Stroke

CLINICAL TRIALS

Mild Hypothermia After Endovascular Treatment for Acute Ischemic Stroke: A Pilot Randomized Controlled Trial

Jin-Heon Jeong, MD*; Jeong-Ho Hong, MD*; Sung-Il Sohn, MD; Hyungjong Park, MD; Jun Young Chang, MD; Kyu Sun Yum, MD; Jihoon Kang, MD; Moon-Ku Han, MD

BACKGROUND: Therapeutic hypothermia is a potent neuroprotective therapy that mitigates ischemic brain injury. This study aimed to investigate the safety and feasibility of mild therapeutic hypothermia after successful endovascular recanalization in patients with acute ischemic stroke due to major vessel occlusion.

METHODS: We conducted a prospective, multicenter, open-label pilot randomized clinical trial at 5 stroke centers in South Korea between December 2016 and November 2019. Patients with acute ischemic stroke who achieved successful recanalization within 8 hours of symptom onset were included. The participants were randomly assigned in a 1:1 ratio to receive either mild therapeutic hypothermia, targeted at 35 °C for 48 hours, or standard care. The primary objective was to assess feasibility and safety outcomes, including protocol adherence, achievement and maintenance of the target temperature, and adverse events related to the intervention. Exploratory efficacy outcomes included a modified Rankin Scale score of 0 to 2 at 3 months and neurological improvement (≥4-point reduction on the National Institutes of Health Stroke Scale score at discharge). Exploratory safety outcomes included mortality, hemorrhagic transformation, and any bleeding.

RESULTS: Forty patients were enrolled in this study, with 20 patients in each group. The target temperature was successfully achieved and maintained in all patients of the mild hypothermia group in accordance with the intervention protocol. At 3 months, the mortality rates were 5% in the mild hypothermia group and 0% in the control group (P=1). A modified Rankin Scale score of 0 to 2 was achieved in 70% and 65% of the mild hypothermia and control groups, respectively (P=0.736). Few adverse events (bradycardia and rhabdomyolysis) were more frequent in the mild hypothermia group but were manageable.

CONCLUSIONS: Mild hypothermia at 35 °C after successful recanalization via endovascular treatment in acute ischemic stroke is safe and feasible, despite some adverse events. This pilot study demonstrated that mild hypothermia is well tolerated in this patient population, and further study is needed to confirm its effectiveness.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: brain injuries ■ hemorrhage ■ hypothermia ■ ischemic stroke ■ reperfusion

Therapeutic hypothermia has demonstrated potent neuroprotective effects in experimental models of ischemic stroke, especially after ischemia-reperfusion injury.[1–4] These models have demonstrated that therapeutic hypothermia reduces infarct size and improves neurological outcomes. Moreover, therapeutic hypothermia is a standard treatment for cardiac arrest, which is a prime example of ischemia-reperfusion injury.[5]

Correspondence to: Moon-Ku Han, MD, PhD, Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea, 173, Gu Mi-ro, Seong-Nam, South Korea. Email mkhan@snu.ac.kr
*J.-H. Jeong and J.-H. Hong contributed equally.
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Nonstandard Abbreviations and Acronyms

HELMET	Mild Hypothermia After Endovascular Treatment in Acute Ischemic Stroke
IQR	interquartile range
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
tPA	tissue-type plasminogen activator

Both experimental and clinical studies have supported the efficacy of therapeutic hypothermia in reducing ischemia-reperfusion injuries after neonatal hypoxic-ischemic events and global cerebral ischemia postcardiac arrest.[5–7] The neuroprotective mechanisms include reducing cerebral metabolism and attenuating reperfusion injury, which are crucial in ischemic events.[4]

Since the updated acute stroke guidelines were released in 2015, endovascular treatment has become the standard of care for acute ischemic stroke.[8] Although this advancement has significantly improved clinical outcomes, concerns about reperfusion injury remain.[9–11] Despite various strategies being investigated to mitigate reperfusion injury, no definitive preventive measures have been established.[10,12–15] Although therapeutic hypothermia has the potential to reduce reperfusion injury, few studies have investigated its application in patients with ischemic stroke, particularly those who have achieved complete recanalization after endovascular treatment. We hypothesized that therapeutic hypothermia could reduce ischemia-reperfusion injury after endovascular treatment for ischemic stroke. This study aimed to investigate the safety and feasibility of mild therapeutic hypothermia after successful recanalization using mechanical endovascular treatment in patients with acute ischemic stroke and proximal arterial occlusion.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

The HELMET trial (Mild Hypothermia After Endovascular Treatment in Acute Ischemic Stroke) is a prospective, open-label, randomized, multicenter pilot study. The study protocol was approved by the ethics committee and internal review board of Seoul National University Bundang Hospital. Informed consent was obtained from all patients or their designated surrogates (Supplemental Methods). Eligible participants were randomly assigned in a 1:1 ratio to either the mild hypothermia or control group. Randomization was centralized to ensure allocation concealment, with a randomization table prepared for each institution using a random permuted block design. Mild hypothermia (32–35 °C) was applied, with the target temperature set at 35 °C to minimize potential side effects. Participants in the mild hypothermia group received therapeutic hypothermia targeting 35 °C for 48 hours, followed by a rewarming process within 30 hours. Although the patients and investigators were not blinded to the treatment assignment, the exploratory efficacy outcome (modified Rankin Scale [mRS] score at 3 months) was assessed by independent clinicians who were blinded to the treatment assignment.

Participants

The trial was conducted at 5 stroke centers in South Korea between December 2016 and November 2019. All centers followed a standardized critical pathway for thrombolysis.[8] Intravenous tPA (tissue-type plasminogen activator) was administered within 3 hours of symptom onset to patients without contraindications. Endovascular treatment was considered for patients with large vessel occlusions within 6 hours of symptom onset, regardless of intravenous tPA. Demographic data, vascular risk factors, laboratory results, and neurological scale scores were collected on admission.

This study included patients with acute ischemic stroke due to internal carotid artery or middle cerebral artery occlusion who achieved successful revascularization (defined as Thrombolysis in Cerebral Infarction grade 2b or 3) within 8 hours of symptom onset.[16] The inclusion criteria were adult patients aged 18 to 80 years with a National Institutes of Health Stroke Scale (NIHSS) score of 6 to 25 and a premorbid mRS score of ≤1. The exclusion criteria were as follows: absence of cerebral artery evaluation before endovascular treatment; emergency stent implantation in an intracranial or extracranial artery; transient ischemic attack or lacunar infarction; platelet count ≤75 000/mm^3; coagulopathy (prothrombin time and international normalized ratio >1.5); hemodynamic instability; acute myocardial infarction; acute unstable angina; severe heart failure (New York Heart Association classification ≥III); sepsis; pregnancy or lactation; premorbid mRS score ≥2; allergy or sensitivity to buspirone, dexmedetomidine, or meperidine; intracranial hemorrhage or hemorrhagic transformation on the initial computed tomography scan; brain tumors or central nervous system infections; participation in other studies within the past 3 months; or a life expectancy of <1 year.

Therapeutic Hypothermia Method

A surface cooling device (Arctic Sun 5000; BD) was used to maintain the target temperature. During induction, intravenous administration of 500 to 1000 mL of 4 °C normal saline was permitted. Mild hypothermia was maintained for 48 hours at a target temperature of 35±0.5 °C, with rewarming at a rate of 0.05 to 0.1 °C per hour. Shivering was strictly controlled using the bedside shivering assessment scale and the Columbia Anti-Shivering Protocol.[17] Core body temperature was monitored hourly using an esophageal thermometer.

Both groups received standard stroke management in accordance with international guidelines. Patients were closely monitored for potential adverse events, such as infection, coagulopathy, and electrolyte imbalance. Vital signs and serum glucose levels were assessed every 6 hours, whereas complete blood counts, serum electrolyte levels, and cardiac enzyme levels were tested daily.

Imaging Protocols

All patients underwent magnetic resonance imaging, including magnetic resonance angiography (or computed tomography angiography as an alternative), to assess their eligibility for endovascular treatment. Brain computed tomography was performed immediately after the endovascular treatment to check for hemorrhagic transformation. Follow-up brain computed tomography scans were performed the following day and 48 hours before rewarming. Follow-up brain magnetic resonance imaging was performed on days 5 to 7.

Statistical Analyses

Categorical variables are presented as numbers and percentages, whereas continuous variables are shown as means and SDs or medians and interquartile ranges (IQRs). Baseline characteristics and clinical outcomes were compared between the 2 groups using χ^2 and Fisher exact tests for categorical variables, and Student *t* test and Mann-Whitney *U* test for continuous variables. Details of the sample size calculation are provided in the Supplemental Methods. A $P<0.05$ was considered statistically significant. All data analyses were performed using SPSS version 27 (IBM Corporation, Armonk, NY).

Study Outcomes

The primary objective of this pilot study was to assess feasibility outcomes, including protocol adherence, achievement, and maintenance of the target temperature in the mild hypothermia group, and adverse events related to the intervention. Exploratory efficacy outcomes included a favorable prognosis, defined as an mRS score of 0 to 2 at 3 months, and neurological improvement, defined as a ≥4-point reduction on the NIHSS score at discharge. Exploratory safety outcomes included mortality at 3 months, symptomatic intracranial hemorrhage, any intracranial hemorrhage, and systemic hemorrhage.[18] Patients were monitored throughout their hospital stay to assess primary feasibility and safety outcomes, as well as exploratory safety and efficacy outcomes. The mRS score was assessed at a 3-month follow-up visit, with telephone interviews conducted if in-person visits were not feasible.

Role of the Funding Source

The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

We enrolled 40 patients: 20 in the mild hypothermia group and 20 in the control group. The baseline characteristics are summarized in Table 1. The flow of patient screening, enrollment, randomization, and analysis is summarized in Figure S1. All patients received the allocated intervention according to protocol, and there were no dropouts; all patients were included in the final analysis. The median ages were 66 (IQR, 60–74) years in the mild hypothermia group and 70 (IQR, 60–75) years in the control group. The proportion of males was high in both groups, with 75% in the mild hypothermia group and 70% in the control group. The baseline NIHSS scores were similar, with a median score of 17 (IQR, 15–20) in the mild hypothermia group and 15 (IQR, 11–19) in the control group. In both groups, 60% of patients received intravenous tPA.

All patients underwent endovascular treatment, with median onset-to-arrival times of 56 minutes in the mild hypothermia group and 66 minutes in the control group. The onset-to-puncture times were 149 and 154 minutes, respectively. Successful recanalization (Thrombolysis in Cerebral Infarction ≥2b) was achieved in all patients, with Thrombolysis in Cerebral Infarction 3 attained in 65% of the mild hypothermia group and 55% of the control group. Atrial fibrillation was present in 70% of the mild hypothermia group and 50% of the control group. Cardioembolism was the leading cause of stroke in 65% of the mild hypothermia group and 55% of the control group.

In the mild hypothermia group, the target temperature was achieved in all patients. The median durations for hypothermia induction, maintenance, and rewarming were 3.7 hours (IQR, 2–4.6), 49.7 hours (IQR, 45.4–49.6), and 24.5 hours (IQR, 20.2–30), respectively. The median time to reach the target temperature was 9.2 hours from symptom onset and 5.3 hours from recanalization. Body temperature was consistently maintained at 35 °C for 48 hours (Figure 1), whereas the control group had a mean body temperature of 37 °C. Shivering was managed according to the Columbia Anti-Shivering Protocol, and the proportion of patients treated at each step is summarized in Supplemental Results.

The exploratory efficacy outcome, a favorable prognosis (mRS score of 0–2) at 3 months, was achieved in 70% (14/20) of the mild hypothermia group and 65% (13/20) of the control group (Table 2; Figure 2). The exploratory safety outcome, mortality at 3 months, occurred in 1 (5%) patient in the mild hypothermia group and none in the control group. No significant differences were observed in the exploratory efficacy and safety outcomes.

Additional exploratory efficacy outcome, defined as an NIHSS score improvement of ≥4 points, was achieved by 80% (16/20) of the patients in both groups. Additional exploratory safety outcomes included hemorrhagic transformation in 30% (6/20) of the mild hypothermia group and 40% (8/20) of the control group, as well as any bleeding events in 15% (3/20) of the patients in both groups.

Table 3 details other adverse events. Bradycardia (heart rate <60 bpm) was significantly more frequent in the mild hypothermia group (90%, 18/20) than in the control group (55%, 11/20; $P=0.013$). Severe bradycardia (heart rate <40 bpm) occurred in 25% (5/20) of the mild hypothermia group and 5% (1/20) of the control group. Rhabdomyolysis was significantly more frequent in the mild hypothermia group (35%, 7/20) than in the control group (5%, 1/20; $P=0.044$). Pneumonia was

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Table 1. Characteristics of the Patients at Baseline

	Mild hypothermia group	Control group	
	n=20	n=20	*P* value
Age, y, median (IQR)	66 (60–74)	70 (60–75)	0.440*
Male	15 (75%)	14 (70%)	0.723
Premorbid mRS score=1	1 (5%)	0 (0%)	1.00†
Baseline NIHSS score, median (IQR)	17 (15–20)	15 (11–19)	0.119*
IV tPA	12 (60%)	12 (60%)	1
Onset-to-arrival time, min, median (IQR)	56 (36–172)	66 (42–181)	0.482*
Onset-to-IV tPA time, min, median (IQR)	75 (60–117)	90 (68–117)	0.326*
Onset-to-puncture time, min, median (IQR)	149 (105–255)	154 (103–266)	0.860*
Interval from onset to target temperature, h, median (IQR)	9.2 (6.9–11.2)		
Interval from recanalization to target temperature, h, median (IQR)	5.3 (4.4–7.7)		
Hypothermia period, h, median (IQR)	77.9 (71.2–83.9)		…
Induction duration	3.7 (2–4.6)		…
Maintain duration	49.7 (45.4–49.6)		…
Rewarming duration	24.5 (20.2–30)		…
Risk factors			
History of stroke or TIA	2 (10%)	3 (15%)	1.00†
Hypertension	10 (50%)	12 (60%)	0.525
Diabetes	3 (15%)	6 (30%)	0.451†
Hyperlipidemia	5 (25%)	4 (20%)	1.00†
Atrial fibrillation	14 (70%)	10 (50%)	0.197
Lesion side, left	8 (40%)	13 (65%)	0.113
Successful recanalization			
TICI 2b	7 (35%)	9 (45%)	0.519
TICI 3	13 (65%)	11 (55%)	
Site of occlusion			
Internal carotid artery	7 (35%)	6 (30%)	0.736
Middle cerebral artery	13 (65%)	14 (70%)	
Cause of stroke			…
Large artery occlusion	4 (20%)	2 (10%)	
Cardioembolic occlusion	13 (65%)	11 (55%)	
Undetermined or others	3 (15%)	7 (35%)	

IQR indicates interquartile range; IV, intravenous; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TICI, Thrombolysis in Cerebral Infarction; and tPA, tissue-type plasminogen activator.

*Mann-Whitney *U* test.

†Fisher exact test.

observed in 40% (8/20) of the mild hypothermia group and 15% (3/20) of the control group. Thrombocytopenia occurred in 25% (5/20) of the mild hypothermia group and 5% (1/20) of the control group.

DISCUSSION

The present pilot randomized controlled trial demonstrated the safety and feasibility of mild hypothermia after successful endovascular treatment in patients with acute ischemic stroke caused by major vessel occlusion. The target temperature was consistently achieved and maintained in all patients of the mild hypothermia group according to the intervention protocol. Notably, therapeutic hypothermia was successfully implemented without requiring intubation. Although adverse events were more frequent, they were manageable, and no significant differences were observed in exploratory outcomes between the groups. These findings support the feasibility of applying mild hypothermia in this specific patient group.

Our hypothesis was that employing mild hypothermia therapy might mitigate reperfusion injury after complete recanalization after endovascular treatment for major cerebral artery occlusion. The incidence of hemorrhagic transformation, a representative adverse effect of reperfusion injury, was lower in the mild hypothermia group than in the control group, but there was

Table 2. Efficacy and Safety Outcomes

	Mild hypothermia group n=20	Control group n=20	*P* value
Exploratory efficacy outcome			
mRS score of 0–2 at 3 mo	14 (70%)	13 (65%)	0.736
Improved neurological outcome	16 (80%)	16 (80%)	1.00*
Exploratory safety outcome			
Mortality at 3 mo	1 (5%)	0 (0%)	1.00*
Hemorrhagic transformation	6 (30%)	8 (40%)	0.507
HT-1	2 (10%)	5 (25%)	
HT-2	2 (10%)	2 (10%)	
PH-1	1 (5%)	1 (5%)	
PH-2	1 (5%)	0 (0%)	
Any bleeding (except ICH)	3 (15%)	3 (15%)	1.00*
GI bleeding	1 (5%)	2 (10%)	
Hematuria	2 (10%)	2 (10%)	

GI indicates gastrointestinal; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; and PH, parenchymal hemorrhage.
*Fisher exact test.

no statistically significant difference.[19] The results of our study indicated that mild hypothermia did not significantly improve the mRS scores at 3 months or the neurological outcomes at discharge. The small sample size may have limited the ability to detect meaningful differences. Frequent adverse events observed, even with mild hypothermia, may have diminished its potential benefits. Moreover, although most patients reached the target temperature at a median of 5.3 hours after recanalization, reperfusion injury likely began immediately, potentially limiting the protective effects of hypothermia.[1–3]

Experimental studies have shown that hypothermia provides neuroprotection after ischemic stroke by reducing infarct size and cerebral edema, and by attenuating inflammation, excitotoxicity, oxidative stress, and blood-brain barrier disruption.[20–28] Hypothermia can inhibit matrix metalloproteinase activity and stabilize the blood-brain barrier, thereby reducing the risk of hemorrhagic transformation.[23–25] In our study, the mild hypothermia group exhibited a lower incidence of hemorrhagic transformation compared with controls, supporting these experimental findings, although this did not translate into significant clinical improvement. Future large-scale trials should refine patient selection and optimize cooling protocols to maximize neuroprotection and safety, particularly in populations at high risk for reperfusion injury. Strategies to reduce systemic complications, such as selective brain cooling or maintaining normothermia, also warrant further investigation.

Several randomized controlled trials have investigated the effects of hypothermia on ischemic stroke. Previous studies have reported mixed results regarding the efficacy of hypothermia in improving the clinical outcomes of patients with stroke. An early study applying moderate hypothermia to patients with malignant ischemic stroke demonstrated a reduction in mortality compared with previous study results.[29] Conversely, another study showed that moderate hypothermia did not improve clinical outcomes in patients with major ischemic stroke (NIHSS score ≥15).[30] In studies applying hypothermia after IV thrombolysis to investigate its neuroprotective effects, no difference in mRS scores at 3 months was observed.[31] Similarly, a multicenter, randomized, phase III clinical trial of mild therapeutic hypothermia for acute ischemic stroke was terminated early due to futility.[32] Our study also failed to demonstrate significant functional benefits.

Unlike previous studies, our study included only patients with ischemic stroke who achieved complete reperfusion (Thrombolysis in Cerebral Infarction ≥2b) after successful endovascular treatment. This subset may benefit more from hypothermia due to the risk of reperfusion injury. We aimed to investigate this patient group and confirm the neuroprotective effects of hypothermia on reperfusion injury. Our study used mild hypothermia (target temperature of 35 °C) rather than moderate hypothermia, which carries a higher risk of adverse events. By targeting mild hypothermia, we aimed to balance neuroprotection with a reduced risk of adverse effects. Although the incidence rate of adverse events, such as severe bradycardia and rhabdomyolysis, was higher in the hypothermia group, these findings are consistent with the known adverse events of hypothermia therapy.[29,33] In addition, we demonstrated that mild hypothermia could be successfully administered without intubation or mechanical ventilation.[34,35]

Our study has some limitations. First, as a pilot trial with a sample size of 40 patients, it lacked the power to conclusively determine the efficacy of mild hypothermia in this population. Larger trials are required to confirm the effects of hypothermia in conjunction with endovascular treatment. Second, the study design was open-label with no blinding of investigators or patients. Considering the nature of hypothermia therapy, which involves the use of machines, complete blinding was impractical. We mitigated potential bias by having independent researchers assess the exploratory efficacy outcomes. Third, the duration of hypothermic therapy may have influenced the results. To minimize adverse effects, we applied mild hypothermia for 48 hours, although the duration could be extended at the discretion of the researchers. One patient underwent hypothermia for >48 hours due to hemorrhagic transformation, which may have affected the results. Fourth,

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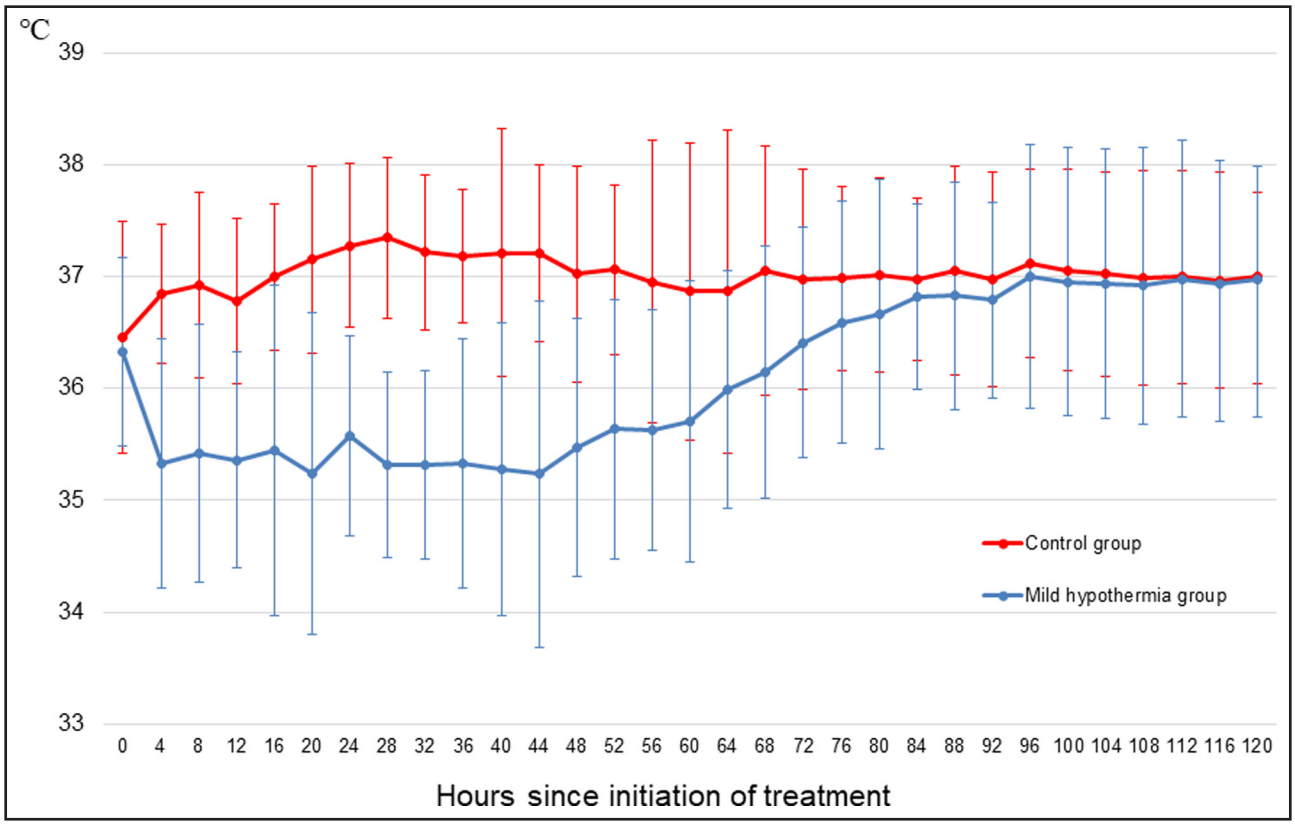

Figure 1. Body temperature of patients during 120 hours in the mild hypothermia and control groups.
The temperature curves show the means of all primary temperature in the mild hypothermia and control groups. The I bars indicate ±2 SD from the mean body temperature within each time interval.

the results may not apply to all patients with acute ischemic stroke. This study specifically examined the effects of mild hypothermia in patients who achieved complete recanalization through endovascular treatment, focusing on its role in reducing reperfusion injury after complete recanalization. Further studies are required to investigate the effects of hypothermia in patients with varying vessel statuses and to determine the optimal temperature for hypothermia treatment. Fifth, most patients tolerated mild hypothermia for 48 hours without the need for intubation; however, we did not systematically collect data on patient-reported experiences or comfort during the intervention.

In conclusion, the HELMET trial demonstrates that mild hypothermia after successful recanalization for acute ischemic stroke with major vessel occlusion is safe and feasible, despite some adverse events. This pilot study demonstrates that mild hypothermia is well tolerated in this patient population, and further study is needed to confirm its effectiveness.

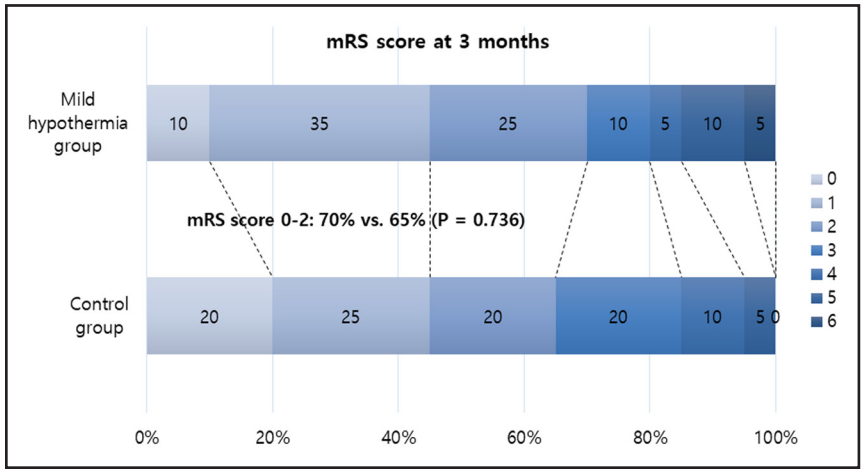

Figure 2. Efficacy outcome.
mRS indicates modified Rankin Scale.

Table 3. Other Adverse Events

Other adverse events	Mild hypothermia group n=20	Control group n=20	*P* value
Bradycardia (HR <60 bpm)	18 (90%)	11 (55%)	0.013
Severe bradycardia (HR <40 bpm)	5 (25%)	1 (5%)	0.182*
Hypotension (MAP <70 mm Hg)	8 (40%)	4 (20%)	0.168
Pneumonia	8 (40%)	3 (15%)	0.077
Other infections	1 (5%)	3 (15%)	0.605*
Hypoglycemia	2 (10%)	0 (0%)	0.487*
Thrombocytopenia (Plt <100 K)	5 (25%)	1 (5%)	0.182*
Increased cardiac enzyme	6 (30%)	2 (10%)	0.235*
Rhabdomyolysis	7 (35%)	1 (5%)	0.044*
Electrolyte imbalance	13 (65%)	13 (65%)	1
Hyponatremia	1 (5%)	0 (0%)	1*
Hypokalemia	10 (50%)	5 (25%)	0.191
Hypomagnesemia	2 (10%)	2 (10%)	1*
Hypophosphatemia	9 (45%)	11 (55%)	0.527*

HR indicates heart rate; MAP, mean arterial pressure; and Plt, platelet.
*Fisher exact test.

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Affiliations

Department of Intensive Care Medicine and Neurology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, South Korea (J.-H.J.). Department of Neurology, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, South Korea (J.-H.H., S.-I.S., H.P.). Department of Neurology, Asan Medical Center, South Korea (J.Y.C.). Department of Neurology, Chungbuk National University Hospital, Cheongju, South Korea (K.S.Y.). Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea (J.K., M.-K.H.).

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Disclosures

None.

Supplemental Material

Supplemental Methods
Table S1
Figure S1
CONSORT Checklist

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