periods of increased core temperature occurred in our patients. This is a possible explanation for our results concerning brain temperature and ICP lacking a significant positive association. Assuming that ICP follows brain temperature more closely in periods of a temperature decrease from hyper- to normothermia, one might conclude that brain temperature and ICP should not interact during stable normothermia/hypothermia.

To the best of our knowledge, the influence of intravascular temperature management on brain temperature and ICP has not been described thoroughly in the literature. Therefore, we addressed this specific question in detail. This small case series project was designed mainly to test the feasibility of influencing brain temperature by intravascular cooling measures. However, there are several limitations of our study to be considered when interpreting the results. Only a small number of patients were included; therefore, data should be interpreted with caution because of low numbers. Because of the limited number of patients included, the mean age of our study cohort is slightly higher than that usually observed in severely head-injured patients in Austrian ICUs.[47] A potential bias resulting from a single-center study, where the treatment conditions might be unique, is minimized by the prospective design of our study. When designing this study, the target temperature was set at 36.5°C for all patients included. Therefore, no rewarming protocol was included in the study design. Future studies should consider a predefined rewarming protocol because this may have an implication on patient outcome. The strength of this trial is achieved by 1 treatment regimen and equal therapeutic conditions for all patients. Our study lacks a control group treated with temperature control methods other than intravascular cooling; however, this current trial was designed as a case series study with special regard to the feasibility and efficacy of the intravascular cooling system and its effect on brain temperature in particular. Findings on the mortality in patients with severe TBI vary widely from 8% to 32%.[47,48] Despite the small number of patients in our cohort, the mortality was within these limits, which is close to the overall

mortality in Austrian ICUs.[47] The outcome at the time of discharge in our patients resembled that reported by other authors for this age group.[49] In a previous controlled study investigating endovascular temperature control, we did not observe an increased number of infectious or thromboembolic complications.[50] Accordingly, there was no increase in the number of side effects that might be associated with the use of intravascular cooling devices such as pneumonia, pneumothorax, and coagulation dysfunction.[28] This underscores the safety and feasibility of intravascular temperature control for the maintenance of prophylactic normothermia in severely head-injured patients.

The importance of brain temperature measurement is pointed out in several studies, clearly demonstrating that brain temperature acts independently from core temperature and cannot be predicted from systemic temperature values.[23-26,35,41] Because both temperature curves may differ from each other, it is essential to clarify the question whether brain temperature can be controlled by intravascular cooling to the same extent as core temperature. Our results show that brain and bladder temperature are closely associated during intravascular temperature control. The continuous course of brain temperature closely following the target temperature set up in the intravascular cooling device points out the strong influence and stabilizing effect of the intravascular cooling system on the course of intracranial temperature. On the strength of these results, future studies including a larger number of patients should be designed including different temperature-control methods and target temperatures in different temperature ranges. In a larger multicenter trial, the efficacy and feasibility of different cooling devices and their impact on ICP and outcome might be assessed.

CONCLUSION

Maintenance of normothermia in patients with severe TBI was feasible and efficacious over a 72-hour period. Brain temperature could be effectively modulated by endovascular temperature management, strictly preventing fever. The stabilization and control of brain temperature could be achieved by maintenance of core temperature. The temperature gradient usually observed in TBI patients was even decreased under the influence of an intravascular cooling device. Although strictly maintaining brain temperature at a normothermic level, we could not find a significant correlation with ICP. Further studies investigating the relationship between brain temperature, core temperature, and ICP under the influence of (intravascular) temperature control are necessary for a better understanding of brain temperature regulation in severe TBI.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34(2):216-222.
2. Dietrich WD, Alonso O, Halley M, Busto R. Delayed posttraumatic brain hyperthermia worsens outcome after fluid percussion brain injury: a light and electron microscopic study in rats. *Neurosurgery*. 1996;38(3):533-541; discussion 541.
3. Miller JD, Becker DP. Secondary insults to the injured brain. *J R Coll Surg Edinb*. 1982;27(5):292-298.
4. Portella G, Beaumont A, Corwin F, Fatouros P, Marmarou A. Characterizing edema associated with cortical contusion and secondary insult using magnetic resonance spectroscopy. *Acta Neurochir Suppl*. 2000;76:273-275.
5. Castillo J, Davalos A, Noya M. Aggravation of acute ischemic stroke by hyperthermia is related to an excitotoxic mechanism. *Cerebrovasc Dis*. 1999;9(1):22-27.
6. Chatzipanteli K, Alonso OF, Kraydieh S, Dietrich WD. Importance of posttraumatic hypothermia and hyperthermia on the inflammatory response after fluid percussion brain injury: biochemical and immunocytochemical studies. *J Cereb Blood Flow Metab*. 2000;20(3):531-542.
7. Dietrich WD. The importance of brain temperature in cerebral injury. *J Neurotrauma*. 1992;9(Suppl 2):S475-S485.
8. Dietrich WD, Bramlett HM. Hyperthermia and central nervous system injury. *Prog Brain Res*. 2007;162:201-217.
9. Dietrich WD, Busto R, Valdes I, Loor Y. Effects of normothermic versus mild hyperthermic forebrain ischemia in rats. *Stroke*. 1990;21(9):1318-1325.
10. Vitarbo EA, Chatzipanteli K, Kinoshita K, Truettner JS, Alonso OF, Dietrich WD. Tumor necrosis factor alpha expression and protein levels after fluid percussion injury in rats: the effect of injury severity and brain temperature. *Neurosurgery*. 2004;55(2):416-424; discussion 424-425.
11. Whalen MJ, Carlos TM, Clark RS, et al. The relationship between brain temperature and neutrophil accumulation after traumatic brain injury in rats. *Acta Neurochir Suppl*. 1997;70:260-261.
12. Dietrich WD, Chatzipanteli K, Vitarbo E, Wada K, Kinoshita K. The role of inflammatory processes in the pathophysiology and treatment of brain and spinal cord trauma. *Acta Neurochir Suppl*. 2004;89:69-74.
13. Thompson HJ, Hoover RC, Tkacs NC, Saatman KE, McIntosh TK. Development of posttraumatic hyperthermia after traumatic brain injury in rats is associated with increased periventricular inflammation. *J Cereb Blood Flow Metab*. 2005;25(2):163-176.
14. Albrecht RF 2nd, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. *Mayo Clin Proc*. 1998;73(7):629-635.
15. Kilpatrick MM, Lowry DW, Firlik AD, Yonas H, Marion DW. Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery*. 2000;47(4):850-855; discussion 855-856.
16. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit Care Med*. 2008;36(5):1531-1535.
17. Stocchetti N, Protti A, Lattuada M, et al. Impact of pyrexia on neurochemistry and cerebral oxygenation after acute brain injury. *J Neurol Neurosurg Psychiatry*. 2005;76(8):1135-1139.
18. Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke*. 1998;29(12):2455-2460.
19. Geffroy A, Bronchard R, Merckx P, et al. Severe traumatic head injury in adults: which patients are at risk of early hyperthermia? *Intensive Care Med*. 2004;30(5):785-790.
20. Suz P, Vavilala MS, Souter M, Muangman S, Lam AM. Clinical features of fever associated with poor outcome in severe pediatric traumatic brain injury. *J Neurosurg Anesthesiol*. 2006;18(1):5-10.
21. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients. *Crit Care Med*. 2004;32(7):1489-1495.
22. Childs C, Vail A, Leach P, Rainey T, Protheroe R, King A. Brain temperature and outcome after severe traumatic brain injury. *Neurocrit Care*. 2006;5(1):10-14.
23. Childs C, Vail A, Protheroe R, King AT, Dark PM. Differences between brain and rectal temperatures during routine critical care of patients with severe traumatic brain injury. *Anaesthesia*. 2005;60(8):759-765.
24. Henker RA, Brown SD, Marion DW. Comparison of brain temperature with bladder and rectal temperatures in adults with severe head injury. *Neurosurgery*. 1998;42(5):1071-1075.

25. Rossi S, Zanier ER, Mauri I, Columbo A, Stocchetti N. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. *J Neurol Neurosurg Psychiatry*. 2001;71(4):448-454.
26. Rumana CS, Gopinath SP, Uzura M, Valadka AB, Robertson CS. Brain temperature exceeds systemic temperature in head-injured patients. *Crit Care Med*. 1998;26(3):562-567.
27. Mellergard P, Nordstrom CH. Intracerebral temperature in neurosurgical patients. *Neurosurgery*. 1991;28(5):709-713.
28. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. *Crit Care Med*. 2009;37(3):1101-1120.
29. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet*. 2008;371(9628):1955-1969.
30. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. 2001;344(8):556-563.
31. Marion DW, Penrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. *N Engl J Med*. 1997;336(8):540-546.
32. Marion DW. Controlled normothermia in neurologic intensive care. *Crit Care Med*. Feb 2004;32(2 Suppl):S43-S45.
33. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. *Crit Care*. 2007;11(4):R91.
34. Schmutzhard E, Engelhardt K, Beer R, et al. Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: a prospective pilot study. *Crit Care Med*. 2002;30(11):2481-2488.
35. Puccio AM, Fischer MR, Jankowitz BT, Yonas H, Darby JM, Okonkwo DO. Induced normothermia attenuates intracranial hypertension and reduces fever burden after severe traumatic brain injury. *Neurocrit Care*. 2009;11(1):82-87.
36. Sahuquillo J, Perez-Barcena J, Biestro A, et al. Intravascular cooling for rapid induction of moderate hypothermia in severely head-injured patients: results of a multicenter study (IntraCool). *Intensive Care Med*. 2009;35(5):890-898.
37. Hinz J, Rosmus M, Popov A, Moerer O, Frerichs I, Quintel M. Effectiveness of an intravascular cooling method compared with a conventional cooling technique in neurologic patients. *J Neurosurg Anesthesiol*. 2007;19(2):130-135.
38. Broessner G, Beer R, Franz G, et al. Case report: severe heat stroke with multiple organ dysfunction - a novel intravascular treatment approach. *Crit Care*. 2005;9(5):R498-R501.
39. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma*. 2007;24(Suppl 1):S14-S20.
40. Schwab S, Spranger M, Aschoff A, Steiner T, Hacke W. Brain temperature monitoring and modulation in patients with severe MCA infarction. *Neurology*. 1997;48(3):762-767.
41. Huschak G, Hoell T, Wiegel M, et al. Does brain temperature correlate with intracranial pressure? *J Neurosurg Anesthesiol*. 2008;20(2):105-109.
42. Soukup J, Zauner A, Doppenberg EM, et al. The importance of brain temperature in patients after severe head injury: relationship to intracranial pressure, cerebral perfusion pressure, cerebral blood flow, and outcome. *J Neurotrauma*. 2002;19(5):559-571.
43. Bouma GJ, Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. *J Neurotrauma*. 1992;9(Suppl 1):S333-S348.
44. Childs C. Human brain temperature: regulation, measurement and relationship with cerebral trauma: part 1. *Br J Neurosurg*. 2008;22(4):486-496.
45. Spiotta AM, Stiefel MF, Heuer GG, et al. Brain hyperthermia after traumatic brain injury does not reduce brain oxygen. *Neurosurgery*. 2008;62(4):864-872; discussion 872.
46. Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M. Optimal temperature for the management of severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. *Neurosurgery*. 2007;61(1 Suppl):256-265; discussion 265-266.
47. Rosso A, Brazinova A, Janciak I, Wilbacher I, Rusnak M, Mauritz W. Severe traumatic brain injury in Austria II: epidemiology of hospital admissions. *Wien Klin Wochenschr*. 2007;119(1-2):29-34.
48. Broessner G, Helbok R, Lackner P, et al. Survival and long-term functional outcome in 1,155 consecutive neurocritical care patients. *Crit Care Med*. 2007;35(9):2025-2030.
49. Hukkelhoven CW, Steyerberg EW, Rampen AJ, et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J Neurosurg*. 2003;99(4):666-673.
50. Broessner G, Beer R, Lackner P, et al. Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease. Bicenter prospective, randomized trial. *Stroke*. 2009;40(12):E657-E665.

COMMENT

Numerous laboratory studies have shown that therapeutic hypothermia can improve neurologic function after experimental cerebral insults. However, prompt initiation of hypothermia as a means of preventing or mitigating deleterious biochemical sequelae after traumatic brain injury (TBI) has not resulted in better outcomes in large prospective, randomized, controlled trials. Other clinicians have begun to use temperature reduction not as a prophylactic treatment, but rather as a targeted intervention to treat increased intracranial pressure (ICP). However, the exact role of hypothermia and its benefits and disadvantages compared with other ICP-lowering therapies remain unclear.

Advocates of aggressive temperature control have also examined the early postinjury period. Many intensive care unit (ICU)–based studies have demonstrated an association between fever and worse outcomes. However, association does not prove causation. The benefits of aggressive treatment and prevention of fevers in this setting continue to be debated.

Against this background, the authors of this report describe their experience with 7 patients: 4 underwent induced normothermia (not active cooling, as implied by the title), and 3 received deliberate hypothermia to treat increases in ICP. They limited the duration of their study to 72 hours, but it is important to note that many TBI patients exhibit fevers and intracranial hypertension beyond this time period. Because this was an uncontrolled study, the authors are not able to provide data to support direct or indirect comparative statements about the advantages of induced normothermia or hypothermia over conventional temperature control. An additional concern is the lack of a defined rewarming protocol; this aspect of temperature control in TBI patients is receiving increasing attention. Finally, despite the recent resurgence of interest in fever control in the ICU, there is still a need for data that directly compare efficacy and complications of different techniques of temperature control, such as surface cooling versus endovascular methods, with each other and with control groups.

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