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Induced Normothermia Attenuates Intracranial Hypertension and Reduces Fever Burden after Severe Traumatic Brain Injury

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Abstract

Introduction—Hyperthermia following a severe traumatic brain injury (TBI) is common, potentiates secondary injury, and worsens neurological outcome. Conventional fever treatment is often ineffective. An induced normothermia protocol, utilizing intravascular cooling, was used to assess the impact on fever incidence and intracranial pressure (ICP) in patients with severe TBI.

Methods—A comparative cohort study of 21 adult patients with severe TBI (GCS = 8) treated with induced normothermia [36–36.5°C rectal probe setting; intravascular cooling catheter (CoolLine®, Alsius Corporation, Irvine, CA)] were matched by age, gender, and severity of injury to 21 historical control severe TBI patients treated with conventional fever control methods. ICP was measured via an external ventricular catheter and time duration for ICP > 25 mmHg was calculated for the initial 72-h monitoring period. Non-parametric rank tests were performed.

Results—Mean ($\pm$ SD) or median [range] demographics did not differ between groups [total $N=42$ (6 female, 36 male, age 36.4 ± 14.8 years and initial GCS 7 [3–8], median and range]. Fever burden in the first 3 days (time >38°C) in the induced normothermia versus control group was significantly less at 1.6% versus 10.6%, respectively ($P=0.03$). Mean ICP for patients with

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induced normothermia versus control was 12.74 ± 4.0 and 16.37 ± 6.9 mmHg, respectively. Furthermore, percentage of time with ICP > 25 mmHg was significantly less in the induced normothermia group ($P = 0.03$).

Conclusion—Induced normothermia (fever prophylaxis via intravascular cooling catheter) is effective in reducing fever burden and may offer a means to attenuate secondary injury, as evidenced by a reduction in the intracranial hypertension burden.

Keywords

Traumatic brain injury; Fever; Normothermia; Intracranial pressure; Critical care medicine

Introduction

Hyperthermia in the acute postinjury period in traumatic brain injury (TBI) patients is known to potentiate several pathophysiologic processes ongoing in the injured brain. Excitotoxicity, free radical production, blood–brain barrier breakdown, cytoskeletal proteolysis, and inhibition of protein kinases are all the known to be exacerbated by fever [1]. Furthermore, fever occurs with high frequency in this patient population, with up to 68% of patients experiencing at least one fever during their intensive care unit stay [2]. These episodes of hyperthermia may be multiple and of extended duration.

Fever in the TBI population may result from multiple causes and for reasons other than infection and has proven difficult to control. Disruption of the hypothalamic set point, tissue ischemia/infarction, surgery, medications, and blood product transfusions may all induce hyperthermia. Early hyperthermia following TBI is associated with a longer ICU length of stay and worsened neurologic outcomes [3]; [4]; [5]. Frequency and duration of fevers are similar in the stroke population, with early occurrence of fever associated with worse outcomes and larger infarcts [6]; [7]; [8]. Early hyperthermia, within 24 h, has been associated with increasing the relative risk of a poor outcome by 2.2 with every 1°C increase [7].

Of additional concern is the reported difference in brain and body core temperatures after a neurological insult, both during fever and during conventional fever management. Schwab et al. [9] reported brain temperatures being approximately 1.5°C higher than rectal temperatures after middle cerebral artery infarction. Henker et al. [10] reported a 2°C disparity between brain and rectal temperature during periods of temperature extremes (temperature > 38°C and < 36°C). Thus, the brain may be within ‘fever range’ and undetected by rectal temperature readings.

In the late 1990s, at the University of Pittsburgh Medical Center, we adopted an aggressive approach to prevent fever spikes in the NeuroTrauma ICU. In 428 consecutive patients with stroke, subarachnoid hemorrhage, or traumatic brain injury, aggressive treatment was instituted at a rectal temperature of 38.0°C. Anti-pyretics such as acetaminophen, surface cooling, and peritoneal ice lavage were instituted in an effort to reduce fever spikes above 38.5°C. Febrile episodes were reduced from 70% to 46.7% overall; however, in patients whose ICU duration of stay was > 14 days, the fever incidence increased to 92% [11]. As this aggressive fever intervention protocol was insufficient, our institution sought improved methods of fever control. Intravascular cooling was investigated, through our participation in a multi-institutional clinical trial, the Neurocritical Care Fever Trial Reduction Group evaluating the safety and efficacy of an intravascular cooling catheter (CoolLine®, Alsius, Corporation, Irvine, CA). From June 2000 through March 2002, 296 adult patients across 13 centers were enrolled in a randomized, prospective trial. On spiking a fever, patients with a diagnosis of a TBI, subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), or

ischemic infarct were randomized to receive either conventional fever management (antipyretics and cooling blanket) or placement of an intravascular cooling catheter. Despite no differences between experimental groups in age, gender, Glasgow Coma Scale (GCS) score, or body mass index, patients treated with intravascular cooling catheters had a 64% reduction in fever burden over the ensuing 72 h [12]. The intravascular cooling catheter did not lead to increased infection rates, or antibiotic and sedation use, and the risk to the patient was not increased beyond that of a standard central line placement.

On the strength of these results, in this study, we initiated a protocol at our site wherein intravascular cooling catheters were placed in patients with severe TBI (GCS ≤ 8) on admission to the NeuroTrauma ICU to evaluate the utility of induced normothermia, i.e., prophylactic maintenance of rectal temperature between 36 and 36.5°C. We present our pilot results from this protocol evaluating the impact of induced normothermia on fever incidence, fever burden, and ICP after severe TBI in a case-control study design.

Materials and Methods

All the patients were treated and data collected in accordance with an Institutional Review Board approved protocol under the guise of the University of Pittsburgh Brain Trauma Research Center.

A comparative matched-cohort study was performed. Consecutively admitted adult patients with severe TBI (GCS ≤ 8) were treated with induced normothermia using a triple-lumen intravascular cooling catheter (CoolLine®, Alsius, Corporation, Irvine, CA). Catheters were placed in patients on ICU admission using Seldinger technique into the superior vena cava via the subclavian vein and remained in place for a minimum of 3 days. Target temperature was set at 36.5°C, and continuously monitored via rectal temperature probe. The intensive care management of TBI was performed in adherence to our standing clinical orders modeled after the Guidelines for the Management of Severe Traumatic Brain Injury [13] which included the placement of an intraventricular catheter for ICP monitoring and cerebrospinal fluid drainage, and brain tissue oxygen, and temperature probes (Licox®, Integra LifeSciences Corporation, Plainsboro, NJ) for monitoring. ICP management was consistent across both cohorts, and patients were excluded from the analysis if they experienced refractory intracranial hypertension resulting in a decompressive craniectomy procedure.

Patients were matched by age (± 2 years), gender, and severity of injury (± 2 GCS points) to historical severe TBI patients in whom hyperthermia (rectal temperature $> 38.0^\circ\text{C}$) was aggressively managed with conventional fever treatment. All the physiological data were continuously monitored and downloaded from the bedside monitor (Hewlett Packard/Philips Medical Systems, Bothell, WA) to a patient data server in minute increments. Percent of time (in minutes) for ICP measurements > 25 mmHg was calculated for the initial 5 day-monitoring period. A subset analysis was undertaken to evaluate time spent with rectal temperature $\geq 38^\circ\text{C}$, with only patients with complete temperature data included in the analysis. Wilcoxon signed rank tests were performed for each set of parameters.

In order to assure that we were not masking a bacterial origin of fever, our trigger for bacterial cultures occurred with either a rectal temperature of 38.0°C or if the intravascular cooling device indicated the machine was working at maximum effort to maintain target temperature.

Results

Twenty-one severe TBI patients were treated with induced normothermia as described above. These patients were matched to historical controls that were treated under the same ICU standing protocol for severe TBI, with conventional fever treatment begun at a rectal temperature of 38.0°C. Median ($\pm$ SD) age, gender, race, and initial GCS were not significantly different between groups (Table 1). Mean rectal temperature, averaged from minute data over the sampling period, was 36.6 ± 0.9 and 37.4 ± 1.4 °C for the induced normothermia and control groups, respectively (Fig. 1). Mean brain temperature, as measured by the invasive brain temperature probe, was 36.5 ± 0.6 and 37.0 ± 0.9 °C for the induced normothermia and control groups, respectively (Fig. 1). Time course for temperature management over the 72-h monitoring period is shown in Fig. 2. In the subset analysis of rectal temperature measurements (30 subjects with complete, minute temperature data, 15 matched in each cohort), fever burden (the percentage of time with rectal temperature ≥ 38 °C) during the first 72 h after NTICU admission in the induced normothermia versus control group was significantly less at 1.6% versus 10.6% respectively ($P = 0.03$) (Fig. 3).

Mean ICP for patients with induced normothermia versus control group, averaged from the minute data over the sampling period was 12.74 ± 4.0 and 16.37 ± 6.9 mmHg, respectively, (Fig. 4). More importantly, intracranial hypertension burden, the percentage of time with ICP > 25 mmHg was significantly less in the induced normothermia group ($2.3 \pm 2.8\%$) compared to the control group ($9.4 \pm 11.4\%$) ($P = 0.03$), and with tighter control (smaller range) (Fig. 5).

Rates of infection and complications were not significantly different between groups.

Discussion

This study demonstrates that fever prophylaxis via induced normothermia significantly attenuates intracranial hypertension and reduces fever burden in patients with severe traumatic brain injury. These results suggest that secondary insults to the brain may be reduced through early placement of intravascular cooling catheters to prevent and/or limit hyperthermia during the acute post-injury phase. Although the study design is not a randomized controlled trial, the strength of this case-control study design is achieved by the stringent matching of age, gender, race, and severity of initial injury presentation of historical controls to those of the test-induced normothermia group, all of which were clinically managed in a single neurotrauma ICU in accordance with a strict protocol as per the Guidelines for the Management of Severe Traumatic Brain Injury [13].

Our results utilizing induced normothermia are consistent with multiple previous hypothermia clinical trials reporting a treatment effect of lowering ICP in the adult [14-22] and the pediatric [23, 24] TBI population. Lack of consistent results regarding neurologic outcome has deterred the medical community from endorsing the usage of hypothermia as a standard of care in severe TBI management [15, 19, 25-27]; [21, 22, 28, 29]. Subset analysis of the National Acute Brain Injury Study: Hypothermia (NABIS:H trial) data [30] examining intercenter variance indicated that rapid reduction in temperature may be critical to achieving impact on neurological outcome. While we await results of a larger study currently in progress at our institution evaluating the impact of induced normothermia on neurological outcome, it may prove that aggressive maintenance of normothermia (and, thus, avoidance of hyperthermia) produces similar results as rapid achievement of hypothermia treatment in a severe TBI population.

Not only may induced normothermia prove equivalent to hypothermia in therapeutic efficacy, the induction and maintenance of normothermia is less technologically demanding than hypothermia, requiring less nursing time than hypothermia treatment and subsequent slow, rewarming of the patient.

In addition, our center's experience with intravascular cooling catheters has highlighted multiple theoretical and practical advantages over conventional fever management with antipyretics and surface cooling, especially in the severe TBI population. Surface cooling, with cooling blankets or skin pads, has the negative effects of triggering both dermal vasoconstriction (reducing heat loss through the skin) and shivering (increasing the metabolic rate in already compromised ICU patients). In the subpopulation of neurologically injured patients, shivering may have an additional negative effect of increasing the ICP. Intravascular cooling systems allow for more precise temperature control with fewer of the peaks and valleys of temperature curves seen with traditional surface cooling [31]. Furthermore, many patients with severe TBI may require treatment for systemic and orthopedic injuries, limiting the body surface area available for surface cooling. This limitation is not encountered with intravascular cooling.

Intravascular cooling is not without its disadvantages. This temperature management method requires the need for an invasive procedure for catheter placement performed by a physician. However, in the severe TBI population, central line access is necessitated to monitor and manage fluid status and for the rapid administration of blood products and intravenous medications. Use of the intravascular cooling catheter employed in the current study has been shown to be equivalent in risk to that of a standard central line [12]. In addition, intravascular cooling catheters pose the theoretical risk of masking a temperature rise from an infectious source with a resultant delay in treatment, although this risk was not substantiated in the prospective randomized induced trial described above [12].

Our current practice is to place intravascular cooling catheters in all the patients admitted with a severe traumatic brain injury diagnosis unless a contraindication to placement of a central line exists. This study was not powered to detect differences in outcome; however, an ongoing study is evaluating the impact of induced normothermia on neurological outcome in an expanded cohort of patients.

Conclusion

Induced normothermia (fever prophylaxis with intravascular cooling catheter) is effective in reducing fever burden and may offer a means to attenuate secondary injury, as evidenced by a reduction in intracranial hypertension and fever burden in an adult population with severe TBI.

Acknowledgments

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Fig. 1.

Induced normothermia versus control cohorts: rectal and brain temperatures. Box plot graphic depiction of rectal and brain temperatures averaged over the 72-h monitoring period. Mean rectal temperature was $36.6 \pm 0.9^{\circ}\text{C}$ and $37.4 \pm 1.4^{\circ}\text{C}$ for the induced normothermia and control group, respectively. Mean brain temperature, as measured by the invasive brain temperature probe, was $36.5 \pm 0.6^{\circ}\text{C}$ and $37.0 \pm 0.9^{\circ}\text{C}$ for the induced normothermia and control group, respectively. The color black represents rectal temperature, and the color gray represents brain temperature

Fig. 2.

Time course temperature management: induced normothermia versus control cohorts.

Hourly mean rectal and brain temperature comparison between induced normothermia and control cohort groups. The color black represents rectal temperature, the color gray represents brain temperature. The solid line represents the control, standard fever treatment group, and the dotted line represents the induced normothermia group

Fig. 3.

Percentage of time within fever range: induced normothermia versus control cohorts. Box plot graphic depiction of total percentage of time rectal temperature was recorded greater than 38°C over the 72-h monitoring period with the induced normothermia versus control group having significantly less (1.6% versus 10.6%, respectively) time within the fever range. Wilcoxon Signed Rank test resulted in a significant difference between the two groups ($P=0.034$)

Fig. 4. Intracranial pressure (ICP): induced normothermia versus control cohorts. Box plot graphic depiction of ICP averaged over the 72-h monitoring period. Mean ICP was 12.74 ± 4.0 and 16.37 ± 6.9 mmHg for the induced normothermia cohort and control cohort groups, respectively. Wilcoxon Signed Rank test resulted in a significant difference between the two groups ($P = 0.027$)

Fig. 5.

Intracranial hypertension burden (percentage of time ICP > 25 mm Hg): induced normothermia versus control cohorts. Box plot graphic depiction percentage of time ICP > 25 mmHg over the 72-h monitoring period. ICP was >25 mmHg $2.3 \pm 2.8\%$ and $9.4 \pm 11.4\%$ for the induced normothermia cohort versus control cohort groups, respectively. Wilcoxon Signed Rank test resulted in a significant difference between the two groups ($P=0.03$)

Table 1

Study population characteristics

	Induced normothermia ^a	Control ^b	Total
<i>N</i>	<i>n</i> = 21	<i>n</i> = 21	<i>N</i> = 42
Gender, male	85.7%	85.7%	85.7%
Age mean $\pm$ SD	36.6 $\pm$ 15.2	36.2 $\pm$ 14.9	36.4 $\pm$ 14.8
Race, caucasian	100%	90.5%	95%
GCS on admission median [range]	7 [3–8]	7 [3–8]	7 [3–8]
GCS 3–5	29%	33%	31%
GCS 6–8	71%	67%	69%

SD standard deviation, GCS glasgow coma scale

^a Invasive cooling catheter, rectal temp set at 36.5°C

^b control, standard fever treatment begun at 38°C