Massive cerebral hemispheric infarction (MCHI), which is primarily caused by an occlusion of either the internal carotid or the proximal middle cerebral artery (MCA), is the most malignant type of supratentorial ischemic stroke. This event can cause fatal intracranial hypertension because of the subsequent space-occupying cerebral edema, leading to herniation. Mortality can be as high as 53% to 78%, even after receiving the strongest medical treatments available.1–5 Consequently, decompressive craniectomy (DC) was proposed to directly release the intracranial pressure (ICP). Several randomized controlled trials (RCTs) have demonstrated that DC can reduce the ICP and reduce mortality to 17% to 36%.2–7

Although DC is a lifesaving treatment, not all patients with MCHI can receive the surgery quickly enough. Additionally, patients who routinely take antiplatelet or anticoagulant drugs are at an increased risk of developing massive bleeding during or after DC, which limits its application. Moreover, the neurological outcomes of patients who accept DC are not always satisfactory.2–4

Because of the limitations of medical and surgical treatment, therapeutic hypothermia has been proposed as an alternative. Preclinical trials have demonstrated that therapeutic hypothermia causes both neuroprotection and ICP reduction.8 Additionally, a systematic review and meta-analysis of RCTs in patients with cardiopulmonary arrest have also shown that hypothermia treatment reduces mortality (risk ratios [RR]=1.35; 95% confidence interval [CI], 1.10–1.65) and improves neurological outcomes (RR=1.55; 95% CI, 1.22–1.96) compared with normothermia treatment.9 Consequently, therapeutic hypothermia may be an option for patients with MCHI.

**Background and Purpose**—We conducted this randomized controlled trial to investigate the effects of therapeutic hypothermia on mortality and neurological outcome in patients with massive cerebral hemispheric infarction.

**Methods**—Patients within 48 hours of symptom onset were randomized to either a hypothermia group or a control group. Patients in the hypothermia group were given standard medical treatment plus endovascular hypothermia with a target temperature of 33 or 34°C. Hypothermia was maintained for a minimum of 24 hours. Patients in the control group were given standard medical treatment only with a target temperature of normothermia. The primary end points were mortality and the modified Rankin Scale score at 6 months.

**Results**—There were 16 patients in the hypothermia group and 17 patients in the control group. At 6 months, 8 patients had died in the hypothermia group versus 7 patients in the control group (P=0.732). The main cause of death was fatal herniation caused by a pronounced rise in intracranial pressure. Seven patients (43.8%) had a modified Rankin Scale of 1 to 3 in the hypothermia group versus 4 patients (23.5%) in the control group (P=0.282). Additionally, of the survivors, patients in the hypothermia group achieved better neurological outcomes compared with those in the control group (7/8, 87.5% versus 4/10, 40.0%; P=0.066; odds ratio=10.5; 95% confidence interval, 0.9–121.4).

**Conclusions**—Mild hypothermia seems to not reduce mortality in patients with massive cerebral hemispheric infarction but may improve the neurological outcome in survivors. An adequately powered multicenter randomized controlled trial seems warranted.

**Clinical Trial Registration**—URL: http://www.chictr.org.cn. Unique identifier: ChiCTR-TCS-12002680. (Stroke. 2016;47:457-463. DOI: 10.1161/STROKEAHA.115.009789.)

**Key Words:** hypothermia ◼ infarction ◼ ischemia ◼ neuroprotection ◼ stroke
The feasibility and safety of therapeutic hypothermia in patients with MCHI have been confirmed in prior studies. However, its effects on mortality and neurological outcome remain unclear, especially in patients who cannot receive DC. Therefore, we conducted a RCT to address this issue. Our aim was to investigate the effects of therapeutic hypothermia on mortality and neurological outcome in patients with MCHI.

Methods

General Design

The trial was a prospective, single-center RCT approved by the Ethics Committee of Xuan Wu Hospital, Capital Medical University, Beijing. Informed consent was obtained from all patients or their designated surrogates. The trial was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-TCS-12002680).

Patient Population

All patients with acute ischemic stroke from December 2010 to August 2013 were screened for eligibility. Patients were eligible if they met all of the following criteria: (1) aged 18 to 80 years, (2) acute unilateral ischemic stroke <48 hours ago, (3) infarction involving at least two thirds of the MCA territory on cranial computed tomography or magnetic resonance imaging, (4) a National Institute of Health Stroke Scale score ≥15 if the nondominant hemisphere was affected or ≥20 if the dominant hemisphere was affected, (5) a reduced level of consciousness indicated by a National Institute of Health Stroke Scale item 1a score of consciousness indicated by a National Institute of Health Stroke Scale score ≥1, and (6) unable to undergo DC because of the premorbid use of antiplatelet or anticoagulant drugs or because the patient declined the procedure.

Patients were excluded if they met any of the following criteria: (1) premorbid modified Rankin Scale (mRS) score >2; (2) secondary hemorrhage involving more than one third of the infarction territory with a space-occupying effect; (3) a Glasgow Coma Scale without a verbal response item score of ≤6; (4) rapidly improving symptoms; (5) both pupils fixed and dilated; (6) simultaneous other brain lesion, including tumors and contralateral or infratentorial infarctions; (7) platelet count <75 000/mm3; (8) severe coagulopathy or cardiac, liver, or kidney disease; (9) vasospastic disease, hematological disease with increased risk of thrombosis, or paralyse; (10) sepsis; (11) premorbid treatment with a monoamine oxidase inhibitor or an allergy to pethidine; (12) inferior vena cava fistula or a filter in its place; (13) pregnancy; or (14) a life expectancy <6 months.

Randomization

Enrolled patients were randomly assigned to a hypothermia group or control group according to a previously generated randomization scheme. The random number was folded and sealed in an envelope before the initiation of the study. The allocation ratio was 1:1. The odd numbers were assigned to the hypothermia group, and the even numbers were assigned to the control group. These envelopes were opened only by an investigator who was not involved in patient screening, treatment, data collection, or analysis.

Standard Medical Treatment

All patients included in the study received standard medical treatment. Patients were admitted into the neurointensive care unit immediately after enrollment. The standard medical treatment was initiated as soon as possible. The temperature of the patients in the control group was sustained between 36.5 and 37.5°C to maintain normothermia. The standard medical treatment is shown in Table I in the online-only Data Supplement.

Endovascular Hypothermia Treatment

Patients randomized to the hypothermia group received additional endovascular hypothermia treatment. An 8.5F 35-cm catheter central line (ICY, Alsius Corporation, Irvine, CA) was inserted into the femoral vein and advanced to the inferior vena cava. This line included a lumen ending in 3 balloons, which were perfused with a sterile normal saline solution via a closed-loop tubing system. It was connected to a mobile temperature-management device (CoolGard, Alsius Corporation). A Foley temperature catheter was used to maintain the bladder temperature (Monatherm, Mallinckrodt Medical, St. Louis, MO) and was also connected to the temperature-management device. This device adjusted the saline temperature according to the patient’s temperature and the target temperature. Hypothermia was initiated as soon as possible after admission. A maximal cooling rate was applied with a target bladder temperature of 33 or 34°C. The hypothermia was maintained for a minimum of 24 hours and could be prolonged to 72 hours depending on the physician’s decision. The rewarming process was controlled and slow. The target temperature was raised 0.5°C every 12 hours, and the rewarming rate was 0.1°C/h. In the event of deterioration because of rebound ICP, the rewarming was interrupted until the patient regained a stable status. The time course of rewarming varied between 24 and 72 hours. Shivering was suppressed with cotton-padded gloves, socks, and a quilt to keep the patient warm. The patients were also given oral buspirone (60 mg), intravenous (IV) pethidine (1 mg/kg loading dose followed by an IV infusion of 25–35 mg/h), IV midazolam (0.1 mg/kg loading dose followed by an IV infusion of 2–3 mg/h), and an IV muscle relaxant (atracurium, 0.4 mg/kg loading dose followed by an IV infusion of 0.3 mg/kg/h; vecuronium, 0.03–0.05 mg/kg loading dose followed by an IV infusion of 0.02-0.03 mg/kg/h). The IV infusion drugs started from the minimum doses and were adjusted according to the severity of shivering.

ICP was invasively and continuously monitored with a transcerebral pressure–temperature monitoring catheter (Camino, Integra NeuroScience, Plainsboro, NJ); this procedure was only performed in patients who agreed to receive ICP monitoring.

Data Collection

The patient characteristics included age; gender; underlying diseases (such as hypertension, coronary heart disease, atrial fibrillation, hyperlipidemia, valvular dysfunction, diabetes mellitus, and stroke); radiological data (affected hemisphere and infarcted area); stroke severity at enrollment (Glasgow Coma Scale score, National Institute of Health Stroke Scale score and Acute Physiology and Chronic Health Evaluation II score); transtentorial herniation; and the administration of thrombolysis, antiplatelet, anticoagulant, or defibrinogen treatment.

The bladder temperature was collected every minute and then downloaded from the temperature-management device using the dedicated software Temp Trend CSV (Alsius Corporation) in the hypothermia group. The axillary temperature was collected every 30 minutes in the control group. Physiological data also included respiratory rate, heart rate, heart rhythm, blood pressure, pulse oxygen saturation, ICP, pupil status, and shivering (score 0, no shivering; score 1, shivering localized to the face or masticatory muscles; score 2, shivering localized to the thorax or extremities; and score 3, shivering involves gross movement of the trunk and extremities). These data were collected every 30 minutes in the hypothermia group and every 4 hours in the control group.

The laboratory data included the erythrocyte count, leukocyte count, platelet count, hemoglobin, international normalized ratio, thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen, total bilirubin, alanine aminotransferase, aspartate aminotransferase, creatine kinase, creatinine, urea, glucose, total protein, albumin, sodium, potassium, magnesium, calcium, phosphorus, amylase, lipase, lactate, and arterial blood gas. The tests were run every 12 hours in the hypothermia group and every other day in the control group. Chest radiography, electrocardiogram, and deep venous ultrasound were also performed every 3 days in both groups.

Complications included hemorrhagic transformation, recurrent infarction, tachycardia (>100 beats/min), bradycardia (<60 beats/
min), arrhythmia, heart failure, hypotension (mean blood pressure <80 mm Hg), pulmonary embolism, pneumonia, gastrointestinal bleeding, gastric retention (gastric residual >200 mL), acute pancreatitis, hiccup, acute liver injury, acute kidney injury, electrolyte disorder, stress hyperglycemia (>11.1 mmol/L), hypoproteinemia (<60 g/L), hypoalbuminemia (<35 g/L), coagulation dysfunction, lower extremity deep vein thrombosis, retroperitoneal or groin hematoma, catheter-related infection, urinary infection, and sepsis.

Outcome Measurement
The primary outcomes were all-cause mortality and the mRS score at 6 months after symptom onset. An investigator who was not involved in the randomization, treatment, or analysis performed the follow-up by calling the patients or surrogates at 6 months. mRS 0 to 3 was regarded as a good neurological outcome. Secondary outcomes included bladder temperature, ICP, and complications.

Statistical Analysis
Based on data from a previous open study of hypothermia in stroke patients, the sample size was calculated to be 168 assuming that the difference of the mean mRS of the 2 groups was 1 and that the standard deviation was 2 (\(\alpha=0.05; \beta=0.10\)).

SPSS 17.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous covariates were presented as the mean± standard deviation or the median (range), as appropriate. Categorical covariates were presented as counts and proportions. Comparisons between 2 groups were performed via a two-tailed \(t\) test or the Mann–Whitney \(U\) test for the continuous covariates and via the Pearson \(\chi^2\) test or Fisher’s exact test for the categorical covariates, as appropriate. Odds ratios and 95% CI were calculated. Adjusted odds ratio was also determined via logistic regression to adjust for possible confounders. All tests were two-tailed, and the level of significance was set to a \(P\) value <0.05.

Results

Patient Characteristics
Thirty-five patients were eligible for the trial, and for 2 of these patients, the insertion of the ICY catheter into the femoral vein was unsuccessful because of severe bleeding at the puncture point or lumen malfunction. Consequently, 33 patients finished the treatment, completed the follow-up, and were eligible for analysis: 16 patients in the hypothermia group and 17 in the control group (Figure 1). The patient characteristics are listed in Table 1. The patients in the hypothermia group were younger and more frequently male.

Feasibility of Endovascular Hypothermia
The time between initiation of hypothermia and stroke onset was 42.0±14.9 hours. Bladder temperature before hypothermia was 37.7±0.8°C. Shivering was observed in 14 patients (87.5%): 2 patients with a score of 1, 8 with a score of 2, and 4 with a score of 3. Shivering could be suppressed by increasing the dose of antishivering drugs. The bladder temperature
curve is shown in Figure 2. The axillary temperature of the patients in the control group was 37.2±0.6°C.

### Effects of Endovascular Hypothermia

#### Neurological Outcome of Survival

At 6 months, more patients in the hypothermia group had good neurological outcomes. Of the surviving patients, those in the hypothermia group achieved significantly better neurological outcomes than those in the control group (7/8, 87.5% versus 4/10, 40.0%; $P=0.066$; odds ratio=10.5; 95% CI, 0.9–121.4; adjusted odds ratio=4.794; 95% CI 0.323–71.103; Figure 3).

#### Mortality

At 6 months, 8 patients in the hypothermia group and 7 patients in the control group had died. The mortality was similar between the 2 groups ($P=0.732$). In the hypothermia group, 7 patients died of herniation: 1 developed herniation before cooling, 1 developed it during the cooling period, 3 developed it during the rewarming period, and 2 developed it after the rewarming. The median rewarming time of these patients was 37.8 (range, 15.0–88.0) hours compared with 48.0 (range, 14.0–51.0) hours for patients without herniation in the hypothermia group ($P=0.490$). In the control group, 6 patients died of herniation, 3 of whom developed herniation before treatment.

#### Intracranial Pressure

In the hypothermia group, 10 patients received ICP monitoring and 5 developed transtentorial herniation. In the 5 patients who had no herniation, ICP was 22.0±5.6 mmHg at the initiation of cooling and decreased to 10.6±3.3 mmHg when the target temperature was reached. During the maintenance period, the ICP was stable at 11.4±3.7 mmHg. It then increased slightly at the end of rewarming to 15.0±5.8 mmHg. All 5 patients were alive at the time of discharge. In the 5 patients who developed herniation, the ICP was 18.7±5.5 mmHg at the initiation of cooling and decreased to 12.4±6.0 mmHg when the target temperature was reached. During the maintenance period, the ICP increased reaching 18.8±7.4 mm Hg at the initiation of rewarming. Additionally, the ICP increased significantly during the rewarming period, reaching 39.4±9.6 mmHg at the end of rewarming. All 5 of these patients died from herniation (Figure 4).

#### Complications

Among the 33 patients in both groups, only 1 patient in the control group did not experience complications. The incidence

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Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia Group (n=16)</th>
<th>Control Group (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>59.8±8.6 (46–75)</td>
<td>68.5±8.5 (53–79)</td>
<td>0.006</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>15/1</td>
<td>10/7</td>
<td>0.039</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>11</td>
<td>13</td>
<td>0.708</td>
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<tr>
<td>Coronary heart disease</td>
<td>3</td>
<td>5</td>
<td>0.688</td>
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<tr>
<td>Atrial fibrillation</td>
<td>5</td>
<td>7</td>
<td>0.721</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>5</td>
<td>2</td>
<td>0.225</td>
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<tr>
<td>Valvular dysfunction</td>
<td>1</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>6</td>
<td>0.438</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>4</td>
<td>1.000</td>
</tr>
<tr>
<td>Infarcted area, 2/3 MCA/MCA/&gt;MCA</td>
<td>5/8/3</td>
<td>4/9/4</td>
<td>0.868</td>
</tr>
<tr>
<td>Mean GCS (range)</td>
<td>9.8±2.2 (7–14)</td>
<td>9.2±2.2 (7–14)</td>
<td>0.468</td>
</tr>
<tr>
<td>Mean NIHSS (range)</td>
<td>19.7±2.9 (15–25)</td>
<td>20.4±3.8 (15–25)</td>
<td>0.541</td>
</tr>
<tr>
<td>Mean APACHE II (range)</td>
<td>13.3±4.0 (8–20)</td>
<td>14.5±4.7 (7–22)</td>
<td>0.433</td>
</tr>
<tr>
<td>Transtentorial herniation</td>
<td>1</td>
<td>3</td>
<td>0.601</td>
</tr>
<tr>
<td>Prior T/A/A/D</td>
<td>7</td>
<td>8</td>
<td>1.000</td>
</tr>
</tbody>
</table>

APACHE II indicates Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow coma scale; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; and T/A/A/D, thrombolysis, antiplatelet, anticoagulant, or defibrinogen treatment.

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Figure 2. Mean patient temperature in the hypothermia and control groups. The mean bladder temperature curves of the hypothermia group included 4 phases: induction period, maintenance period, rewarming period, and normothermia period. The axillary temperatures of the control group were sustained at normothermia (36.5–37.5°C).
of complications is shown in Table 2. The total incidence of complications was significantly higher in the hypothermia group than in the control group ($P=0.001$). The incidences of bradycardia, electrolyte disorder, gastrointestinal bleeding, gastric retention, and stress hyperglycemia were significantly higher in the hypothermia group. However, the complications in the hypothermia group were not severe, and none of them caused patient death.

**Discussion**

Our results show that, among survivors, patients with MCHI treated with mild hypothermia had a better neurological outcome than those in the control group. Seven patients of the 8 survivors in the hypothermia group had mRS of 1 to 3, whereas in the control group, only 4 of the 10 survivors had a mRS of 3. The mortality of the 2 groups was equal.

Hypothermia treatment thus seems to improve neurological outcome in patients with MCHI. Although the mechanism of neuroprotection in response to hypothermia remains unclear, hypothermia seems to alleviate brain damage through several mechanisms: prevention of blood–brain barrier disruption; reduction of cerebral glucose metabolism and oxygen consumption; reduction of the accumulation of excitotoxic neurotransmitters, intracellular acidosis, intracellular calcium influx, and oxygen-free radical production; alteration of the expression of cold shock proteins; reduction of brain edema; minimization of the risk of thrombosis; and decreasing the risk of epileptic activities.26–36

Prior studies have shown that the mortality associated with this condition is high, even after the strongest medical treatments available. Additionally, although DC could improve the mortality, the neurological outcome of patients with MCHI remained unsatisfactory.2–4 Therefore, if hypothermia combined with medical treatment could improve neurological outcomes and avoid the need for DC, this treatment would be the best option, especially in patients who would be high-risk candidates for surgery. Unfortunately, in our study, we found that the mortality was equal between the hypothermia and control groups. Eight patients in the hypothermia group and 7 patients in the control group died. The main cause of death was herniation because of fatal intracranial hypertension. Although the ICP of patients who developed herniation in the hypothermia group was 12.4±6.0 mm Hg at target temperature, it increased gradually during the maintenance period to 18.8±7.4 mm Hg and severely rebounded during rewarming reaching 39.4±9.6 mm Hg. This result was consistent with those of Saul and Ducker37 and Marmarou et al. 38 The incidences of herniation in their studies were 28% and 46%, respectively. Additionally, there was an increased possibility of herniation and death when the ICP exceeded 20 mm Hg.

The rewarming rate is associated with increased ICP. Schwab et al15 found that a shorter rewarming period (<16 hours) was associated with a more pronounced rise in ICP. Therefore, we controlled the rewarming rate and increased it by 0.5°C every 12 hours. We even decelerated the rewarming rate to 0.5°C every 24 hours in patients with a high risk of herniation. Although the rewarming time was slightly shorter in the herniated patients, the difference was not significant (median, 37.8 versus 48.0 hours; $P=0.490$). It is possible that an even slower rate should be used to rewarm patients to avoid ICP rebound.

We also hypothesized that the size of territory of infarction could contribute to an increase in ICP. In our study, the territories of the infarcted area in herniated patients were much larger than those in nonherniated patients. Among 7 herniated hypothermia patients, there were 3 with affection of a combination of MCA and anterior cerebral artery and 3 with affection of the entire MCA, whereas in the remaining 9 nonherniated hypothermia patients there were 5 with complete MCA, but none with combined MCA/ anterior cerebral

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**Figure 3.** Modified Rankin scale (mRS) of the patients at 6 months after stroke onset. There was a favorable trend toward the hypothermia group compared with the control group (hypothermia group, 7/8; control group, 4/10; $P=0.066$; odds ratio [OR]=10.5; 95% confidence interval [CI], 0.9–121.4; adjusted OR=4.794; 95% CI, 0.323–71.103) in the surviving patients.

**Figure 4.** The course of intracranial pressure (ICP) of 10 patients in the hypothermia group. The ICP values of herniated (n=5) and nonherniated (n=5) patients decreased during the induction period of hypothermia. During the maintenance and rewarming periods, it remained stable in nonherniated patients but increased slowly during the maintenance period and rebounded during the rewarming period in herniated patients.
Table 2. Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Hypothermia Group (n=16)</th>
<th>Control Group (n=17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent infarction</td>
<td>0</td>
<td>2</td>
<td>0.485</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>1</td>
<td>2</td>
<td>1.000</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>7</td>
<td>2</td>
<td>0.057</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>9</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1</td>
<td>3</td>
<td>0.601</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6</td>
<td>3</td>
<td>0.259</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>8</td>
<td>1.000</td>
</tr>
<tr>
<td>Lower extremity deep venous thrombosis</td>
<td>4</td>
<td>2</td>
<td>0.398</td>
</tr>
<tr>
<td>Electrolyte disorder</td>
<td>16</td>
<td>9</td>
<td>0.003</td>
</tr>
<tr>
<td>Coagulation dysfunction</td>
<td>14</td>
<td>15</td>
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<tr>
<td>Gastric retention</td>
<td>8</td>
<td>2</td>
<td>0.026</td>
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<tr>
<td>Stress hyperglycemia</td>
<td>6</td>
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<tr>
<td>Hypoalbuninemia</td>
<td>11</td>
<td>7</td>
<td>0.166</td>
</tr>
<tr>
<td>Acute liver injury</td>
<td>2</td>
<td>1</td>
<td>0.601</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>2</td>
<td>0</td>
<td>0.227</td>
</tr>
<tr>
<td>All cases</td>
<td>109</td>
<td>74</td>
<td>0.001</td>
</tr>
</tbody>
</table>

There was no heart failure, pulmonary embolism, hiccup, acute pancreatitis, catheter-related infection, urinary infection, sepsis, retroperitoneal, or groin hematoma.

Conclusions

Hypothermia treatment represents a new option for patients with MCHI. Although we did not observe hypothermia to lower the mortality, it is a promising treatment that could improve the neurological outcomes in surviving MCHI patients.

Acknowledgments

We thank all of the patients and families who participated in this trial.

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Disclosures

None.

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