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Feasibility and Safety of Mild Therapeutic Hypothermia in Poor-Grade Subarachnoid Hemorrhage: Prospective Pilot Study

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Therapeutic hypothermia (TH) improves the neurological outcome in patients after cardiac arrest and neonatal hypoxic brain injury. We studied the safety and feasibility of mild TH in patients with poor-grade subarachnoid hemorrhage (SAH) after successful treatment. Patients were allocated randomly to either the TH group (34.5℃) or control group after successful clipping or coil embolization. Eleven patients received TH for 48 hours followed by 48 hours of slow rewarming. Vasospasm, delayed cerebral ischemia (DCI), functional outcome, mortality, and safety profiles were compared between groups. We enrolled 22 patients with poor-grade SAH (Hunt & Hess Scale 4, 5 and modified Fisher Scale 3, 4). In the TH group, 10 of 11 (90.9%) patients had a core body temperature of < 36℃ for > 95% of the 48-hour treatment period. Fewer patients in the TH than control group (n = 11, each) had symptomatic vasospasms (18.1% vs. 36.4%, respectively) and DCI (36.3% vs. 45.6%, respectively), but these differences were not statistically significant. At 3 months, 54.5% of the TH group had a good-to-moderate functional outcome (0–3 on the modified Rankin Scale [mRS]) compared with 9.0% in the control group (P = 0.089). Mortality at 1 month was 36.3% in the control group compared with 0.0% in the TH group (P = 0.090). Mild TH is feasible and can be safely used in patients with poor-grade SAH. Additionally, it may reduce the risk of vasospasm and DCI, improving the functional outcomes and reducing mortality. A larger randomized controlled trial is warranted.

Keywords: Therapeutic Hypothermia; Target Temperature Management; Subarachnoid Hemorrhage; Cerebral Vasospasm; Delayed Cerebral Ischemia; Aneurysm; Rewarming

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a devastating, although uncommon, type of stroke with high morbidity and mortality rates (1). Preclinical studies have shown that therapeutic hypothermia (TH) is a promising treatment for ischemic stroke, and large-scale studies are currently examining the effects of hypothermia on the outcome of ischemic stroke (2-4). However, hypothermia as a treatment for hemorrhagic stroke is not fully understood. There is limited experimental and clinical evidence that TH effectively improves the clinical outcome for patients with SAH, except for a reduction in intracranial pressure (5-9). Induced hypothermia during aneurysm surgery is currently not routinely recommended, but may be a possible option in patients with good-grade aneurysmal SAH (10).

There are currently insufficient data to draw any conclusions on the benefits of TH, particularly in patients with poor-grade aneurysmal SAH. A high-quality randomized clinical trial of intraoperative mild hypothermia to improve postoperative neurological deficits in patients with poor-grade aneurysmal SAH might be feasible (11).

The aim of this pilot randomized controlled trial was to investigate the safety and feasibility of mild TH using endovascular or surface cooling devices in poor-grade SAH patients after successful clipping or coil embolization.

MATERIALS AND METHODS

Patient selection

We performed a single-center randomized controlled study to evaluate the safety and feasibility of mild TH in patients with poor-grade SAH. Patients with poor-grade SAH treated with microsurgical clipping or coil embolization at the Ulsan University Hospital, Ulsan, Korea were enrolled between May 2015 and February 2016. Computed tomography (CT) was performed on all patients and images were interpreted by the attending emergency physician. Patients with a suspected SAH were analyzed by CT angiography or intra-arterial digital subtraction angiography to identify potential intracranial aneurysms. Determination of aneurysm treatment was a multidisciplinary decision based on characteristics of the patient and aneurysm. Emergency microsurgical clipping or endovascular treatment with or without surgical decompression was performed within 24 hours of symptom onset in patients with SAH. We recorded pa-

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Table 1. Baseline characteristics and demographics in patients with mild hypothermia and controls

Parameters	Hypothermia (n = 11)	Control (n = 11)	*P* value
Age, yr*	43–73 (54.5)	33–72 (51.2)	0.562
Sex, No. (%)†			
Male	4 (36.4)	5 (45.5)	1.000
Female	7 (63.6)	6 (54.5)	
Weight, kg*	50–82 (62.4)	49–80 (63.7)	0.562
Height, cm*	154–177 (164.6)	152–175 (161.4)	0.300
BMI, kg/m^2*	17.84–26.17 (22.84)	19.38–29.05 (24.44)	0.116
Temperature baseline, °C	36.4–36.6 (36.5)	35.8–36.9 (36.5)	0.949
Time from symptom onset to induction of TH, median ± SD, hr	10 (4.5–12.0)	-	-
Time from TH to reach 34.5°C, median ± SD, hr	2 (0.5–7.0)	-	-
Modified Fisher Scale, mean*	3.9	4.0	0.748
Hunt & Hess Scale, mean*	4.2	4.1	0.748
WFNS Scale, mean*	4.6	4.7	0.748
Aneurysm, No. (%)†			1.000
Anterior circulation	9 (81.8)	8 (72.7)	
Posterior circulation	2 (18.2)	3 (27.3)	
Treatment, No. (%)			1.000
Coiling	8 (72.7)	9 (81.8)	
Clipping	3 (27.3)	2 (72.7)	

The distributions of categories and sample sizes were too small for statistically valid comparison.
BMI = body mass index, TH = therapeutic hypothermia, SD = standard deviation, WFNS = World Federation of Neurological Surgeons.
*Mann-Whitney U test; †Fisher's exact test.

tient characteristics at admission, including demographic data, neurological and neuroradiological data, risk factors for delayed cerebral ischemia (DCI), laboratory findings, in-hospital complications, and mortality (Table 1). We also measured the core body temperature of all patients with esophageal probe.

The inclusion criteria for this pilot trial were: 1) 18–80 years of age; 2) spontaneous SAH owing to ruptured intracranial saccular aneurysm; 3) complete aneurysm closure by microsurgical clipping or coil embolization within 24 hours of symptom onset; 4) poor-grade SAH defined as Hunt & Hess Scale 4, 5 and modified Fisher Scale 3, 4 at study enrollment; and 5) TH with achievement of target temperature within 1 hour of intervention (12).

The exclusion criteria were as follows: 1) older than 80 years of age; 2) systemic inflammation response syndrome or sepsis at study enrollment; 3) increased bleeding tendency or ongoing life-threatening hemorrhage; 4) multiple or dissecting aneurysms; and 5) disagreement among the patient's family about treatment.

Sample size and randomization

Considering the mortality rate of poor-grade SAH patients of nearly 50%, an alpha error of 0.05 and a 1:1 ratio of TH and control patients, the estimated sample size for a study with 70% power was 22 patients (11 in each group) in "a priori" power analysis with G*power software v.3.1 (13). Twenty-two patients were randomized in a 1:1 ratio based on using sealed and numbered envelopes using computational random-number generator from an independent third party. After informed consent was received, randomization was done by opening sealed allocation envelopes either "TH" or "control" treatment group.

TH protocol

Patients in the TH group were cooled with an endovascular cooling catheter (Zoll Medical, Chelmsford, MA, USA) placed in the inferior vena cava or with a surface cooling pad device (Arctic Sun; Medivance, Inc., Louisville, CO, USA) applied to the patients. The cooling procedure was initiated as soon as the catheter or cooling pad was installed after securing the ruptured aneurysm and continued until the core body temperature reached 34.5°C–35.0°C. The target temperature was 34.5°C, which avoided overcooling or severe complications (5,14). The core body temperature was recorded every hour using a thermometer at the tip of an esophageal probe. Shivering during mild TH was evaluated using the Bedside Shivering Assessment Scale and patients with a score > 1 was treated with deeper sedation or with a bolus of intravenous meperidine and muscle relaxant in refractory cases (15).

The cooling procedure was maintained for 48 hours then gradual rewarming was initiated. The target rate of active controlled rewarming was 0.5°C of temperature elevation every 12 hours with the reference to the other clinical trial protocol (rewarm target temperature 36.5°C) (4).

Imaging

SAH was initially diagnosed based on CT and aneurysms were identified using CT angiography or intra-arterial digital subtraction angiography. Comprehensive image analysis was performed

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by a neuroradiologist blinded to the laboratory and clinical data. Follow-up imaging was performed within 24 hours and consecutive scans were carried out at 48- to 72-hour intervals depending on the clinical aspects.

A macrovascular vasospasm was confirmed as an angiographic vasospasm by intra-arterial digital subtraction angiography. Transcranial Doppler blood flow measurements were routinely performed on the day of admission for baseline velocities and on the third and seventh postoperative days for monitoring cerebral vasospasm following SAH by an experienced neurosurgeon who specialized in ultrasound examination. Transcranial Doppler vasospasm was defined as the mean cerebral blood flow velocity in any vessel > 120 cm/s (16). Patients with a mean cerebral blood flow velocity ranging from 120 to 200 cm/s were suspected to have vasospasm, and transcranial Doppler was repeated every 2 days until the velocities normalized. In all cases of Doppler-based vasospasm with any evidence of clinical symptoms, angiographic vasospasm was confirmed by diagnostic subtraction angiography.

DCI was defined as the presence of the focal neurological deterioration or a decrease in the Glasgow Coma Scale of at least 2 points and an infarction on the CT scan that was not visible at admission or immediately following treatment (17).

Adverse events

The rate of adverse events occurring during hypothermia and until 5 days of admission is listed in Table 2. The vital signs of all patients were monitored and daily laboratory follow-up was conducted. Blood pressure and core body temperature were monitored at least every hour on the intensive care unit. Bradycardia was defined as a heart rate of less than 50/min; tachycardia was defined as any heart rate over 100/min; hypotension was defined as a mean arterial pressure < 80 mmHg; and hypertension was defined as a blood pressure of > 185/105 mmHg.

Pneumonia was defined as the following 3 criteria: 1) positive chest radiograph; 2) at least of 1 sign of acute infection (documented temperature > 38°C, white blood cell [WBC] count < 4,000 mm^3/L or > 12,000 mm^3/L; and 3) at least 2 of following: new onset purulent sputum, worsening symptom, rale or bronchial breath sounds, and worsening gas exchange (18). Congestive heart failure was identified by a positive finding on the chest radiograph or echocardiography. Acute myocardial infarction was defined by increased levels of creatinine kinase or troponin-T, and by an ST-T wave change on the electrocardiograph. A parenchymal hemorrhage of the brain was defined as any hemorrhage on the follow-up CT, and brain edema was identified as: 1) localized brain region hypodensities exerting mechanical pressure on the surrounding structures; 2) effacement of the hemispheric sulci and basal cisterns; or 3) bilateral disruption of the hemispheric gray-white matter junction at the level of the centrum semiovale (19). Hypokalemia (< 3.5 mmol/L), hyponatremia (< 135 mEq/L), thrombocytopenia (< 100,000/μL), hyperglycemia (> 200 mg/dL), hypoxemia (PaO_2 < 50 mmHg), hypercapnia ($PaCO_2$ > 45 mmHg), acidosis (arterial blood pH < 7.35), and alkalosis (arterial blood pH > 7.45) were also determined.

Table 2. Adverse events in hypothermia and control patients within 5 days of admission

Adverse events	Hypothermia (n = 11)	Control (n = 11)	*P* value
Shivering	4	0	0.090
Pneumonia	3	5	0.659
Urinary tract infection	0	0	-
Bradycardia	1	0	1.000
Tachycardia	6	10	0.149
Hypotension	4	2	0.635
Hypertension	4	5	1.000
Congestive heart failure	0	0	-
AMI	0	0	-
Electrolyte imbalance			
Hypokalemia	9	8	1.000
Hyponatremia	1	1	1.000
Thrombocytopenia	0	1	1.000
Hyperglycemia	2	7	0.080
Blood gas analysis			
Hypoxemia	1	4	0.311
Hypercapnia	3	3	1.000
Acidosis	5	3	0.659
Alkalosis	7	8	1.000

Treatment groups were compared with Fisher's exact test.
AMI = acute myocardial infarction.

Outcome assessment

The primary outcome measure for feasibility controlling temperature was the percentage of patients whose core body temperature remained at < 36°C for > 95% of the 48-hour treatment period. The clinical outcome, including modified Rankin Scale (mRS) scores, was also evaluated 3 months after admission. The mRS scores were evaluated by a neurosurgeon or stroke neurologist unrelated to this study. The clinical outcomes were classified as either good (mRS = 0–2) or poor (mRS = 4–6) 3 months after admission. The radiological outcome and mortality were evaluated after 1 month.

General neurocritical care treatment

All eligible patients received standard neurocritical treatment in our stroke center according to the guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage (20). Aneurysms were occluded by microsurgical clipping or endovascular coil embolization within the first 24 hours of admission. All patients receiving TH were sedated using midazolam in combination with remifentanil for analgesia. When the patient's temperature in the control group was exceeded above 37.8°C for > 1 hour, conventional fever management was begun with pro-

pacetamol intravenously.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. A 2-sided *P* value of < 0.05 was considered statistically significant. Baseline characteristics, demographics, and adverse events were compared between the patient groups by Mann-Whitney U and Fisher's exact tests. Radiological and clinical outcomes were evaluated using χ^2 and Fisher's exact tests. Continuous variables without normal distribution were reported as medians and interquartile ranges.

Ethics statement

This study protocol was reviewed and approved by the Institutional Review Board and Ethics Committee of Ulsan University Hospital, Ulsan, Korea (IRB No. 2015-03-025). Informed consent was obtained from patients' relatives or legal representatives to treat patients who met the inclusion criteria.

RESULTS

Seventy-five patients with aneurismal SAH were surgically managed in our institute between May 2015 and February 2016. Twenty-six patients had poor-grade SAH, and 22 of these patients were included in our study after being screened by the inclusion/exclusion criteria.

General demographics

Twenty-two patients (9 males, 13 females; average age 52.82 ± 10.18 years) met the inclusion criteria. Eleven patients were randomly assigned to the TH group and 11 patients to the control group. Baseline characteristics did not differ between the TH and control groups (Table 1). Additionally, there were no differences in the location and treatment of the aneurysm between the 2 groups (*P* = 1.000).

Feasibility of TH

We accomplished the primary outcome in 10 out of 11 patients

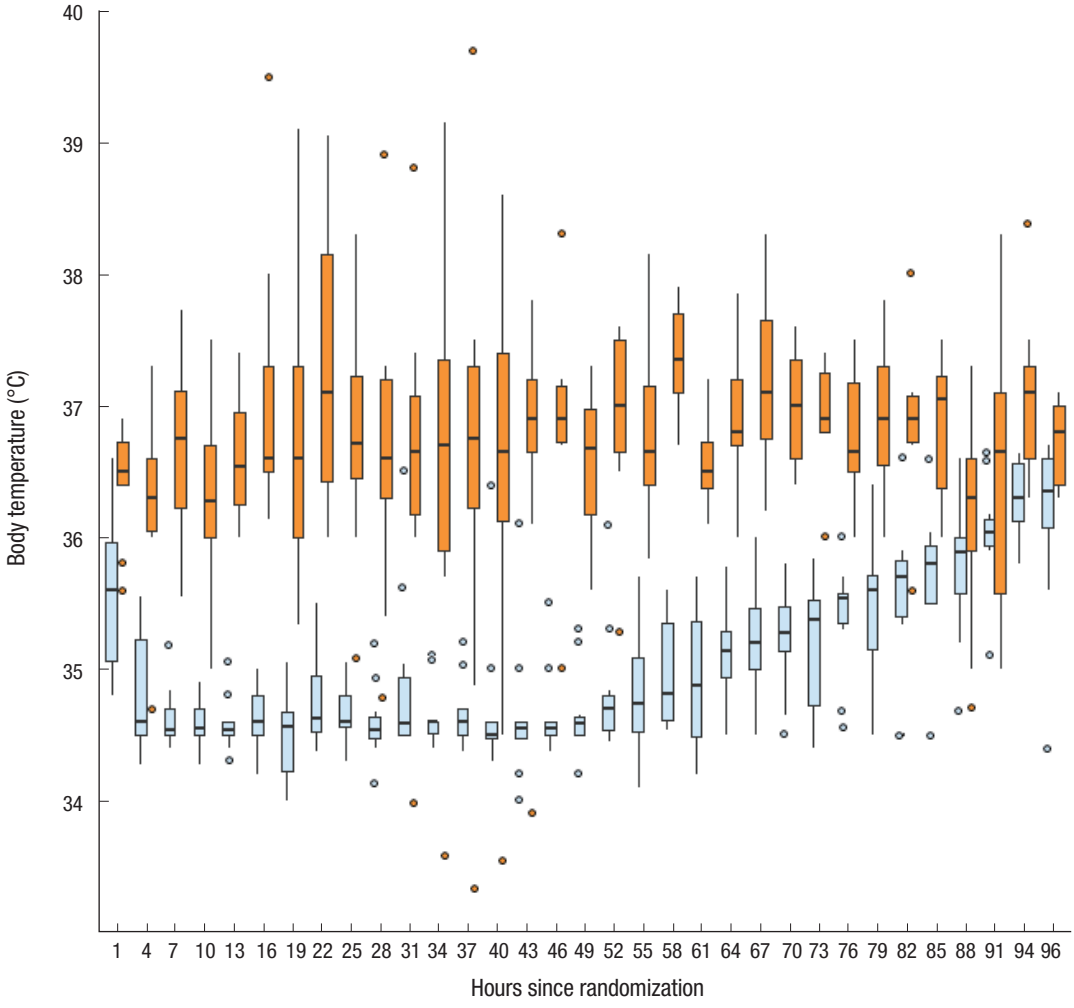

Fig. 1. Comparison of core body temperature changes in TH and control.

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Table 3. Radiological and clinical outcomes in hypothermia and control patients

Outcomes	Hypothermia (n = 11)	Control (n = 11)	*P* value
Parenchymal hemorrhage*	8	6	0.659
DCI	4	5	1.000
Symptomatic vasospasm*	2	4	0.635
VP shunt for delayed hydrocephalus*	2	2	1.000
mRS at 3 mon*	1–5 (3.3)	2–6 (4.8)	0.089
mRS (0–2)*	3 (27.3)	1 (9.1)	0.586
mRS (0–3)*	6 (54.5)	1 (9.1)	0.063
mRS (4–6)†	5 (45.5)	10 (90.9)	0.063
Mortality at 1 mon*	0	4	0.090

DCI = delayed cerebral ischemia, VP = ventricular-peritoneal, mRS = modified Rankin Scale.
*Fisher's exact test; †Chi-squared test.

receiving TH. The median time from symptom onset to induction of TH was 10 hours (range, 4.5–12.0 hours). Six patients receiving TH reached a core body temperature of < 36°C in a median time of 2 hours (0.5–7.0 hours) and the core temperature was well maintained at 33.4°C–36.0°C (34.6°C ± 0.34°C). Three patients in the TH group (27.2%) were cooled using an intravascular cooling device. After cooling, patients were warmed up for 45 hours (range, 21–57 hours) (Fig. 1). Only one patient was not warmed up actively because the patient regained consciousness and TH was terminated at 48 hours after induction of hypothermia. No technical malfunction of the cooling devices was identified.

Safety of TH

Overall adverse events were more common in the control group (n = 74) compared with the TH group (n = 62). However, the occurrence of each individual adverse event did not differ significantly between the TH and control group (Tables 2 and 3). In particular, pneumonia was reported in 3 patients from the TH group (27.2%) and in 5 patients in the control group (45.5%) (P = 0.659). All pneumonia patients were successfully treated with empirical antibiotics. Hyperglycemia occurred in 2 patients in the TH group (18.1%) and in 7 patients in the control group (63.6%) (P = 0.080), despite the continuous intravenous administration of insulin. No significant differences in other laboratory findings were observed between the TH and control groups (Table 2).

Radiological outcomes

In the TH group, 10 patients had adverse radiological events: 8 parenchymal hemorrhages, 4 delayed cerebral infarctions, 2 symptomatic vasospasms, and 2 cases of delayed hydrocephalus treated with ventricular-peritoneal (VP) shunting. Patients in the TH group had fewer symptomatic vasospasms (18.1% vs. 36.4%; P = 0.635), and DCI (36.3% vs. 45.6%; P = 1.000) compared with the control group. However, radiological outcomes were not significantly different between the 2 groups (Table 3).

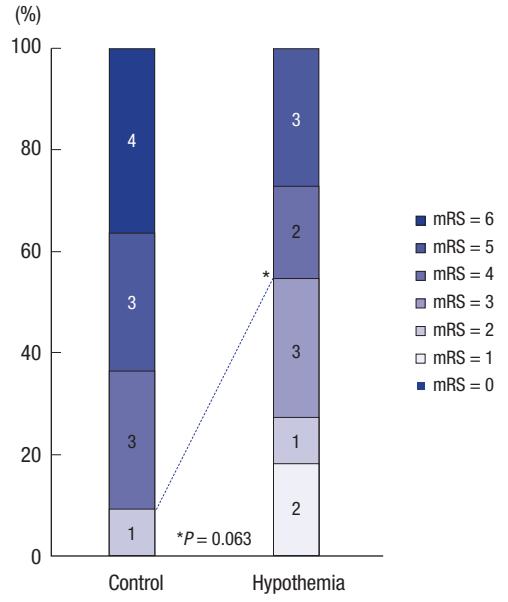

Fig. 2. Distribution of 3-month mRS scores of hypothermia (n = 11) and control patients (n = 11).
mRS = modified Rankin Scale.
*P = 0.063.

Functional outcome and mortality

There was a higher proportion of good-to-moderate outcomes in the TH group compared with the control group (mRS ≤ 3 at 3 months, 54.5% vs. 9.1%; P = 0.063) (Table 3, Fig. 2). The frequency of poor outcomes (mRS = 4–6) was doubled in the control group (45.5% vs. 90.9%; P = 0.063) (Table 3, Fig. 2). The overall mRS scores were not significantly different at 3 months (P = 0.090). The mortality rate was higher in the control group at 1 month (0.0% vs. 36.4%; P = 0.090).

DISCUSSION

This study is the first randomized controlled trial to investigate the safety and feasibility of mild TH using well-controlled equipment on patients with poor-grade SAH after successful intervention. Mild TH treatment of poor-grade SAH reduced symptomatic vasospasm and DCI, which were associated with better clinical outcomes. Additionally, we identified serious adverse events that were not significantly different between the groups during therapy.

Our TH protocol had 4 important differences from recent studies: 1) a poor-grade group rather than a good-to-moderate grade group was analyzed; 2) the target core body temperature was 34.5°C; 3) hypothermia treatment was performed within 1 hour after (not during) the intervention; and 4) TH was maintained and controlled rewarming was performed for 48 hours to prevent imminent rebound brain edema and pyrexia.

Recent clinical studies of SAH patients have demonstrated that TH is an additional limited treatment for refractory vaso-

spasm and DCI rather than an acute major treatment strategy (21-23). However, many aspects of hypothermia as a treatment for SAH remain unknown. Until recently, induced hypothermia during surgical treatment of aneurysm was not routinely recommended. It may represent a reasonable option in selected cases (class III; level of evidence B) (20).

We observed limited effects of TH following SAH, which is in contrast to the findings of ischemic stroke and post cardiac arrest care. We believe that the discrepancy between our findings and previously published findings can be explained by variations in the severity of hemorrhage and different hypothermia protocols described in previous studies. We hope, demonstrating a successful clinical outcome of TH in severe SAH would make this approach more applicable to the general SAH patient population.

When and how TH is administered after hospital admission should also be considered. Treatment of SAH with TH has been mostly reported before and during intervention (5,6,12,22). However, patient with poor-grade SAH are at higher risk of re-bleeding compared to good-grade SAH (5). Hypothermia can impair blood clotting and induces platelet dysfunction at temperature ≤ 35°C. Bleeding diathesis and ongoing bleeding are contraindications for the use of TH (24). Nevertheless, we assumed applying TH in poor-grade SAH patient before securing the aneurysm might carry a significant re-bleeding risk. Early securing of the aneurysm minimizes its risk of re-bleeding (20). Therefore, we induced TH in selected patients following proper intervention to secure the ruptured aneurysm and reduce the risk of bleeding. Nonetheless, TH was induced earlier (within 24 hours) in our study compared with previous studies (within 48 hours) (14).

The ideal target temperature, initiation, and duration of TH for treating SAH have not been well established. Following cardiac arrest, the current guidelines recommend a target temperature of 32–36°C. TH should be initiated as soon as possible and maintained for at least 24 hours after the return of spontaneous circulation (25). We selected a target temperature of 34.5°C to avoid overcooling and unexpected complications while still maintaining the neuroprotective effect of mild TH in accordance with previous findings (8,26). Some experts advocate cooling at a slightly higher temperature of 34.5°C–35.0°C in patients with suspected or active bleeding (27). TH was maintained for 48 hours followed by gradual rewarming of 0.5°C every 12 hours to manage clinical deterioration after brain ischemic events (4,12,22).

Fever is very common during neurocritical treatment, affecting 30%–60% of patients with ischemic stroke, traumatic brain injury, intracerebral hemorrhage, and SAH (28,29). Many clinical studies have confirmed that fever is an independent predictor of adverse outcomes following stroke and post-anoxic injury after cardiac arrest (7,29-32). Additionally, the pathophysiological response to SAH is a marked reduction in and increased fluctuation of blood flow to the brain parenchyma, which causes hypoxic damage through changes in the levels of certain intermediate substances (33). Additionally, the brain is vulnerable to oxygen deficiency; thus, deprivation of oxygen will cause neuronal necrosis, apoptosis, and lethal brain edema, resulting in neurological deficits.

We can recommend application of TH for patients with poor-grade SAH because such treatment can control fever and provide neuroprotection. Hypothermia is a highly promising treatment during neurocritical care. TH reduced the risk of cerebral edema and hemorrhagic complications and improved clinical functional outcome after ischemic stroke (4,24,34). Studies on human patients have shown that mild intraoperative hypothermia can reduce the production of reactive oxygen radicals by leukocytes, thereby diminishing cell damage during the process of inflammation (35).

This pilot study evaluated the feasibility and safety of TH in SAH patients. The mean time it took to reach the target temperature was faster in our study (4 hours to 34.5°C) compared with a previous study (48 hours to 35°C) (14). Most patients in the TH group were rewarmed for 45 hours. Only one patient did not remain stable during TH with an automatic temperature control device. This patient regained consciousness and TH was terminated after consultation with the neurosurgeon.

Major adverse events did not differ significantly between groups in our study. TH can induce undesirable physiological changes and adverse effects, such as hypotension, electrolyte imbalance, cardiovascular events, impaired coagulation function, and increased infection risk (36). In our study, the rate of pneumonia was lower in our study compared with previous findings (14,37). This might be explained by differences in the duration of TH between the present study and previous studies (5,7,14). All pneumonia patients were successfully treated with empirical antibiotics.

A positive finding from our study is the reduced risk of vasospasm and DCI. Decreased DCI and vasospasm in TH group compared with control group has been described previously (6,14,38). The mortality at 1 month was higher in the control group and good-to-moderate functional outcomes were more frequent in the TH group at 3 months. However, our study sample did not have enough statistical power to demonstrate a significant difference. We hope that future studies will demonstrate that TH can be effective in treating SAH patients.

Our study has several limitations. First, this was a pilot study and should be interpreted with caution. Second, the observed clinical benefits of hypothermia were limited because of the small sample size. A larger sample size may be needed to identify a meaningful difference between TH and control groups. Third, despite well-designed neurocritical care treatment guidelines, a hidden bias may exist between TH and control groups in critical care because the treating physicians were not double

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blinded. Fourth, the induction time of TH was confined after successful intervention. Fifth, the different use of cooling devices was not reflected in TH group.

In conclusion, in this prospective pilot study, mild TH can be feasible and safely used in patients with poor-grade SAH. The rate of adverse events during TH was similar to standard care of poor grade SAH, therefore TH is an acceptable treatment. We also found that mild TH after successful intervention may reduce the risk of vasospasm and DCI, and lead to improved functional outcomes and reduced mortality in patients with poor-grade SAH. In the future, larger randomized controlled studies should be conducted to determine the safety and clinical impact of TH in poor-grade SAH patients following successful intervention.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Choi W, Kwon SC. Data curation: Choi W, Kwon SC, Lee WJ. Formal analysis: Choi W, Kwon SC. Funding acquisition: Kwon SC. Investigation: Choi W, Kwon SC, Choi B, Lee H, Park ES, Ahn R. Writing - original draft: Choi W, Kwon SC. Writing - review & editing: Choi W, Kwon SC.

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