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Mild induced hypothermia for patients with severe traumatic brain injury after decompressive craniectomy

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ABSTRACT

Purpose: To evaluate the efficacy and safety of mild induced hypothermia for intracranial hypertension in patients with traumatic brain injury after decompressive craniectomy.
Methods: A total of 60 adults with intracranial pressure (ICP) of more than 20 mm Hg after decompressive craniectomy were randomly assigned to standard care (control group) or hypothermia (32°C-35°C) plus standard care. Then, ICP, cerebral perfusion pressure, Glasgow Outcome Scale score, and complications were assessed.
Results: There was a significant difference in ICP and cerebral perfusion pressure between the 2 groups. Favorable outcomes occurred in 12 (40.0%) and 7 (36.5%) patients in the hypothermia and control groups, respectively ($P = .267$). Kaplan-Meier curves revealed a marked difference in survival between the hypothermia and control groups ($P = .032$). There were significant differences in pulmonary infection and electrolyte disorders between the hypothermia and control groups ($P = .038$ and .033, respectively).
Conclusion: Mild induced hypothermia can reduce intracranial hypertension after decompressive craniectomy, decreasing patient mortality. Hypothermia should be considered one of the main treatments for intracranial hypertension after decompressive craniectomy in patients with traumatic brain injury.

1. Introduction

About 1 million people die annually, whereas 10 million are seriously injured in accidents, which constitute the primary cause of traumatic brain injury (TBI). Low-income and industrial countries have the highest mortality and disability rates, respectively, in patients with severe closed TBIs [1-3]. To improve patient outcomes, several options are available, including decompressive craniectomy, hyperosmolar therapy, prophylactic hypothermia, cerebrospinal fluid drainage, sedation and analgesia, muscle relaxants, pentobarbital treatment, and hyperventilation [4]. Decompressive craniectomy provides satisfactory intracranial pressure (ICP) control and a favorable outcome in neurocritical care patients with refractory intracranial hypertension, and has been used for the treatment of intracranial hypertension associated with TBI [5,6]. However, with secondary causes of injury, a subset of patients still have intracranial hypertension after decompressive craniectomy, which is more difficult to treat. Whether hypothermia can also be used to reduce intracranial hypertension in such patients remains unknown. The aim of this study was to evaluate the efficacy and safety of mild induced hypothermia for intracranial hypertension in patients with severe TBI after decompressive craniectomy.

2. Methods

2.1. Study design

This was a randomized, controlled, double blind trial; informed consent was obtained from patients' families. Each subject was assigned to 1 of 2 treatment groups in the neurologic intensive care unit of our brain center, using a randomization table. Allocation and randomization were concealed to blind study investigators for patient grouping, and the allocation sequence was protected until assignment. The attending physicians were not involved in data collection, and the nursing staff and surgical team were not aware of the patient grouping. Therefore, biased grouping was avoided. This study was approved by the medical ethics committee of Nanfang Hospital, Southern Medical University.

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2.2. Patients

From January 2012 to January 2016, 60 patients admitted to the intensive care unit in our department after TBI showed elevated ICP (>20 mm Hg) after decompressive craniectomy within 24 hours. All patients met the following criteria: (1) primary, closed TBI; (2) ICP >20 mm Hg after decompressive craniectomy, with no overt reversible cause; (3) >16 years of age; (4) men or nonpregnant women; (5) clear history of head injury; (6) GCS 3-8 on admission or after resuscitation; (7) availability of a cooling device or technique for more than 72 hours; and (8) brain injury confirmed by sequential computed tomography scanning within 6 hours of trauma. Patients were excluded with one or more of the following criteria: (1) pregnancy; (2) younger than 16 years or older than 70 years; (3) multiple injuries, hemorrhagic shock, or no bilateral pupil fixed on initial examination; (4) no spontaneous breathing; (5) bilateral hemi-craniectomy or bifrontal craniectomy selection; (6) external ventricular drainage for ICP control or monitoring; and (7) history of serious heart, lung, brain and other diseases.

The participants were randomly assigned to standard (control group, ≥36°C) and hypothermia plus standard (hypothermia group, 32°C-35°C) treatment groups. Randomization was performed by the method of minimization for allocation to balance assignments according to gender, age, Glasgow Coma Scale (GCS) motor score, causes of injury, and pupillary response. The control group comprised 30 patients with 28 men and 2 women; meanwhile, the hypothermia group was composed of 30 patients, including 23 men and 7 women. General patient characteristics were similar between the 2 groups. All patients were administered routine treatments in the intensive care unit of the neurosurgery department according to "Guidelines for the management of severe traumatic brain injury," published by the *American Brain Injury Association* in 2007.

Unilateral hemi-craniectomy was performed within 6 hours of injury. For ICP monitoring, Codman Micro Sensor (Codman & Shurtleff Inc, Raynham, Mass) was used. Postoperative ICP was recorded every hour, with intracranial hypertension managed according to the Brain Trauma Foundation guidelines.

Hypothermia was induced with a water-circulating cooling blanket (Blanketro II 222R, Cincinnati, USA). Rewarming was considered after 48 hours at a rate of 0.25°C per hour, provided that ICP was 20 mm Hg or less for more than 24 hours.

In the control group, patient body temperature was maintained in the normal range, between 36°C and 37°C. Cooling in patients with body temperature lower than 38.5°C was carried out with an ice bag; antipyretic analgesics were used with body temperature higher than 38.5°C. Active anti-infective treatment was administered when infection was suspected.

2.3. Data collection

The following data were recorded: baseline demographic characteristics; Glasgow Outcome Scale (GOS) score at 6 months after injury; ICP at randomization; temperature at randomization; mean arterial pressure, cerebral perfusion pressure (CPP), and temperature measured hourly on days 1 through 5; and complications such as intracranial infection, pulmonary infection, electrolyte imbalance, hyperglycemia, stress ulcer, and renal malfunction. Electrolyte disorders are defined as follows: hypernatremia (serum sodium >145 mmol/L), hyperkalemia (serum potassium >5 mmol/L), hyponatremia (serum sodium <135 mmol/L), and hypokalemia (serum potassium <3. 5 mmol/L). Unfavorable and favorable outcomes were defined at 6 months after injury by GOS scores of 1-3 and 4-5, respectively.

2.4. Statistical analysis

Data were analyzed with SPSS version 20.0. (IBM Corp, Armonk, NY). Descriptive statistics were presented as frequency (percentage) or mean ± SD. Categorical variables were compared by the χ^2 test or Fisher exact test. Kaplan-Meier survival curves were generated and compared by the log-rank test. $P < .05$ was considered statistically significant.

3. Results

The 60 patients who underwent primary decompressive craniectomy for TBI included 51 men and 9 women. Mean age was 41.07 ± 14.56 years (range, 18-63 years). Head injuries resulted from traffic accidents (n = 47), falls (n = 10), and other causes (n = 3). Neurologic assessment before decompressive craniectomy showed a mean GCS of 4.98 ± 1.57. Pupillary examination identified 31 patients with one or no nonreacting pupil, and 29 with both nonreacting pupils. Computed tomographic scan revealed 39 cases of intracranial hemorrhage, 16 of diffuse brain injury, and 5 of contusion/other anomalies. The main patient characteristics are shown in Table 1.

3.1. ICP and CPP

A repeated-measures analysis was performed to compare the 2 groups from days 1 to 7 after randomization in ICP and CPP (Fig. 1). There were significant differences in ICP and CPP between the 2 groups (hypothermia vs control; $P < .001$).

3.2. Outcome

The surviving patients were followed up at the outpatient department for a period ranging from 6 to 48 months. Six months after brain injury, no significant difference in overall neurologic outcome (GOS score) between the 2 groups was found (Table 2). Favorable outcomes occurred in 12 (40.0%) and 7 (36.5%) patients of the hypothermia and control groups, respectively ($P = .267$). Mortality rates were 10.0% in the hypothermia group and 33.3% in control patients ($P = .057$). Fig. 2 depicts Kaplan-Meier survival curves for both patient groups with or without hypothermia, revealing a marked difference ($P = .032$).

3.3. Complications

The main complications observed in patients with TBI are summarized in Table 3. There were significant differences in pulmonary infection and electrolyte disorders between the hypothermia and control groups ($P = .038$ and .033, respectively). Among the 30 patients treated with hypothermia, hypernatremia occurred in 11 and hyperkalemia in 3 patients. In the control group, hypernatremia occurred in 4 and hyperkalemia in 1 patients. Hypernatremia was

Table 1
Clinical characteristics of study patients with severe TBI

Variable	Hypothermia (n = 30)	Control (n = 30)	*P*
Age (y)	42.47 ± 13.93	39.67 ± 15.26	.461
GCS score			
GCS of 5-8, no. (%)	13 (43.4)	12 (40.0)	1.000
GCS of 3-4, no. (%)	17 (56.7)	18 (60.0)	
Pupillary response			
Both reacting, no. (%)	13 (43.3)	16 (53.3)	.327
Bilaterally fixed/dilated, no. (%)	1 (3.3)	3 (10.0)	
Unilaterally fixed/dilated, no. (%)	16 (53.3)	11 (36.7)	
Mechanism of injury			
Traffic accident, no. (%)	24 (80.0)	23 (76.7)	.794
Fall accident, no. (%)	4 (13.3)	6 (20.0)	
Others, no. (%)	2 (6.7)	1 (3.3)	
Major findings on computed tomographic scans			
Intracranial hematoma, no. (%)	18 (60.0)	21 (70.0)	.711
Diffuse brain injury, no. (%)	9 (30.0)	7 (23.3)	
Contusions and others, no. (%)	3 (10.0)	2 (6.7)	