Therapeutic Hypothermia After Recanalization in Patients With Acute Ischemic Stroke

Ji Man Hong, MD, PhD; Jin Soo Lee, MD, PhD; Hee-Jung Song, MD; Hye Seon Jeong, MD; Huimahn Alex Choi, MD; Kiwon Lee, MD

Background and Purpose—Therapeutic hypothermia improves outcomes in experimental stroke models, especially after ischemia-reperfusion injury. We investigated the clinical and radiological effects of therapeutic hypothermia in acute ischemic stroke patients after recanalization.

Methods—A prospective cohort study at 2 stroke centers was performed. We enrolled patients with acute ischemic stroke in the anterior circulation with an initial National Institutes of Health Stroke Scale ≥10 who had successful recanalization (≥thrombolysis in cerebral ischemia, 2b). Patients at center A underwent a mild hypothermia (34.5°C) protocol, which included mechanical ventilation, and 48-hour hypothermia and 48-hour rewarming. Patients at center B were treated according to the guidelines without hypothermia. Cerebral edema, hemorrhagic transformation, good outcome (3-month modified Rankin Scale, ≤2), mortality, and safety profiles were compared. Potential variables at baseline and during the therapy were analyzed to evaluate for independent predictors of good outcome.

Results—The hypothermia group (n=39) had less cerebral edema (P=0.001), hemorrhagic transformation (P=0.016), and better outcome (P=0.017) compared with the normothermia group (n=36). Mortality, hemicraniectomy rate, and medical complications were not statistically different. After adjustment for potential confounders, therapeutic hypothermia (odds ratio, 3.0; 95% confidence interval, 1.0–8.9; P=0.047) and distal occlusion (odds ratio, 7.3; 95% confidence interval; 1.3–40.3; P=0.022) were the independent predictors for good outcome. Absence of cerebral edema (odds ratio, 5.4; 95% confidence interval, 1.6–18.2; P=0.006) and no medical complications (odds ratio, 9.3; 95% confidence interval, 2.2–39.9; P=0.003) were also independent predictors for good outcome during the therapy.

Conclusions—In patients with ischemic stroke, after successful recanalization, therapeutic hypothermia may reduce risk of cerebral edema and hemorrhagic transformation, and lead to improved clinical outcomes. **(*Stroke*. 2014;45:134-140.)**

Key Words: hypothermia ■ ischemia ■ ischemic ■ neuroprotection ■ reperfusion injury ■ stroke

Therapeutic hypothermia (TH) is potently neuroprotective in experimental stroke models and clinically proven to improve outcomes in patients after cardiac arrest and neonatal encephalopathy because of hypoxia-ischemia.[1–3] Preclinical studies show that TH is far more beneficial and consistent in temporary middle cerebral artery (MCA) occlusion than in permanent MCA occlusion models.[4,5] Similarly in humans, TH after cardiac arrest improves outcomes most likely by preventing ischemia-reperfusion injury. Animal studies and clinical trials suggest TH might be more effective in patients with severe stroke with successful recanalization by providing neuronal protection.[1,2]

The recanalization rates of intravenous recombinant tissue-type plasminogen activator for proximal arterial occlusion are low.[6] Moreover, previous in vitro analyses reported that the activity of tissue-type plasminogen activator was considerably reduced during therapeutic cooling experiments.[7,8] Combination trials of intravenous thrombolysis and hypothermia are ongoing.

Despite preliminary trials of TH in patients with acute ischemic stroke, no large randomized trials of TH in acute ischemic stroke exist.[9] Previous stroke trials have reported that TH is associated with increased risk of pneumonia or infectious complications.[9,10] However, in patients undergoing TH for cardiac arrest, TH has not been associated with an increased risk of pneumonia.[3] Moreover, a recent study reported that despite the association of TH with an increased risk of pneumonia, longer duration of intensive care unit stay, and prolonged mechanical ventilation dependency, these factors did not affect neurological outcome and intensive care unit survival.[11]

We investigated the effects of mild hypothermia (34.5°C) in intubated patients with adequate sedation during a period of 48 hours of cooling and 48 hours of rewarming. All patients had large hemispheric acute ischemic strokes (anterior circulation involvement with initial National Institutes of Health Stroke Scale [NIHSS], ≥10), and their occlusive lesions were successfully recanalized with endovascular confirmation.

Received August 7, 2013; accepted October 3, 2013.

From the Department of Neurology, Ajou University School of Medicine, Suwon, South Korea (J.M.H., J.S.L.); Department of Neurology, Chungnam National College of Medicine, Daejon, South Korea (H.-J.S., H.-S.J.); and Department of Neurology and Neurosurgery, University of Texas Health Science Center at Houston (J.M.H., H.A.C., K.L.).

Correspondence to Ji Man Hong, MD, PhD, Department of Neurology, School of Medicine, Ajou University, 5 San, Woncheon-dong, Yongtong-gu, Suwon-si, Kyunggi-do 442–749, South Korea. E-mail dacda@hanmail.net

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.003143**

Clinical and radiological factors were compared between TH patients and conventionally treated controls. Our primary hypothesis was that TH would be associated with improved radiological and clinical outcomes.

Subjects and Methods

Patient Selection

Between March 2010 and June 2012, patients consecutively admitted to 2 tertiary care hospitals were enrolled. Both stroke centers used a common critical pathway for thrombolysis. On presentation, computed tomographic (CT) scans were obtained and early ischemic signs were interpreted according to the documented protocol. Within 3 hours from onset, intravenous tissue-type plasminogen activator was administrated. Patients with suspicion for large vessel occlusion given CT angiography or clinical syndrome and without contraindications for endovascular treatment were brought to the angiographic suite. Intra-arterial treatment was considered as long as the onset-to-decision interval was <5 hours, regardless of intravenous tissue-type plasminogen activator infusion. Conscious sedation during intra-arterial procedure was chosen to reduce delay to next treatments. MR scans for strokes were obtained while preparing for angiography. Admission characteristics including demographic data, vascular risk factors, stroke pathogenesis, laboratory and neurological scales were collected.

Inclusion criteria for this study were (1) ischemic stroke involving the anterior circulation (NIHSS, ≥10); (2) acute infarction with diffusion-weighted imaging (DWI) confirmation; and (3) endovascular recanalization (thrombolysis in cerebral ischemia, ≥2b) within 6 hours after symptom onset, or spontaneous recanalization.

Care in both tertiary referral stroke centers fulfilled the Brain Attack Coalition's standardized criteria,[12] and their stroke units have also obtained certification from the Korean Stroke Association. Center A, Ajou University Medical Center, serves a southern area of the Kyonggi province with a population of 4 000 000. Center B, Chungnam National University Medical Center, serves a central area in the southern Chumgchung province and Daegeon metropolis with a population of 3 500 000. This study was approved by the institutional review board at both institutes.

Cooling Protocol

In center A, patients were cooled with either an endovascular cooling catheter (Alsius) placed in the inferior vena cava via a femoral venous sheath or a surface cooling device (Arctic Sun). All cooled patients were mechanically ventilated to provide airway protection; midazolam was used for sedation and vecuronium for neuromuscular blockade. Cooling induction began as soon as the catheter was placed; cooling rate was set at maximum until 35°C then was set at 34.5°C to avoid overcooling or severe complications during induction. Induction time was defined as the total time in minutes from initial cooling to target temperature. Temperature was recorded every hour from thermometers at the tip of endovascular sheath and at the tip of the esophageal catheter. Core body temperatures were plotted with an esophagus temperature probe. Hypothermia therapy was maintained for 48 hours, and rewarming was performed >48 hours under sedation. The rate of rewarming was determined as 0.5°C of temperature elevation per every 12 hours. Antipyretic and antishivering agents besides paralytics were not used during hypothermia.

Patient Management

All patients were treated with a standard quality of stroke care based on international guidelines.[13] In case of refractory cerebral edema despite maximally conservative treatments such as head elevation and osmotherapy, surgical hemicraniectomy was performed. In all patients, a bedside swallowing assessment was performed as soon as possible after admission to the hospital. Nutrition was supplied via Levin tube in patients with swallowing difficulty. To prevent aspiration pneumonia, nurses frequently auscultated lungs and evaluated patients for any signs of respiratory compromise and dysphagia. Patients with presumed pneumonia or urinary tract infection were actively treated with appropriate antibiotics. Other bowel and bladder care was performed according to the usual standard clinical practice.

Imaging Analysis

On initial noncontrast CT, the Alberta Stroke Program Early CT Score (ASPECTS) was evaluated.[14] Angiographically, the status of the recanalization was graded as thrombolysis in cerebral ischemia ≥2b: grade 0, no perfusion; grade 1, minimal perfusion; grade 2a, partial filling of less than one-half the occluded arterial distribution; grade 2b, partial filling of one-half or greater of the occluded arterial distribution; and grade 3, full perfusion.

A 48-hour CT scan was obtained. Hemorrhagic transformation (HT) was classified into 4 subtypes: hemorrhagic infarction type 1: small petechiae along the margins of the infarct; hemorrhagic infarct type 2: confluent petechiae within the infarcted area but without a space-occupying effect; parenchymal hematoma type 1: hematoma in <30% of the infarcted area with some space-occupying effect; and a parenchymal hematoma type 2: hematoma in >30% or the infarcted area with a substantial space-occupying effect.[15] Brain edema was classified as grade 1: effacement of the cortical sulci; grade 2: ventricular asymmetry; and grade 3: midline shift.[16] The comprehensive imaging analyses from 2 institutes was performed by consensus of neurologists blinded to laboratory and clinical outcomes. CT scans were performed on admission and 24 to 36 hours (48 hours) after cerebral angiography confirming relevant vessel recanalization. Additional CT scans were obtained if necessary. MR scans including DWI for stroke burden were also undertaken on admission and 5 days after symptom. Infarction volume was calculated by multiplying the area of the lesions on initial DWI and section thickness. DWI lesions were categorized as cortical, subcortical, and combined patterns.

Medical Complications

All patients had 24-hour ECG monitoring and daily cardiac enzymes monitoring. Blood pressure and body temperature were monitored at least every hour during intensive care unit and stroke unit administration. Gastrointestinal bleeding was monitored by observing nasogastric tube suctioning. According to commonly used criteria, diagnosis of early-onset pneumonia was made if there was presence of a clinically compatible finding at auscultation and new pulmonary infiltrate on chest radiograph (persistent for 48 hours) associated with an increased serum white cell count.[11] Serum concentrations of sodium, potassium, and magnesium were investigated every day during intensive care unit or stroke unit stay. Prothrombin time, partial thromboplastin time, d-dimer, and fibrin degradation product were identified for detection of coagulation abnormality. Hyperglycemia was treated with continuous insulin therapy aimed at blood glucose levels between 100 and 200 mg/dL.

All medical complications were recorded if they occurred during the therapeutic period. They were classified into cardiac dysrhythmia, electrolytes, and chemistry abnormalities, coagulopathy (bleeding of any severity or disseminated intravascular coagulation), hypotension requiring vasopressor therapy, deep vein thrombosis, and infectious complications. Cardiac dysrhythmias included both asymptomatic and serious; serious dysrhythmia was defined as those causing hemodynamic instability, requiring antiarrhythmic therapy or leading to an interruption of TH. Deep vein thrombosis was screened via a clinical suspicion by experienced nursing staffs, and ultrasonography was performed if the index of suspicion was high. The medical complications were comprehensively analyzed in every patient by a consensus through during daily rounds with intensivists and neurologists. All patients received standard stroke care in a comprehensive stroke unit until patients became stable neurologically.

Outcome Assessment

Neurological deficit was assessed by serial NIHSS scores by certificated stroke nurses or stroke neurologists at least every 4 hours. Neurological scales were checked daily until discharge and every 3

month thereafter. The clinical outcome was primarily dichotomized into good (0–2 points) and poor (3–6 points) groups using a modified Rankin Scale (mRS) score at 90 days after stroke onset. We used other criteria for good outcome: an mRS of 0 to 1 points versus 2 to 6 points. Ninety-day mortality was observed.

Statistical Analysis

Continuous variables are shown as mean±SD or median (interquartile range), whereas categorical variables are presented as absolute and relative frequency. Differences were compared between groups using a Pearson χ^2 test or Fisher exact test for categorical variables, and a Student *t* test or Mann–Whitney *U* test for continuous variables. To predict the potential variables for good outcome (mRS<3) or poor outcome (mRS≥3), these variables were specified into 2 types: baseline variables (ie, general demographics, risk factors, involved vessels, volume and patterns on DWI, recanalized modalities, and recanalization status) and variables during therapy (ie, classifications of HT, cerebral edema, hemicraniectomy, and ≥1 medical complication). To identify independent variables to predict good outcome, 2 types of variables were, respectively, entered into a univariate logistic regression model, potential factors that were not significant (P>0.1) in the univariate analyses were sequentially deleted from the full logistic regression models using a stepwise method. All statistical analyses were performed using commercially available software (SPSS for windows, version 12.0; SPSS Inc, Chicago, IL). P<0.05 was considered statistically significant.

Results

General Demographics

We identified 75 patients (41 men; 66.2±15.4 years of age) who met the inclusion criteria. Thirty-nine patients were in the TH group, and 36 patients were nonhypothermia group. Baseline characteristics (initial NIHSS or ASPECTS, DWI volume or patterns), stroke risk factors, initial laboratory findings did not differ between TH and nonhypothermia groups (Table 1). There were no differences of onset-to-CT time (P=0.415) and vessel involvements (P=0.279).

Radiological and Clinical Outcomes

TH was associated with less HT (no HT: 39% versus 14%; P=0.016) had less cerebral edema (no cerebral edema, 54% versus 17%; P=0.001). The TH group had a higher proportion of good outcome (Figure 1; mRS≤2 at 3 months, 45% versus 23%; P=0.017 and mRS≤1 at 3 months, 31% versus 8%; P=0.015). Mortality (15% versus 14%; P=0.855) and hemicraniectomy rate (10% versus 14%; P=0.629) were not different (Table 2).

Medical Complications

On average, induction time was 378±355 minutes, maintenance temperature 34.4±0.99°C, and 95% of patients were cooled using an endovascular catheter.

Overall medical complications did not differ between TH and nonhypothermia groups (28% versus 47%; P=0.089). Interestingly, pneumonia occurred 8% in TH and 31% in nonhypothermia (P=0.004). However, no differences in other complications were observed (Table 3).

Multiple Regression Analysis for Good Outcome

To evaluate prognostic associations with hypothermia and other variables, we analyzed 2 types of variables (Table 4): factors at baseline and factors during the therapy. When baseline factors were entered into the final multivariate model 1 with stepwise-backward conditional mode, TH (odds ratio, 3.01; 95% confidence interval, 1.02–8.90; P=0.047) and involvement of MCA M2 (odds ratio, 7.32; 95% confidence interval, 1.33–40.31; P=0.022) were independent predictors for good outcome. Age and involvement of MCA M1 were deleted from the final model 1.

When examining factors during therapy that impact on clinical outcome, absence of cerebral edema (odds ratio, 5.41; 95% confidence interval, 1.61–18.17; P=0.006) and absence of adverse events (odds ratio, 9.31; 95% confidence interval, 2.17–39.9; P=0.003) as independent predictors for good outcome, mild cerebral edema and hemicraniectomy were not independently associated with outcome.

Table 1. General Demographics and Recanalization Modes in Patients With or Without Hypothermia

	Hypothermia (n=39)	No Hypothermia (n=36)	*P* Value
General demographics			
Age	64.5±17.0	68.1±13.3	0.314
Men	23 (59)	18 (50)	0.435
Initial NIHSS (median)	17 (15–18)	15.5 (12–17)	0.076
Onset-to-CT time (median, min)	131 (77–185)	108 (43–173)	0.415
Initial ASPECTS (median)	6 (5–9)	7 (6–9)	0.453
DWI volume (mean, mL)	80.1±115.3	66.5±138.8	0.643
Risk factors			
Hypertension	26 (66.7)	23 (63.9)	0.801
Diabetes mellitus	6 (15.4)	6 (16.7)	0.880
Current smoker	10 (25.6)	8 (22.2)	0.396
Hyperlipidemia	6 (15.4)	7 (19.4)	0.643
Cardiac problem	29 (74.4)	22 (61.1)	0.219
Involved vessels			0.279
ICA	14 (35.9)	9 (25.0)	
MCA M1	19 (48.7)	24 (66.7)	
MCA M2	6 (15.4)	3 (8.3)	
Involved side			0.926
Right	21 (53.8)	17 (47.2)	
Left	18 (46.2)	19 (52.8)	
DWI patterns			0.530
Cortical	12 (79.5)	26 (72.2)	
Subcortical	8 (20.5)	10 (27.8)	
Combined	19 (48.7)	13 (36.1)	
Recanalized modalities			0.890
None	2 (5.1)	2 (5.6)	
IV tPA	6 (15.3)	7 (19.4)	
IA-mech or both	31 (79.5)	27 (75.0)	

Data are: n (%), mean±SD, median (interquartile range). ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; DWI, diffusion-weighted imaging; IA, intra-arterial; ICA, internal carotid artery; IV, intravenous; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

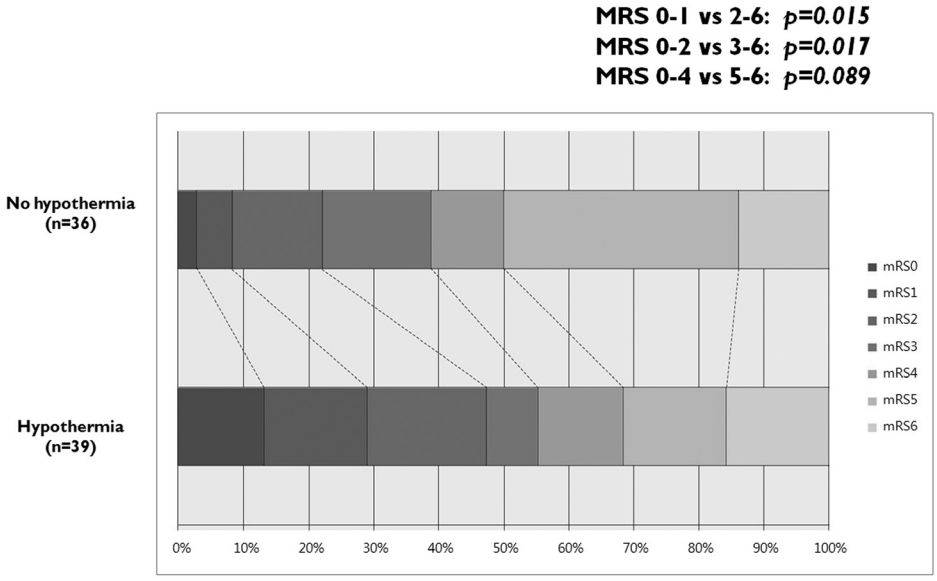

Figure 1. Distribution of 3-month modified Rankin Scale (mRS; from 0=no symptoms from stroke to 6=death) between patients who underwent recanalization with hypothermia and without hypothermia, indicating significant differences (mRS, 0–1 vs 2–6 with *P*=0.015; mRS, 0–2 vs 3–6 with *P*=0.017).

Discussion

In patients with stroke, use of TH after recanalization significantly reduced cerebral edema, HT, and was associated with better clinical outcomes. After adjustment for potential confounders, TH and presence of distal, rather than proximal, occlusion were independent predictors of good outcome. In addition, we found the absence of cerebral edema and absence of medical complications during the therapy to be independent outcome predictors.

Our hypothermia protocol differs from other TH trials in 4 specific ways. (1) We specifically targeted ischemia-reperfusion injury by selecting patients with angiographically proven, recanalized ischemic stroke; (2) we chose a target temperature of 34.5°C[1,2]; (3) we had a relatively long duration (48 hours) of hypothermia and controlled rewarming (additional 48 hours) to mitigate cerebral edema and HT[17,18]; (4) we intubated and deeply sedated all of our patients to prevent pneumonia and shivering.[9]

Preclinical and clinical studies suggest that hypothermia is most beneficial in protecting against ischemia-reperfusion injury.[1,2,4,19,20] Our data further support this finding because we only selected those with successful recanalization.

Table 2. Radiological and Clinical Outcomes in Patients With or Without Hypothermia (n=75)

	Hypothermia (n=39)	No Hypothermia (n=36)	*P* Value
HT			0.051
None	15 (38.5)	5 (13.9)	0.016 (vs all HT)
HT1	8 (20.5)	9 (25.0)	
HT2	1 (2.6)	7 (19.4)	
PH1	8 (20.5)	8 (22.2)	
PH2	7 (17.9)	7 (19.4)	
Cerebral edema			0.004
None	21 (53.8)	6 (16.7)	0.001 (vs all CE)
Mild	9 (23.1)	14 (38.9)	
Midline shift	9 (23.1)	16 (44.4)	
Clinical outcomes			
mRS (0–1) at 3 mo	12 (30.8)	3 (8.3)	0.015
mRS (0–2) at 3 mo	19 (48.7)	8 (22.2)	0.017
mRS (0–3) at 3 mo	22 (56.4)	14 (38.9)	0.129
Mortality at 1 mo	6 (15.4)	5 (13.9)	0.855
Hemicraniectomy	4 (10.3)	5 (13.9)	0.629

CE indicates cerebral edema; HT, hemorrhagic transformation; mRS, modified Rankin Scale; and PH, parenchymal hemorrhage.

Table 3. Overall Medical Complications in Patients With or Without Hypothermia (n=75)

	Hypothermia (n=39)	No Hypothermia (n=36)	*P* Value
Hypothermia			
Time from recanalization to induction, min	75±21		…
Induction time, min	378±355		…
Maintenance temp, °C	34.4±0.99		…
Endovascular method (ALSIUS)	37 (94.9)		…
Surface method (Arctic SUN)	2 (5.1)		…
MCs			…
≥1 MC	11 (28.2)	17 (47.2)	0.089
Bradycardia	3 (7.7)	1 (2.8)	…
Elevated CK	2 (5.1)	2 (5.6)	…
Cardiac events (T-inversion, non-STEMI)	1 (2.6)	0 (0.0)	…
Hypokalemia	2 (5.1)	0 (0.0)	…
Pulmonary edema	2 (5.1)	1 (2.8)	…
Decreased blood pressure	1 (2.6)	0 (0.0)	…
Pneumonia	2 (5.1)	11 (30.6)	…
UTI	0 (0.0)	2 (5.6)	…
Deep vein thrombosis	0 (0.0)	0 (0.0)	…
GI bleeding	0 (0.0)	1 (2.8)	…

CK indicates creatine kinase; GI, gastrointestinal; MC, medical complication; STEMI, ST-segment–elevation myocardial infarction, T-inversion, T-wave inversion; and UTI, urinary tract infection.

Table 4. Multivariate Logistic Regression Analysis for Prediction of Good Outcome (mRS, 0–2)

Characteristics	Good Outcome Group (n=27)	Poor Outcome Group (n=48)	*P* Value	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Variables on baseline (model 1)							
General demographics							
Age, y	61.2±17.1	69.1±13.7	0.032	0.97 (0.94–0.99)	0.036	…	…
Women, n (%)	14 (51.9)	20 (41.7)	0.395	1.51 (0.58–3.89)	0.396	…	…
NIHSS (median)	17	16	0.589	1.05 (0.89–1.23)	0.583	…	…
ASPECTS (median)	7	7	0.189	1.02 (0.83–1.25)	0.864	…	…
CT time (median, min)	125	120	0.611	1.00 (0.99–1.00)	0.611	…	…
DWI volume (mean, mL)	45.8±43.8	89.2±153.0	0.155	0.99 (0.99–1.00)	0.203	…	…
Hypothermia	19 (70.4)	20 (41.7)	0.017	3.33 (1.22–9.09)	0.019	3.01 (1.02–8.90)	0.047
Risk factors, n (%)							
Hypertension	15 (55.6)	34 (70.8)	0.182	0.52 (0.19–1.37)	0.185	…	…
Diabetes mellitus	4 (14.8)	8 (16.7)	0.834	0.870 (0.24–3.21)	0.834	…	…
Current smoker	7 (25.9)	8 (16.7)	0.336	1.75 (0.56–5.51)	0.339	…	…
Hyperlipidemia	6 (22.2)	7 (14.6)	0.402	1.67 (0.50–5.62)	0.405	…	…
Cardiac problem	17 (63.0)	34 (70.8)	0.483	0.70 (0.26–1.90)	0.484	…	…
Involved vessels			0.018				
ICA	8 (29.6)	15 (31.3)		0.93 (0.33–2.59)	0.884	…	…
MCA M1	12 (44.4)	31 (64.6)		0.44 (0.17–1.15)	0.093	…	…
MCA M2	7 (25.9)	2 (4.2)		8.05 (1.54–42.20)	0.014	7.32 (1.33–40.31)	0.022
DWI patterns			0.365				
Cortical	8 (29,6)	17 (35.4)		0.77 (0.28–2.12)	0.610	…	…
Subcortical	9 (33.3)	9 (18.8)		2.17 (0.74–6.38)	0.160	…	…
Combined	10 (37.0)	22 (45.8)		0.69 (0.27–1.83)	0.461	…	…
Recanalized modalities			0.885				
None	1 (3.7)	3 (6.3)		0.58 (0.06–5.83)	0.641	…	…
IV tPA	5 (18.5)	8 (16.7)		1.14 (0.33–3.90)	0.839	…	…
IA-mech or both	21 (77.8)	37 (77.1)		1.04 (0.34–3.22)	0.945	…	…
Recanalization			0.280				
TICI 2b	13 (48.1)	17 (35.4)		1.69 (0.65–4.41)	0.282	…	…
TICI 3	14 (51.9)	31 (64.6)		0.59 (0.23–1.54)	0.282	…	…
Variables during the therapy (model 2)							
HT			0.412				
None	5 (18.5)	12 (25.0)		1.90 (0.66–5.49)	0.236	…	…
HT1	1 (3.7)	7 (14.6)		0.68 (0.21–2.20)	0.521	…	…
HT2	10 (37.0)	10 (20.0.8)		0.23 (0.03–1.94)	0.175	…	…
PH1	6 (22.2)	10 (20.8)		1.09 (0.35–3.41)	0.888	…	…
PH2	5 (18.5)	9 (18.8)		0.99 (0.29–3.31)	0.980	…	…
Cerebral edema			0.003				
None	16 (59.3)	11 (22.9)		4.89 (1.76–13.58)	0.002	5.41 (1.61–18.17)	0.006
Mild	3 (11.1)	20 (41.7)		0.18 (0.05–0.66)	0.010	…	…
Midline shift	8 (29.6)	17 (35.4)		0.77 (0.28–2.12)	0.610	…	…
Surgery			0.016				
Hemicraniectomy	0 (0.0)	9 (18.8)		0.00 (0.00 -)	<0.001	…	…
No MCs	24 (88.9)	23 (47.9)	<0.001	8.70 (2.31–32.78)	0.001	9.31 (2.17–39.90)	0.003

ASPECTS indicates Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; DWI, diffusion-weighted imaging; HT, hemorrhagic transformation; IA, intra-arterial; ICA, internal carotid artery; IV, intravenous; MC, medical complication; MCA, middle cerebral artery; mech, mechanical; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hemorrhage; TICI, thrombolysis in cerebral ischemia; and tPA, tissue-type plasminogen activator.

The ideal target temperature for neuroprotection is yet to be established. Current guidelines recommend a target temperature of 32°C to 34°C in patients with return of spontaneous circulation after cardiac arrest.[21] However, hypothermia can lead to a number of undesirable physiological changes or side effects, such as hypovolemia attributable to cold diuresis,

cardiovascular changes, electrolyte disorders, impaired coagulation cascade, shivering, and increased infection risk.[22] The risk of hypotension is increased >6-fold with a target temperature of 32°C compared with target temperatures of 33°C and 34°C.[23] The success of any TH study depends on the control of these side effects. We chose a target temperature of 34.5°C to try to avoid undesirable complications of TH while still gaining neuroprotective properties of TH.[19,24]

Compared with the previous trials on cardiac arrest and acute ischemic stroke,[1,2,9] our protocol had a longer duration of cooling and rewarming. Clinical deterioration after ischemic stroke attributable to HT and cerebral edema usually occurs between 2 and 5 days after stroke.[25,26] A study in 215 patients with severe traumatic brain injury treated with TH, long-term cooling (5 days) was more efficacious than short-term cooling (2 days).[17] Long-term cooling was associated with a significant reduction in intracranial pressure and improved clinical outcomes, with no difference of medical complications.[17] Interestingly, short-term hypothermia was associated with a significant rebound intracranial pressure effect after rewarming that was not seen in long-term hypothermia.[17] The time course of edema after stroke and extrapolation from traumatic brain injury hypothermia studies suggest a prolonged course of TH with slow and controlled rewarming may be important for the success of TH protocols for patients with stroke.

In preliminary stroke trials, the higher rates of pneumonia during TH have been a concern.[9,10] Transient immune suppression from stroke itself and aspiration attributable to the shivering treatment with meperidine have been implicated as causes for the increased risk of pneumonia.[9] Aspiration during TH seems to be the likely culprit given no increase in risk of other infections. Additionally, an increased risk of pneumonia has not been seen during TH for cardiac arrest. A meta-analysis of studies of TH for cardiac arrest reported no proportional differences of pneumonia between TH and historical controls.[3] In another meta-analysis in TH patients after cardiac arrest, besides arrhythmia and hypokalemia, serious complications were rare, and no difference in pneumonia was found between TH and normothermia groups.[27] One difference between cardiac arrest TH studies and stroke TH studies is intubation and mechanical ventilation. Our study suggests that intubation and mechanical ventilation of patients with stroke may protect against pneumonia. The low rates of pneumonia in our TH group compared with other studies suggest the importance of a secure airway for the prevention of pneumonia.

A strength of our study is the focus on the possible mechanism of the impact of hypothermia on outcomes. An antiedema mechanism to explain the beneficial effect of moderate TH in the treatment of severe space-occupying MCA infarction has been suggested.[10] TH has been shown to prevent perihemorrhagic edema in patients with large spontaneous intracerebral hemorrhage.[18] Our study corroborates similar antiedema properties of prolonged TH (Figure 2). The brain is notably susceptible to oxidative stress because of its high consumption of oxygen and high concentration of oxidative injury-prone substrates. After stroke, excessive production of free radicals leads to breakdown of the blood–brain barrier, which contributes to cerebral edema and brain hemorrhage.[28,29] This leads to a rapid reduction of scavenger antioxidants in blood after stroke and more remarkably after recanalization.[30] TH reduces the temperature in damaged brain, attenuates all processes of the ischemic cascade, blocks generation of free radical species, and halts the deleterious pathways leading to brain edema.[31,32] This mechanism may be most profound in patients after large vessel recanalization as reperfusion of a large stroke may accelerate neuronal damage.[6,33,34]

Our study has some limitations. First, our study is a pilot study and should be interpreted with caution. Despite well-balanced baseline characteristics and a homogenous population, hidden biases between populations and differences in care between the 2 centers may exist. The trend toward higher NIHSS and infarct volume, and lower ASPECTS in the HT center suggests subtle differences but strengthens the associations found. Second, differences in treatment protocols, besides TH, are possible and may have been the basis for differences in rates of medical complications. To minimize

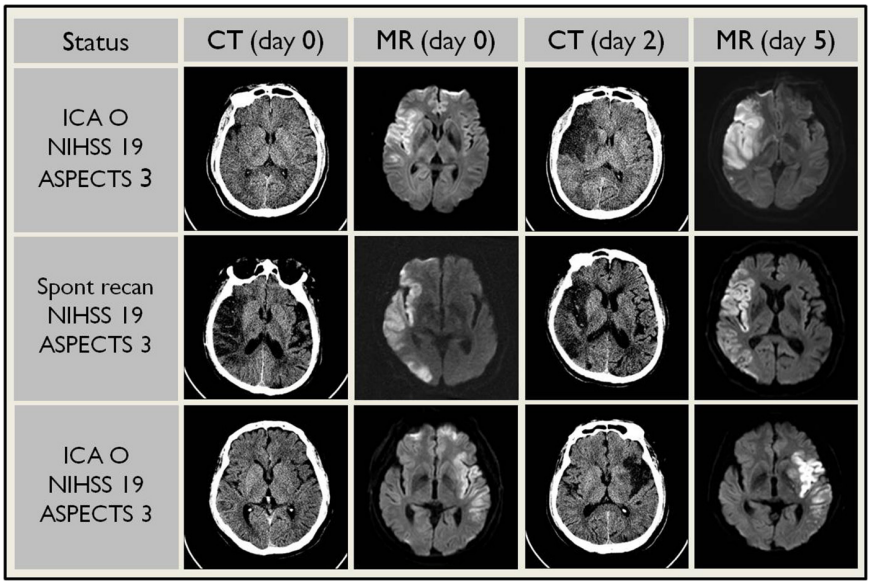

Figure 2. Absence of edema and hemorrhagic transformation in therapeutic hypothermia. Sequential change of the images in 3 patients in the hypothermia group at days computed tomography (CT) 0, MR 0, CT 2, and MR 5 days after admission. ASPECTS indicates Alberta Stroke Program Early CT Score; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; O, occlusion; and Spont recan, spontaneous recanalization.

the difference in definitions of medical complications, members from both centers adjudicated all medical complications jointly. Third, neurologists have considerable concerns about the inability to monitor neurological status in patients who are sedated and paralyzed. However, through the acquisition of pupil responses to light and repetitive CT scans, we were able to find important clinical changes appropriately, such as herniation, cerebral edema, HT, and new onset of ischemia.

In conclusion, we found TH to be associated with a decreased risk of brain edema, HT, and better clinical outcome. In future TH trials for acute stroke, a comprehensive protocol emphasizing an extended period of hypothermia and rewarming, airway protection, and vigorous medical treatments may be crucial for success. A randomized clinical trial may be warranted to investigate the impact of hypothermia as adjuvant therapy in patients with successful recanalization after thrombolysis.

Disclosures

None.

References

1. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
2. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Eng J Med* 2002;346:549–556.
3. Sagalyn E, Band RA, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. *Crit Care Med*. 2009;37(suppl 7):S223–S226.
4. Ridenour TR, Warner DS, Todd MM, McAllister AC. Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. *Stroke*. 1992;23:733–738.
5. Zhang RL, Chopp M, Chen H, Garcia JH, Zhang ZG. Postischemic (1 hour) hypothermia significantly reduces ischemic cell damage in rats subjected to 2 hours of middle cerebral artery occlusion. *Stroke*. 1993;24:1235–1240.
6. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al; CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948–954.
7. Yenari MA, Palmer JT, Bracci PM, Steinberg GK. Thrombolysis with tissue plasminogen activator (tPA) is temperature dependent. *Thromb Res*. 1995;77:475–481.
8. Wolberg AS, Meng ZH, Monroe DM III, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. *J Trauma*. 2004;56:1221–1228.
9. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S, et al; ICTuS-L Investigators. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. *Stroke*. 2010;41:2265–2270.
10. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke*. 1998;29:2461–2466.
11. Perbet S, Mongardon N, Dumas F, Bruel C, Lemiale V, Mourvillier B, et al. Early-onset pneumonia after cardiac arrest: characteristics, risk factors and influence on prognosis. *Am J Respir Crit Care Med*. 2011;184:1048–1054.
12. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, Brass LM, et al; Brain Attack Coalition. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke*. 2005;36:1597–1616.
13. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655–1711.
14. Demchuk AM, Coutts SB. Alberta Stroke Program Early CT Score in acute stroke triage. *Neuroimaging Clin N Am*. 2005;15:409–19, xii.
15. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.
16. Moldes O, Sobrino T, Millán M, Castellanos M, Pérez de la Ossa N, Leira R, et al. High serum levels of endothelin-1 predict severe cerebral edema in patients with acute ischemic stroke treated with t-PA. *Stroke*. 2008;39:2006–2010.
17. Jiang JY, Xu W, Li WP, Gao GY, Bao YH, Liang YM, et al. Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab*. 2006;26:771–776.
18. Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke*. 2010;41:1684–1689.
19. van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR. Hypothermia in animal models of acute ischaemic stroke: a systematic review and meta-analysis. *Brain*. 2007;130(pt 12):3063–3074.
20. Jacobs S, Hunt R, Tarnow-Mordi W, Inder T, Davis P. Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 2007:CD003311.
21. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S768–S786.
22. Choi HA, Badjatia N, Mayer SA. Hypothermia for acute brain injury–mechanisms and practical aspects. *Nat Rev Neurol*. 2012;8:214–222.
23. Al-Senani FM, Graffagnino C, Grotta JC, Saiki R, Wood D, Chung W, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation*. 2004;62:143–150.
24. Kallmünzer B, Kollmar R. Temperature management in stroke—an unsolved, but important topic. *Cerebrovasc Dis*. 2011;31:532–543.
25. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
26. Lim TS, Hong JM, Lee JS, Shin DH, Choi JY, Huh K. Induced-hypertension in progressing lacunar infarction. *J Neurol Sci*. 2011;308:72–76.
27. Xiao G, Guo Q, Shu M, Xie X, Deng J, Zhu Y, et al. Safety profile and outcome of mild therapeutic hypothermia in patients following cardiac arrest: systematic review and meta-analysis. *Emerg Med J*. 2013;30:91–100.
28. Polidori MC, Frei B, Cherubini A, Nelles G, Rordorf G, Keaney JF Jr, et al. Increased plasma levels of lipid hydroperoxides in patients with ischemic stroke. *Free Radic Biol Med*. 1998;25:561–567.
29. Heo JH, Han SW, Lee SK. Free radicals as triggers of brain edema formation after stroke. *Free Radic Biol Med*. 2005;39:51–70.
30. Hong JM, Bang OY, Chung CS, Joo IS, Gwag BJ, Ovbiagele B. Influence of recanalization on uric acid patterns in acute ischemic stroke. *Cerebrovasc Dis*. 2010;29:431–439.
31. Wu TC, Grotta JC. Hypothermia for acute ischaemic stroke. *Lancet Neurol*. 2013;12:275–284.
32. Simard JM, Kent TA, Chen M, Tarasov KV, Gerzanich V. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. *Lancet Neurol*. 2007;6:258–268.
33. Sims JR, Rordorf G, Smith EE, Koroshetz WJ, Lev MH, Buonanno F, et al. Arterial occlusion revealed by CT angiography predicts NIH stroke score and acute outcomes after IV tPA treatment. *AJNR Am J Neuroradiol*. 2005;26:246–251.
34. Hallevi H, Barreto AD, Liebeskind DS, Morales MM, Martin-Schild SB, Abraham AT, et al; UCLA Intra-Arterial Therapy Investigators. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. *Stroke*. 2009;40:1780–1785.

Therapeutic Hypothermia After Recanalization in Patients With Acute Ischemic Stroke

Ji Man Hong, Jin Soo Lee, Hee-Jung Song, Hye Seon Jeong, Huimahn Alex Choi and Kiwon Lee

Stroke. 2014;45:134-140; originally published online November 7, 2013;
doi: 10.1161/STROKEAHA.113.003143
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Correction

The version of the article, "Therapeutic Hypothermia After Recanalization in Patients With Acute Ischemic Stroke" by Hong et al (*Stroke*. 2014;45:134–140) that published online ahead-of-print on November 7, 2013 contained an error in the author byline, figure 2, and in text. For the author byline, Dr Hye Seon Jeong's name appeared as, Hae-Sun Jung. In text, a duplication of thrombolysis in cerebral ischemia has been removed and a typographical error for Celsius Control Console has been changed to Alsius. This has been corrected in the online and print version of the article.

(*Stroke*. 2014;45:e12.)

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/01.str.0000438982.12807.b9**