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Prophylactic, Endovascularly Based, Long-Term Normothermia in ICU Patients With Severe Cerebrovascular Disease

Bicenter Prospective, Randomized Trial

Gregor Broessner, MD; Ronny Beer, MD; Peter Lackner, MD; Raimund Helbok, MD; Marlene Fischer, MD; Bettina Pfausler, MD; Janelle Rhorer, MS; Lea Küppers-Tiedt, MD; Dietmar Schneider, MD; Erich Schmutzhard, MD

Background and Purpose—We sought to study the effectiveness and safety of endovascular cooling to maintain prophylactic normothermia in comparison with standardized, stepwise, escalating fever management to reduce fever burden in patients with severe cerebrovascular disease.

Methods—This study was a prospective, randomized, controlled trial with a blinded neurologic outcome evaluation comparison between prophylactic, catheter-based normothermia (CoolGard; ie, body core temperature 36.5°C) and conventional, stepwise fever management with anti-inflammatory drugs and surface cooling. Patients admitted to 1 of the 2 neurointensive care units were eligible for study inclusion when they had a (1) spontaneous subarachnoid hemorrhage with Hunt & Hess grade between 3 and 5, (2) spontaneous intracerebral hemorrhage with a Glasgow Coma Scale score ≤ 10 , or (3) complicated cerebral infarction requiring intensive care unit treatment with a National Institutes of Health Stroke Scale score ≥ 15 .

Results—A total of 102 patients (56 female) were enrolled during a 3.5-year period. Fifty percent had a spontaneous subarachnoid hemorrhage, 40% had a spontaneous intracerebral hemorrhage, and 10% had a complicated cerebral infarction. Overall median total fever burden during the course of treatment was 0.0°C hour and 4.3°C hours in the catheter and conventional groups, respectively ($P < 0.0001$). Prophylactic normothermia did not lead to an increase in the number of patients who experienced a major adverse event. No significant difference was found in mortality and neurologic long-term follow-up.

Conclusions—Long-term, catheter-based, prophylactic normothermia significantly reduces fever burden in neurointensive care unit patients with severe cerebrovascular disease and is not associated with increased major adverse events. (*Stroke*. 2009;40:00-00.)

Key Words: stroke ■ fever ■ normothermia ■ endovascular cooling

Fever, defined as elevation of body core temperature $>38^{\circ}\text{C}$, is common in critically ill patients.^{1,2} More than 80% of all neuro-intensive care unit (ICU) patients will develop at least 1 febrile episode during hospitalization.^{3,4} Importantly, it has been shown that even elevation of brain temperature alone is markedly deleterious in the setting of intracranial pathology, such as ischemic stroke or intracerebral hemorrhage (ICH).⁵⁻⁷ Multiple pathophysiologic mechanisms of hyperthermia have been discussed to be potentially harmful: enhanced release of excitatory neurotransmitters, exaggerated free oxygen-radical production, blood-brain barrier breakdown, increased ischemic depolarization in the focal ischemic penumbra, enhanced inhibition of protein

kinases, and worsening of cytoskeletal proteolysis leading to secondary and worsening primary (neuronal) injury.^{5,8-11} Even under physiologic circumstances, brain temperature exceeds body core temperature by 0.5°C to 1.5°C.^{12,13} In some individuals with severe brain injury and body core temperature $>38^{\circ}\text{C}$, this difference may exceed 2.5°C.¹⁴ Temperatures beyond 40°C cause transient vasoparalysis in humans, resulting in cerebral metabolic uncoupling and loss of pressure-flow autoregulation.¹⁵ All of these aspects suggest that it might be beneficial to start treatment of fever in patients with severe brain injury at an early stage or even to maintain normothermia prophylactically. In many diseases, fever is an independent predictor of unfavorable outcome,

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and therefore, early treatment of hyperthermia has nowadays become the standard of care.^{2,6,16–18} Currently, various techniques, including antipyretic drugs, surface cooling, and intravascular devices, are used alone or in combination to treat fever.^{18–23} All of these procedures have certain advantages and disadvantages; their selection may depend, beside others, on the standard level of care, patient comfort, disease severity, nursing workload, comorbidities, and last but not least, financial considerations. Intravascular devices have been shown to be superior in maintaining hypothermia with a significantly lower variation of target temperature.²⁴ Although short-term hypothermia is nowadays considered to improve outcome in patients after resuscitation from cardiac arrest, data on prolonged hypothermia in patients with acute intracranial pathology are controversial.²¹ Because severe adverse effects of mild to moderate hypothermia (ie, body core temperature 33°C to 35°C) may outweigh its beneficial effects in ICU patients with various diseases, the use of therapeutic hypothermia is still under debate.^{25,26} Given this uncertainty, it seemed reasonable to study whether maintaining prophylactic normothermia may be both efficacious and safe.

This prospective, pilot trial was designed to investigate the efficacy and safety of prophylactic long-term normothermia (ie, maintaining body core temperature at 36.5°C) with an intravascular device compared with a strict escalating, conventional fever management protocol in patients with life-threatening cerebrovascular disease.

Patients and Methods

Setting

From January 2003 to June 2006, patients were enrolled in the study performed at 2 centers. The University Hospital Innsbruck (Austria) is a 1600-bed tertiary care hospital with ≈74 000 admissions per year. The neuro-ICU is a 10-bed neurocritical care unit admitting, on a nonelective basis, ≈450 to 500 adults per year.

The University Hospital Leipzig (Germany) is a 1350-bed tertiary care hospital with ≈45 000 admissions per year. The neuro-ICU is a 9-bed neurocritical care unit admitting, on a nonelective basis, ≈450 adults per year. The affiliated stroke unit has 12 beds and admits ≈750 stroke patients per year.

Study Approval

The study protocol was approved by each institutional review board (protocol No. UN1734). According to Austrian law, informed consent was obtained either before enrollment of competent patients or as soon as the patient regained competence, the treatment having already been started. For the Leipzig center, informed consent was obtained either from competent patients or, when noncompetent, from their next of kin, according to German law.

Inclusion/Exclusion Criteria

Patients admitted to 1 of the 2 centers were determined through screening to be eligible and were prospectively enrolled. Only patients with spontaneous subarachnoid hemorrhage (SAH) with Hunt & Hess grade 3 to 5, spontaneous ICH with a Glasgow Coma Scale (GCS) score ≤10, or cerebral infarction (CI) with a National Institutes of Health Stroke Scale score (NIHSS) ≥15 requiring ICU management (ie, basilar artery occlusion, large territorial middle cerebral artery infarction) were prospectively enrolled in the study. To be enrolled, requirement of a central venous line was obligatory. Exclusion criteria were age <18 years, active sepsis syndrome, history of heparin-induced thrombocytopenia, moribund status, contraindication for the placement of a central venous line catheter,

thrombolytic treatment within the past 12 hours, spontaneous hypothermia <35.5°C at enrollment, active cardiac dysrhythmia resulting in hemodynamic instability, impossibility of measuring the urinary bladder temperature, and pregnancy.

Baseline Data, Sample Size, Enrollment, and Randomization

According to the study protocol, the sample size for this trial of ≈50 patients in each group (100 total) provides 99% power to detect a difference in mean fever burden of 25°C hours (SD=5.6°C hours). Even if one assumes a dropout rate as high as 30%, 50 patients in each group still provides 95% power to detect a smaller difference of 5°C hours (SD=5.6°C hours) between the 2 groups. One hundred two patients were randomized in a 1:1 ratio based on a permuted blocked randomization list to provide an approximate balance between treatment groups. The randomization list was stratified by site. Randomization was done by opening sealed allocation envelopes (indicating either “endovascular” or “conventional” treatment group). The baseline examination consisted of patient demographic data; documentation of body core temperature; body mass index; general physical examination, including blood pressure, pulse rate, and ECG; as well as a neurologic examination/scoring (GCS, Hunt & Hess grade, and NIHSS) by a full-time neurologist/neurocritical care specialist. At enrollment, brain imaging (ie, cerebral computed tomography scan, magnetic resonance imaging), chest x-ray, and extensive blood analyses were performed. Patients were then randomized to the 2 treatment arms: (1) conventional fever management or (2) prophylactic endovascularly based normothermia with a target temperature of 36.5°C (CoolGard 3000 and CoolLine devices; Alsius Corp, Irvine, Calif).

Cooling Procedure

In all patients, body core temperature (ie, primary temperature) was measured in the urinary bladder by a Foley catheter (Kendall, Curity, Tyco Healthcare Group). In both treatment arms, the fever threshold was set at a temperature >37.9°C for >1 hour, and exceeding this threshold led to additional predefined conventional, stepwise fever management described next. This predefined management was applied similarly in the device and control groups when body temperature exceeded this threshold. The threshold of 37.9°C was chosen because treatment of fever is often begun at this temperature in clinical routine. When a patient exceeded the threshold temperature for >1 hour, standardized, stepwise fever management was begun, starting with acetaminophen 500 mg PO or by nasogastric tube. When temperature remained above the threshold for another hour, fever management was escalated on an hourly basis with ibuprofen 500 mg PO, followed by pethidine 100 mg IV and finally with a surface cooling blanket (Blanketrol, Cincinnati Sub-Zero). When the temperature dropped below 37.9°C at any time, the stepwise management was stopped. For patients who did not respond to this fever management, the entire procedure was repeated again, starting with acetaminophen.

In patients randomized to the endovascular treatment group, the intravascular device (CoolLine) was inserted into the subclavian vein, and positioning was verified by chest x-ray. Temperature control was initiated with a maximum delay of 2 hours after randomization. Target temperature was set at 36.5°C to maintain normothermia, and endovascular treatment was strictly adhered to for the respective period (ie, 168 hours for ICH and CI and 336 hours for SAH patients). The technical aspects of the CoolGard system and CoolLine catheter have been described in detail before.^{2,18,20} When the CoolGard device was insufficient for maintaining normothermia and patient temperature was >37.9°C, conventional fever management was added as described previously.

All patients randomized to the conventional treatment group received a conventional subclavian catheter (Arrow International Inc, Reading, Pa) and a urinary bladder Foley catheter for measurement of primary temperature (Kendall, Curity, Tyco Healthcare Group). Patient temperature was documented hourly, and fever threshold was set at a bladder temperature >37.9°C, because this

level often indicates treatment of fever in clinical routine. Thus, we believe that the control group reflects clinical routine treatment of fever. When a patient exceeded the threshold temperature for >1 hour, standardized, stepwise fever management was begun as described. Prophylactic administration of fever management (acetaminophen, ibuprofen, pethidine, surface cooling blanket) in the control group at 36.5°C (ie, physiologic level) is, to the best of our knowledge, clinically not indicated and would have led to “over-medication” with respect to ethical considerations and not only in terms of side effects. Shivering was treated after a predefined treatment algorithm with pethidine 100 mg IV in both treatment arms.

Statistical Methods

The distributions of continuous variables are summarized, along with means, SDs, and quartiles. Categorical variables are summarized with counts and frequencies. Baseline demographics and disease characteristics were compared between the 2 treatment groups by *t* tests for continuous data, a Fisher’s exact test for sex, an exact Pearson’s χ^2 test for cerebrovascular disease, and exact Kruskal-Wallis tests for Hunt & Hess, NIHSS, and GCS scores. No adjustments were made for multiplicity. Adverse events were compared between treatment groups with Fisher’s exact test. Adverse event summaries exclude events that started before randomization or that were missing onset and stop dates.

The primary efficacy end point for this study was fever burden, as defined by the area under the temperature curve (AUC). The calculation of fever burden has been described in detail previously.¹⁸ The primary analysis compared the median AUC (fever burden) between the 2 treatment groups. For patients in either the ICH group or the severe CI group, fever burden was assessed between randomization and day 7 (168 hours) or until neuro-ICU discharge, whichever was earlier. Fever burden for patients with SAH was assessed until day 14 (336 hours) or neuro-ICU discharge, whichever was earlier. The relatively long duration of the study period, especially in SAH patients, was chosen on the assumption that if prophylactic normothermia proved to have neuroprotective effects, it should be applied while the risk of secondary (neuronal) injury leading to impaired outcome was highest.

Because fever burden distributions were not normally distributed, the median total fever burden, or AUC, and the median daily fever burden in each treatment group were compared with Wilcoxon rank-sum tests. Each patient’s daily fever burden was calculated as the patient’s total fever burden divided by the total number of hours the patient was in the neuro-ICU and then multiplied by 24 hours. In the control group, temperatures were recorded hourly for each patient. The CoolGard device recorded the temperature more frequently (every minute). To compare the treatment groups consistently, calculation of fever burden was based on hourly temperature data.

Secondary outcome criteria of nursing intensity and neurologic status were summarized descriptively, and neurologic status was compared between treatment groups. Neurologic status based on the modified Rankin Scale (MRS) and the Glasgow Outcome Scale (GOS) was compared between treatment groups by exact Wilcoxon-Mann-Whitney tests. Nursing intensity for each patient was defined as the total percentage of a 24-hour shift (two 12-hour shifts combined) that the nurse required for temperature management for that patient; boxplots were used to summarize descriptively the distribution of nursing intensity over time for the 2 treatment groups.

Safety was assessed by collecting information about both adverse events and major adverse events (MAEs). An MAE was defined as bacteremia, malignant cerebral edema, pneumothorax, sepsis, or death. All adverse events were centrally coded as either infectious or noninfectious. Safety events were summarized as adverse events and MAEs, in relation to study treatment, and for 3 study intervals: randomization through discharge from the neuro-ICU, randomization through 30 days, and randomization through 6 months.

For data analysis, audits of source data were conducted by an independent institute. Statistical analyses were performed with SAS

Table 1. Demographics, Baseline Characteristics, and Interventions

Baseline Variable	CoolGard (n=51)	Control (n=51)	P Value
Diastolic BP, mean±SD, mm Hg	79.3±19.4	80.3±13.5	0.77
Systolic BP, mean±SD, mm Hg	142.2±25.7	149.3±31.1	0.21
Pulse, mean±SD, per minute	76.0±20.0	76.6±14.9	0.86
Weight, mean±SD, kg	77.9±14.6	77.5±12.8	0.88
Height, mean±SD, cm	170.1±7.7	170.5±9.3	0.81
BMI, mean±SD, kg/m ²	26.8±4.9	26.6±5.2	0.81
Age, mean±SD, y	58.5±12.8	58.7±14.4	0.95
Body core temperature, mean±SD, °C	36.3±0.82	36.2±0.94	0.50
Sex, n (%), male	21 (41)	25 (49)	0.55
Cerebrovascular disease, n (%)			0.60
CI	4 (8)	6 (12)	
ICH	19 (37)	22 (43)	
SAH	28 (55)	23 (45)	
Hunt & Hess score (for SAH patients), n (%)			0.51
3	16 (57)	15 (65)	
4	4 (14)	3 (13)	
5	7 (25)	4 (17)	
Missing	1 (4)	1 (4)	
NIHSS score (for CI patients), n (%)			0.47*
19	0	1 (17)	
22	2 (50)	0	
33	0	1 (17)	
35	0	1 (17)	
37	0	1 (17)	
Missing	2 (50)	2 (33)	
GCS (for ICH patients), n (%)			0.47
3	7 (37)	11 (50)	
4	2 (11)	1 (5)	
5	2 (11)	3 (14)	
6	3 (16)	0	
7	0	1 (5)	
8	2 (11)	4 (18)	
9	0	2 (9)	
10	3 (16)	0	
Interventions in SAH patients, n (%)			0.06
Coiling	21 (75)	13 (57)	
Clipping	0 (0)	4 (17)	
None	7 (25)	6 (26)	
Interventions in ICH patients, n (%)			0.73
Neurosurgery	7 (37)	7 (32)	
None	12 (63)	15 (68)	
Interventions in CI patients, n (%)			0.74
Reperfusion therapy	1 (25)	1 (17)	
None	3 (75)	5 (83)	

BP indicates blood pressure; BMI, body mass index. Treatment groups were compared with *t* tests (continuous variables), Fisher’s exact tests (dichotomous variables), exact Pearson’s χ^2 tests (unordered categorical variables), and exact Kruskal-Wallis tests (ordered categorical variables). All tests were based on a 2-sided Type I error of 0.05.

*The distributions of categories and sample size were too small for a statistically valid comparison.

Table 2. Any Adverse Event by Infection Status

Infection Type	Through Neuro-ICU Discharge			Through Day 30			Through Month 6		
	CoolGard n (%)	Control n (%)	P Value	CoolGard n (%)	Control n (%)	P Value	CoolGard n (%)	Control n (%)	P Value
Overall	48 (94)	43 (84)	0.20	49 (96)	44 (86)	0.16	49 (96)	44 (86)	0.16
Infectious	48 (94)	40 (78)	0.04	49 (96)	41 (80)	0.03	49 (96)	41 (80)	0.03
Noninfectious	19 (37)	20 (39)	1.00	19 (37)	20 (39)	1.00	19 (37)	20 (39)	1.00

Denominators for percentages were based on 51 patients in each treatment group. Patients who experienced >1 event of a given infection type or >1 event overall were counted only once for that infection type and overall infection type. The number of patients at each time point who experienced at least 1 adverse event of a given infection type were compared with Fisher's exact tests and a 2-sided Type I error rate of 0.05.

9.1 (SAS/STAT 9.1, SAS Institute Inc, Cary, NC; 2004) or StatXact 8.0 (Cytel Studio, Cambridge, Mass; 2007) software.

Results

Demographics

The study enrolled 102 patients (51 in each treatment group), with 55% female, a mean (\pm SD) age of 58 (\pm 13.6) years, and a mean (\pm SD) weight of 78 (\pm 13.6) kg (Table 1). All patients were white. Baseline demographics were evenly distributed across both treatment groups.

Fifty-one patients (55% CoolGard, 45% control) were enrolled with spontaneous SAH with a median Hunt & Hess score of 3, 41 patients (37% CoolGard, 43% control) had spontaneous ICH with a median GCS of 4, and 10 patients (8% CoolGard, 12% control) had complicated CI. Median NIHSS score in patients with complicated ischemic stroke was 28. Although the trial did not stratify enrollees at randomization by disease type, the trial was relatively balanced within each of the SAH, ICH, and CI disease groups.

Safety

At least 1 adverse event between randomization and the 6-month follow-up was reported for 49 (96%) CoolGard and 44 (86%) control patients ($P=0.16$, Table 2). At least 1 infectious adverse event was reported for 49 (96%) CoolGard and 41 (80%) control patients ($P=0.03$). Of the patients who

experienced an adverse event, all but 2 experienced at least 1 event before discharge. The most frequent adverse events experienced at least once during the study across both treatment groups were pneumonia (70%) and urinary tract infections (33%). Three CoolGard patients experienced adverse events that were considered by the investigators to be at least remotely related to the study procedure (1 patient had 2 instances of a positive blood culture for coagulase-negative staphylococci, 1 patient had a positive blood culture for bacteremia, and 1 patient had an episode of shivering); all events resolved with no permanent sequelae.

An MAE was reported for 25 (49%) CoolGard patients and 20 (39%) control patients ($P=0.43$, Table 3). Bacteremia and pneumothorax were each reported for 10% or fewer patients in each group. One patient in the CoolGard group experienced a case of malignant cerebral edema, and 1 patient in the control group experienced sepsis and multiorgan failure. Of the events that were coded either infectious or noninfectious, the 2 groups were similar in the number of patients during the study who experienced an infectious MAE (4 CoolGard, 8 control; $P=0.36$) or a noninfectious MAE (17 CoolGard, 11 control; $P=0.27$). Of the 45 patients with an MAE, most (35 patients) experienced at least 1 event within the first 30 days. Seven patients experienced MAEs that were considered to be related to the study treatment: 2 controls and 1 CoolGard

Table 3. Major Adverse Events

Infection Type	Adverse Event Term	Through Neuro-ICU Discharge			Through Day 30			Through Month 6		
		CoolGard n (%)	Control n (%)	P Value	CoolGard n (%)	Control n (%)	P Value	CoolGard n (%)	Control n (%)	P Value
Overall	Any MAE	16 (31)	16 (31)	1.00	18 (35)	17 (33)	1.00	25 (49)	20 (39)	0.43
	Death	10 (20)	8 (16)	0.80	12 (24)	10 (20)	0.82	18 (35)	14 (27)	0.52
Infectious	Any MAE	3 (6)	6 (12)	0.49	4 (8)	6 (12)	0.74	4 (8)	8 (16)	0.36
	Bacteremia	3 (6)	5 (10)	0.72	3 (6)	5 (10)	0.72	3 (6)	5 (10)	0.72
	Death	0	0		1 (2)	0	1.00	1 (2)	2 (4)	1.00
Noninfectious	Sepsis	0	1 (2)	1.00	0	1 (2)	1.00	0	1 (2)	1.00
	Any MAE	12 (24)	10 (20)	0.81	13 (25)	11 (22)	0.82	17 (33)	11 (22)	0.27
	Cerebral Edema	1 (2)	0	1.00	1 (2)	0	1.00	1 (2)	0	1.00
Unknown	Death	9 (18)	8 (16)	1.00	10 (20)	9 (18)	1.00	13 (25)	9 (18)	0.47
	Pneumothorax	4 (8)	2 (4)	0.68	4 (8)	2 (4)	0.68	5 (10)	2 (4)	0.44
Unknown	Death	1 (2)	0	1.00	1 (2)	1 (2)	1.00	4 (8)	3 (6)	1.00

Denominators for percentages were based on 51 patients in each treatment group. Patients who experienced >1 event of a given infection type or >1 event overall were counted only once for that infection type and overall infection type. The number of patients at each time point who experienced at least 1 adverse event of a given infection type were compared with Fisher's exact tests and a 2-sided Type I error rate of 0.05.

Table 4. Fever Burden

Disease Category	Total Fever Burden in Hours (AUC)			Fever Burden per Patient per Day		
	CoolGard (n=51)	Control (n=51)	<i>P</i> Value	CoolGard (n=51)	Control (n=51)	<i>P</i> Value
Overall			<0.0001			<0.0001
No.	51	51		51	51	
Mean±SD	1.5±3.3	9.3±14.5		0.18±0.38	1.27±2.63	
Median	0.0	4.3		0.0	0.54	
SAH			<0.0001			<0.0001
No.	28	23		28	23	
Mean±SD	1.5±3.3	10.9±13.9		0.14±0.26	1.40±3.16	
Median	0.0	7.5		0.0	0.54	
Non-SAH (CI and ICH)			0.0005			0.0004
No.	23	28		23	28	
Mean±SD	1.5±3.4	8.0±15.1		0.23±0.50	1.17±2.15	
Median	0.0	3.9		0.0	0.55	
CI			0.59			0.75
No.	4	6		4	6	
Mean±SD	5.4±7.3	2.1±2.8		0.81±1.03	0.33±0.39	
Median	3.0	0.8		0.49	0.21	
ICH			<0.0001			<0.0001
No.	19	22		19	22	
Mean±SD	0.7±1.2	9.6±16.7		0.10±0.18	1.40±2.38	
Median	0.0	4.6		0.0	0.66	

P values were based on Wilcoxon rank-sum tests, $\alpha=0.05$. Fever was defined as body temperature $>37.9^{\circ}\text{C}$.

patient had an episode of bacteremia, and 1 control and 3 CoolGard patients developed pneumothorax.

Thirty-two patients died during the study (18 [35%] CoolGard, 14 [27%] control; $P=0.52$, Table 3). Eighteen deaths occurred before discharge (10 [20%] CoolGard, 8 [16%] control). No death was considered to be related to the study treatment, and no death before discharge was considered due to infection.

Efficacy (Fever Burden)

As shown in Table 4, the median total AUC during the trial was higher in the control group (4.3°C hours) than in the CoolGard group (0.0°C hour; mean AUC, 9.3°C hours control vs 1.5°C hours CoolGard). The overall excessive median fever burden (AUC control–AUC CoolGard) was 4.3°C hours (Wilcoxon rank-sum test, $P<0.0001$). Although randomization was not stratified by disease type, post hoc analyses of fever burden by disease type suggested similar differences for both SAH patients (median difference of 7.5°C hours, $P<0.0001$) and non-SAH patients (median difference of 3.9°C hours, $P<0.005$). Similarly, the median fever burden per patient per day was less in the CoolGard group (0.0°C hour per patient per day) than in the control group (0.54°C hour per patient per day) ($P<0.0001$; mean AUC, 1.27°C hours control vs 0.18°C hour CoolGard) with similar differences for both SAH and non-SAH patients.

Nursing Intensity

The Figure summarizes nursing intensity for a 24-hour shift during each day of the study period for patients in both

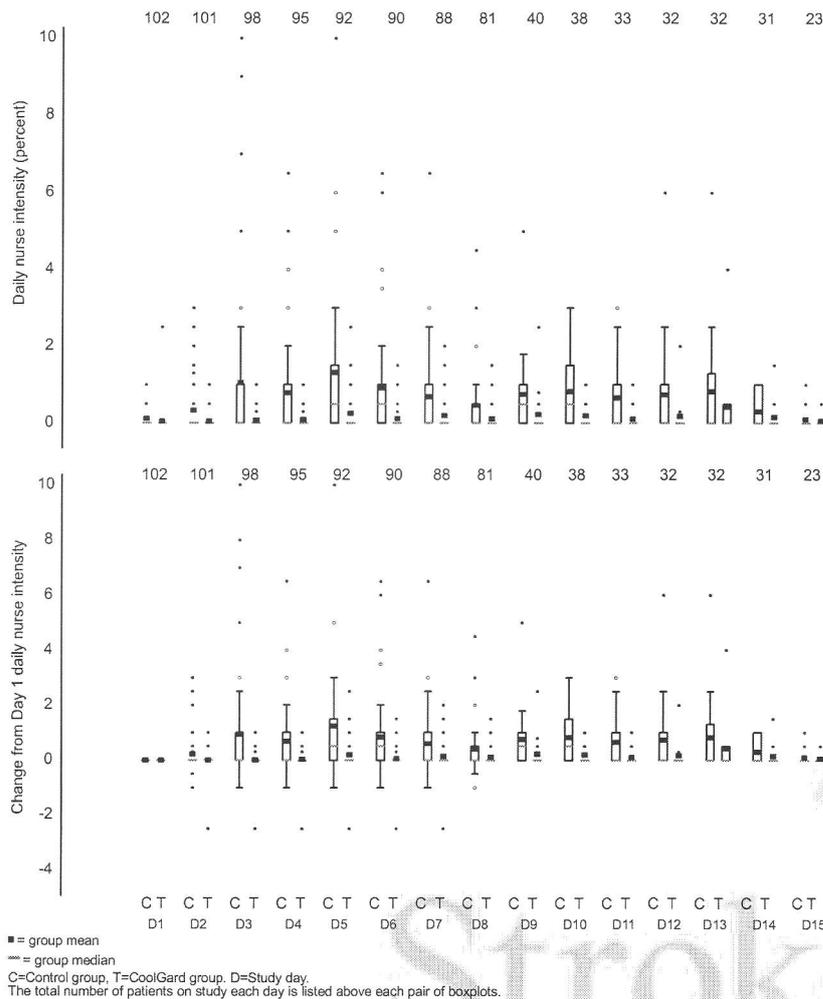
treatment groups. For each of the 15 study days, a boxplot for each treatment group indicates the daily nursing intensity as a percentage of a 24-hour shift as well as the corresponding change from baseline in percentage of a 24-hour shift. The boxes represent the 25th and 75th percentiles surrounding the median, the bars extending from the boxes represent the majority of the distribution of the data, and the dots extending past the bars indicate outliers in the data. Throughout the study period, the boxplots for the control group were spread farther apart. This indicates more variability in the percentage of time needed for temperature management beginning on day 3, which is consistent with typical fever management in neuro-ICU patients. In contrast, the boxplots for CoolGard patients required a consistently low percentage of nursing time for temperature management throughout the study period.

Neurologic Assessment

Table 5 summarizes the GOS and MRS scores for patients through month 6. At the 6-month follow-up visit, 17 (33%) CoolGard patients and 21 (41%) control patients had GOS scores of either 4 or 5. Similarly, 14 (27%) CoolGard and 15 (29%) control patients had MRS scores of 0 to 2. Scores between treatment groups were similar at discharge, day 30, and month 6 ($P>0.40$ for all Wilcoxon-Mann-Whitney tests for both GOS and MRS at each time point).

Duration of Stay in Neuro-ICU

The 2 treatment groups did not differ in the number of days between randomization and discharge from the neuro-ICU.



The mean number of days (\pm SD) in the neuro-ICU was 29.5 (\pm 25.8) in the CoolGard group and 24.2 (\pm 18.4) in the control group (t test, $P=0.24$). The median length of stay was 22 days in the CoolGard group and 21 days in the control group (maximum stay, 153 days for 1 CoolGard patient and 84 days for 1 control patient). Within the first 30 days of the study, 31 CoolGard patients and 39 control patients had been discharged from the neuro-ICU. When a patient died before discharge, the death date was used for calculating the duration of stay in the NICU.

Discussion

Maintaining Normothermia

This prospective, randomized trial was designed to study the efficacy and safety of prophylactic, catheter-based, long-term normothermia in patients with life-threatening cerebrovascular disease. Fever is usually defined as elevation of body core temperature $>38^{\circ}\text{C}$.^{1,2} Numerous studies in humans and animals have shown that fever is an independent predictor of unfavorable short- and long-term outcomes in various diseases, especially in patients with severe neurologic illness.²⁷⁻²⁹ Therefore, combating hyperthermia, especially in ICU patients, seems to be a primary treatment goal.^{30,31} To

the best of our knowledge, this is the first study to test the safety and efficacy of prophylactically applied, intravascular, sustained, long-term normothermia in comparison with a control group being treated with a standardized, stepwise, conventional antipyretic regimen adhering strictly to a predefined protocol. Baseline characteristics, demographic data, and interventions were evenly distributed in the 2 treatment arms (Table 1). The primary outcome measure was fever burden, defined as the AUC when body temperature exceeded the fever threshold of 37.9°C . The endovascular treatment was statistically significant ($P<0.0001$) in reducing fever burden in the overall analysis and in the respective subgroups, with the exception of severe ischemic stroke. Even though the control group received standardized, conventional fever management with nonsteroidal anti-inflammatory drugs and surface cooling, the intravascular device led to a median difference of 4.3°C hours in overall fever burden and in the subgroup of SAH patients, an even more impressive median difference of 7.5°C hours. These results clearly demonstrate that an endovascular cooling approach is significantly superior to antipyretic treatment with anti-inflammatory drugs in combination with conventional surface cooling. Thus, if a patient has severe cerebrovascular disease and a central

Table 5. Neurologic Function

	Discharge		Day 30		Month 6	
	CoolGard n (%)	Control n (%)	CoolGard n (%)	Control n (%)	CoolGard n (%)	Control n (%)
GOS						
Death	9 (18)	8 (16)	12 (24)	10 (20)	18 (35)	14 (27)
Persistent vegetative state	6 (12)	7 (14)	3 (6)	4 (8)	0	3 (6)
Severe disability	25 (49)	24 (47)	21 (41)	21 (41)	9 (18)	9 (18)
Moderate disability	8 (16)	7 (14)	7 (14)	6 (12)	8 (16)	9 (18)
Good recovery	3 (6)	5 (10)	2 (4)	5 (10)	9 (18)	12 (24)
Intubated	0	0	3 (6)	1 (2)	0	0
Lost to follow-up	0	0	2 (4)	1 (2)	7 (14)	4 (8)
Missing	0	0	1 (2)	3 (6)	0	0
<i>P</i> value	0.81		0.55		0.41	
MRS						
No symptoms	0	0	1 (2)	1 (2)	3 (6)	4 (8)
No significant disability	3 (6)	5 (10)	2 (4)	4 (8)	6 (12)	8 (16)
Slight disability	2 (4)	3 (6)	1 (2)	3 (6)	5 (10)	3 (6)
Moderate disability	8 (16)	3 (6)	8 (16)	3 (6)	3 (6)	4 (8)
Moderately severe disability	9 (18)	7 (14)	8 (16)	7 (14)	6 (12)	7 (14)
Severe disability	20 (39)	25 (49)	13 (25)	18 (35)	3 (6)	7 (14)
Death	9 (18)	8 (16)	12 (24)	10 (20)	18 (35)	14 (27)
Intubated	0	0	3 (6)	1 (2)	0	0
Lost to follow-up	0	0	2 (4)	1 (2)	7 (14)	4 (8)
Missing	0	0	1 (2)	3 (6)	0	0
<i>P</i> value	0.78		0.92		0.51	

Denominators for percentages were based on 51 patients in each treatment group. *P* values were based on exact Wilcoxon-Mann-Whitney tests comparing each treatment group's distribution of GOS or MRS scores at each time point and did not include patients who were either intubated, lost to follow-up, or had missing GOS or MRS scores. All comparisons were based on a two-sided Type I error rate of 0.05.

venous line is indicated, clinicians might consider placing an intravascular device because it combines efficacious temperature control and central venous access.

Safety

Although overall mortality was slightly higher in the endovascular group (18 [35%] vs 14 [27%] deaths), there was no significant difference either before discharge from the neuro-ICU (10 deaths CoolGard vs 8 deaths control, $P=0.80$) or at the 6-month follow-up (18 deaths CoolGard vs 14 deaths control, $P=0.52$) between the respective treatment arms. It must be kept in mind that only patients with life-threatening cerebrovascular disease were included in this study. Variations in mortality and high mortality rates are accepted and inherent for such a patient population.^{32,33} This lack of a difference in neuro-ICU mortality suggests that device-related mortality is rather unlikely. No differences were observed for either overall adverse events or MAEs. CoolGard patients in this study, however, experienced an increased proportion of infectious adverse events (CoolGard 96% vs control 80%, $P=0.03$), but all such events were considered either mild or moderate and resolved with no sequelae. Therapeutic hypothermia may be associated with increased risk for infections due to immunosuppression.³⁴ Whether this also holds true for prophylactic normothermia is still under debate and should be investigated in future

prospective trials addressing this question. However, for MAEs, the rates of neither major infectious nor noninfectious adverse events differed between the 2 treatment arms. The only noninfectious MAE to occur nominally more frequently in the CoolGard group was pneumothorax, but the frequency did not differ statistically between the 2 groups ($P=0.44$). This may be explained by the fact that patients randomized to the CoolGard group more often needed an additional central venous line because the CoolLine only provides 3 "working" lumina, and therefore, the risk for pneumothorax was increased in this group. All reported pneumothoraces were detected during the study period.

Neurologic Functional Outcome

Although we were successful in achieving the primary end point with a significant reduction of fever burden by intravascular prophylactic normothermia, the study did not lead to improved neurologic outcome at the 6-month follow-up. Various reasons must be considered when interpreting this observation. First, this study was designed to discriminate a potential difference in fever burden between the 2 treatment arms. In a pilot study, the difference was up to 10-fold; based on those data, the estimated case rate for this study was 100 patients.¹⁸ It might be speculated that the difference in long-term neurologic outcome is much smaller, and therefore, the number of patients in the current study was far too small

to discriminate a difference. Especially for the given neurologic diseases (SAH, ICH, CI), the initial severity of the disease itself is the strongest predictor for long-term outcome, and therefore, it might be assumed that differences in outcomes are very small.³⁵ Globally, mortality in patients with spontaneous SAH ranges from 32% to 67% and has been reported to be as high as 42% in patients with spontaneous ICH.^{32,33,36,37} For patients with severe grades of these diseases (SAH Hunt & Hess ≥ 3 and ICH GCS ≤ 10), the observed neuro-ICU mortality was much lower, being 20% (SAH) and 16% (ICH) (35% vs 27% at 6-month follow-up) in the CoolGard and conventional groups, respectively. Therefore, an additional reduction in mortality in the neuro-ICU in this study by means of normothermia seems even more difficult to achieve. The control group was treated by strictly following a standardized, stepwise, fever management protocol, and these patients received significantly more anti-inflammatory drugs. This treatment approach can therefore be classified as active control and might also have had an additional effect on outcome. In animal models, inhibition of cyclooxygenase through nonsteroidal anti-inflammatory drugs reduced infarct size after induced focal cerebral ischemia.^{38,39} The underlying pathophysiologic concept is still unclear, but inhibition of intercellular adhesion molecule-1 and the effects of nonsteroidal anti-inflammatory drugs on platelets and endothelial function are possible.³⁹ Especially for patients with SAH, a systemic inflammatory response syndrome, even in the absence of infection, is common and independently associated with symptomatic vasospasm and worse outcome.⁴⁰ Finally, it is unclear whether and to what extent the use of anti-inflammatory drugs in critical care patients interacts with inflammatory processes and thereby modifies the course of the diseases.

A major limitation of our study was the lack of a predefined rewarming regime. CoolGard treatment was stopped immediately after the 168 or 336 hours of normothermia. Many patients experienced a rebound temperature elevation after this abrupt discontinuation. After the planned study period, however, temperature data were not collected consistently for all patients in this study. Today, it is accepted that such a rebound effect may nullify the potential neuroprotective effect.^{41,42} This important issue requires further study.

Because of the treatment procedures, blinding of clinical staff was not possible. Nevertheless, we believe in the stability of our results, given that fever management was strictly performed according to a predefined protocol and the neurologist evaluating neurologic outcome was blinded regarding treatment allocation.

Conclusions

We present a bicenter prospective, randomized, controlled trial of prophylactic long-term normothermia (36.5°C) with an endovascular device versus a standardized algorithm with per-protocol escalation of stepwise fever management in critically ill patients with severe cerebrovascular diseases. The intravascular device significantly reduced fever burden. MAEs were evenly distributed between the 2 treatment arms. This is the first study to show that endovascularly based, prophylactic normothermia maintained for 168 to 336 hours

is feasible and efficacious in neurocritical care patients. Although significantly reducing the fever burden, we did not find a significant difference in neurologic outcome or overall rate of adverse events. Future studies may investigate different target temperatures or the additional use of anti-inflammatory drugs in combination with physical cooling, such as endovascular devices, in patients with severe stroke.

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Disclosures

None.

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