Therapeutic Hypothermia After Recanalization in Patients With Acute Ischemic Stroke

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Background

- Therapeutic hypothermia (TH) is potently neuroprotective in experimental stroke models.
- Clinically proven to improve outcomes in patients after cardiac arrest and neonatal encephalopathy because of hypoxia-ischemia.
  - Preventing ischemia-reperfusion injury.
  - Providing neuronal protection.

Previous studies of TH

- No large randomized trials of TH in acute ischemic stroke exist.
- TH is associated with increased risk of pneumonia or infectious complications, longer duration of intensive care unit stay, and prolonged mechanical ventilation dependency
  - Did not in patients with cardiac arrest
  - Did not affect neurological outcome and intensive care unit survival

Purpose

- Investigate the clinical and radiological effects of therapeutic hypothermia in acute ischemic stroke patients after recanalization.

Methods – Patients selection

- Between 2010/3 – 2012/6, patients consecutively admitted to 2 tertiary care hospitals were enrolled.
- Inclusion criteria:
  (1) ischemic stroke involving the anterior circulation (NIHSS, ≥10)
  (2) acute infarction with diffusion-weighted imaging (DWI) confirmation
  (3) Endovascular recanalization (thrombolysis in cerebral ischemia, ≥2b) within 6 hours after symptom onset, or spontaneous recanalization.

Methods – Cooling protocol

- Either a endovascular cooling catheter (Alsius) placed in the inferior vena cava via a femoral venous sheath or a surface cooling device (Arctic Sun).
- Induction: cooling rate was set at maximum until 35°C then was set at 34.5°C.
- 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.

Methods – Imaging analysis

- Alberta Stroke Program Early CT Score
- Status of the recanalization was graded as thrombolysis in cerebral ischemia ≥2b
  - grade 2b: partial filling of one-half or greater of the occluded arterial distribution
- A 48-hour CT scan was obtained. Hemorrhagic transformation(HT) was classified into 4 subtypes.
- Brain edema: 3 grades
- MR scans including DWI for stroke burden were also undertaken on admission and 5 days after symptom.

Methods – Medical Complications

- All medical complications were recorded if they occurred during the therapeutic period.
  - Cardiac dysrhythmia
  - Electrolytes, and chemistry abnormalities
  - Coagulopathy (bleeding of any severity or disseminated intravascular coagulation)
  - Hypotension requiring vasopressor therapy
  - Deep vein thrombosis
  - Infectious complications

Methods – Outcome Assessment

- NIHSS scores
- 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.
- an mRS of 0 to 1 points versus 2 to 6 points.
- Ninety-day mortality

Results

- 75 patients (41 men; 66.2±15.4 years of age) who met the inclusion criteria; 39 patients in the TH group.
- Baseline, stroke risk factors, initial laboratory findings did not differ between TH and nonhypothermia groups.
- No differences of onset-to-CT time (*P=0.415) and vessel involvements (P=0.279).*

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)	

Results

- TH was associated with less HT and *had less cerebral edema.*
- The TH group had a higher proportion of good outcome.
- Mortality *and* hemicraniectomy rate *were not* different .

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.

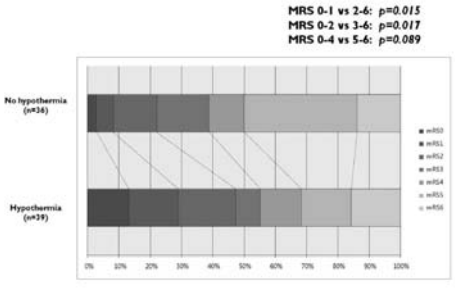

Figure 1. Distribution of 3-month modified Rankin Scale (mRS; from 0=no symptoms from stroke to 6=death) between patients who underwent recanalization with hypothermia and without hypothermia, indicating significant differences (mRS, 0–1 vs 2–6 with *P*=0.015; mRS, 0–2 vs 3–6 with *P*=0.017).

Results

- Overall medical complications did not differ between TH and nonhypothermia groups.
- Interestingly, pneumonia occurred 8% in TH and 31% in nonhypothermia (*P=0.004*).

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.

Results:

Multiple Regression Analysis for Good Outcome

- To evaluate prognostic associations with hypothermia and other variables.
  - factors at baseline
  - factors during the therapy
- TH *and* involvement of MCA M2 *were independent predictors* for good outcome.
- Absence of cerebral *and absence* of adverse events *as independent predictors for good outcome*

Discussion

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

Different TH protocol in the study

- Specifically targeted ischemia-reperfusion injury by selecting patients with angiographically proven, recanalized ischemic stroke.
- Chose a target temperature of 34.5°C.
- Had a relatively long duration (48 hours) of hypothermia and controlled rewarming (additional 48 hours) to mitigate cerebral edema and HT.
- Intubated and deeply sedated all of our patients to prevent pneumonia and shivering.

Strength of the study

- An antiedema mechanism to explain the beneficial effect of moderate TH in the treatment of severe space-occupying MCA infarction has been suggested.
- Corroborates similar antiedema properties of prolonged TH. (prevent perihemorrhagic edema in patients with large spontaneous intracerebral hemorrhage)
- 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.

Limitations

- Hidden biases between populations and differences in care between the 2 centers may exist.
- Differences in treatment protocols between the 2 centers.
- The inability to monitor neurological status in patients who are sedated and paralyzed.

Conclusions

- TH to be associated with a decreased risk of brain edema, HT, and better clinical outcome.
- A comprehensive protocol of TH 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.

Thanks for your attention.