Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system

Michael N. Diringer, MD; for the Neurocritical Care Fever Reduction Trial Group

Context: **Elevated temperature worsens injury in experimental focal and global ischemia and brain trauma. Fever is common in patients with acute neurologic illness and independently predicts poor outcome. Conventional means of treating fever are not very effective in this population.**

Objective: **To study the effectiveness of a catheter-based heat exchange system in reducing elevated temperatures in critically ill neurologic and neurosurgical patients.**

Design, Intervention, Setting, and Population: **This was a prospective randomized, nonblinded trial that compared conventional treatment of fever (acetaminophen and cooling blankets) with conventional treatment plus an intravascular catheter-based heat exchange system (Alsius, Irvine, CA). Patients admitted to one of 13 neurologic intensive care units in academic medical centers were eligible if they a) suffered subarachnoid hemorrhage, intracerebral hemorrhage, ischemic infarction, or traumatic brain injury; b) had a temperature >38°C on two occasions or for >4 continuous hrs; and c) required central venous access.**

Main Outcome Measure: **The fever burden (area under the curve >38°C) for 72 hrs was compared in an intention to treat analysis. Safety of the catheter system was monitored.**

Results: **A total of 296 patients were enrolled over 20 months. Forty-one percent had subarachnoid hemorrhage, 24% had traumatic brain injury, 23% had intracerebral hemorrhage, and 13% had ischemic stroke. The groups were matched in terms of age, body mass index, sex, and Glasgow Coma Scale score distribution. Fever burden was 7.92 vs. 2.87°C-hrs in the conventional group and catheter groups, respectively (64% reduction, $p < .01$). There was no higher rate of infection or the use of sedatives, narcotics, or antibiotics in the catheter group. The catheter did not significantly increase risk to the patient beyond that of a central catheter.**

Conclusions: **The addition of this catheter-based cooling system to conventional management significantly improves fever reduction in neurologic intensive care unit patients. (Crit Care Med 2004; 32:559–564)**

KEY WORDS: fever; head injury; subarachnoid hemorrhage; intracerebral hemorrhage; ischemic stroke; central venous catheter

Elevated temperature worsens outcome in experimental models of cerebral ischemia and brain trauma; this is associated with increased levels of excitotoxins and oxygen radicals, destabilization of cell membranes, and increased number of abnormal electrical depolarizations (1–5). Even an increase in temperature of 0.5°C results in a greater zone of injury and neuronal loss (5–8). Fever is common in critically ill neurologic and neurosurgical patients, and its causes include not only infections but also the release of endogenous pyrogens due to neuronal injury or the presence of blood in the cerebral parenchymal, ventricles, and subarachnoid space.

Fever is an independent predictor of poor outcome in patients with ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage (9–14). The impact of fever control on clinical outcome, however, has not yet been tested, in large part due to the lack of an effective means to control fever. Despite this, taking measures to reduce fever is recommended by guidelines for the management of ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and traumatic brain injury (15–18). The most commonly used antipyretic is acetaminophen, although aspirin, ibuprofen, or indomethacin are used when the risk of bleeding is considered low.

Acetaminophen is not very effective at preventing or reducing fever. When high-dose acetaminophen was given prospectively to ischemic stroke patients, the average temperature during the first 24 hrs after admission was 0.4°C lower than placebo-treated patients and no different after 5 days (19). In a prospective, randomized study of 220 febrile neurologic intensive care unit (ICU) patients, half were treated with acetaminophen and half with acetaminophen plus air-cooled blanket therapy. In the acetaminophen group about one third of patients remained febrile, and the air-cooled blanket did not improve fever control (20).

Physical means used to lower temperature include surface cooling with water or air-filled cooling blankets, ice packs, nasogastric or rectal lavage, and alcohol baths. These methods may have limited efficiency due to skin vasoconstriction and shivering. In one study, (20) 12% of patients refused or were unable to tolerate the air-cooled blanket therapy. External cooling with rotary fans, cooling blankets, and alcohol sponge baths are also time consuming and challenging for the nursing staff (21). The goal of this study was to test the hypothesis that in neurologic ICU patients, an intravascular

The Neurocritical Care Fever Reduction Trial Group members are as follows (in alphabetical order): Thomas P. Bleck, MD; Cherylee Chang, MD; Kenneth A. Collins, MBBS; Michael N. Diringer, MD; Jeffrey Frank, MD; Camilo R. Gomez, MD*; Carmelo Graffagnino, MD*; Marc D. Malkoff, MD; Donald Marion, MD*; Marek Mirski, MD; Bart Nathan, MD; Stephen E. Olvey, MD; Troy Paynor, MD; Paul M. Vespa, MD* (*Protocol Design Committee members).

From the Department of Neurology, Washington University School of Medicine, St. Louis, MO.

Supported by Alsius, Irvine, CA. Dr. Diringer is a paid consultant for Alsius.

Copyright © 2004 by Lippincott Williams & Wilkins

DOI: 10.1097/01.CCM.0000108868.97433.3F

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

catheter-based cooling system was more effective in controlling fever than conventional means.

MATERIALS AND METHODS

The Neurocritical Care Fever Reduction Trial Group performed an Investigational Device Exemption Study (G990263) to evaluate the CoolGard/Cool Line catheter system (Alsius, Irvine, CA). The study was conducted in compliance with all Food and Drug Administration regulations with the approval of each participating center's institutional review board. Written informed consent was obtained in all cases. This study follows a successful feasibility study and publication of systems performance (22).

Patients >17 yrs of age were eligible if they a) had a persistent fever (temperature of >38°C for 4 continuous hrs or two temperature spikes of >38°C within 72 hrs, the second occurring within 4 hrs of enrollment); b) clinically required central venous access; and c) were admitted with a diagnosis of subarachnoid hemorrhage, intracerebral hemorrhage, traumatic brain injury (Glasgow Coma Scale score <10), or ischemic stroke (National Institutes of Health Stroke Scale score >7).

Patients with the following were excluded: hypothermia (core temperature <36.5°C), active sepsis, spinal cord injury, active cardiac dysrhythmia with hemodynamic instability (determined by enrolling physician), pregnancy, use of barbiturate coma, use of >325 mg/day of aspirin, or if the patient was unlikely to remain in the ICU for 72 hrs.

Sample size was calculated using PASS 6.0 (Power and Sample Size Calculator, Number Cruncher Statistical Systems, Kaysville, UT) based on a 20-patient randomized investigational pilot study (22) that estimated fever burden in the control group to be 9.27 ± 8.5°C-hrs (mean ± SD); the hypothesis that the catheter would result in a 30% reduction in fever burden; a type I error of 0.05; and a statistical power of 80%. The sample size was calculated to be 111 patients in each group. The final sample size was increased to 148 patients per group for a total of 296 patients to account for possible incomplete data collection defined as missing temperature measurements for >4 consecutive hrs or a total duration of temperature measurements <65 hrs.

Design. Randomization was determined using computer-generated group assignment. Patients were block randomized 1:1 based on diagnosis and study site to either the control group (CON) or catheter group (CATH). Both cohorts were treated using a standardized fever management protocol (Table 1), and the CATH cohort was also treated with the CoolGard/Cool Line catheter system for 72 hrs. The catheter could continue to be used for up to 7 days. The patient's bladder temperature was continuously monitored and recorded hourly during the study. All data were subjected to a 100% audit, which verified that the reported data agreed with source documents.

Device. The CoolGard/Cool Line catheter system has three components: the CoolGard external heat exchange and control unit, the Cool Line Catheter heat exchange catheter, and the Start-up Kit tubing set. The 8.5-Fr Cool Line intravascular heat exchanger catheter simultaneously functions as a single- or double-lumen central venous catheter. It is placed in the subclavian jugular or femoral vein using standard techniques. Normal saline is pumped from the CoolGard unit, via the tubing set, through two balloons coaxially mounted on the catheter in a closed loop that returns the saline to the CoolGard system. The CoolGard alters the temperature of the circulating saline to maintain the patient's temperature at a programmed value. Heat is transferred from the blood to the saline inside the balloon. With appropriate settings, the Cool Line intravascular heat exchange catheter has a cooling power of 60 W and can achieve cooling rates of up to 2.5°C/hr.

Patient Management and Monitoring. Baseline chest radiograph and blood, urine, and sputum cultures were obtained at the time of enrollment. White blood cell count was monitored daily. Additional cultures were obtained and a chest radiograph performed if the white blood cell count rose by 20% or temperature exceeded 38.0°C. Ventilator warming device temperatures were maintained at 37°C. Antipyretic medications not listed in the fever management protocol were avoided. Due to the very low frequency of shivering in earlier studies, no standardized treatment was required.

All adverse events were reported by the local principal investigator along with their assessment as to the relationship to the study device. The safety monitoring committee independently reviewed these assessments. All deaths were review by an independent review board, which was blinded to treatment.

End Points. The primary effectiveness end point in this study was total fever burden during the first 72 hrs of treatment. The fever burden was calculated, based on previously established methodology for assessment of antipyretic therapy, as the product of the fever and its duration (23–26). An example of the fever burden in an individual patient from each group is depicted in Figure 1. Fever burden between the two cohorts was compared using a logarithmic scale to account for the curtailed normal distribution of the recorded patient temperatures above 38°C. The use of antipyretics, surface-cooling devices, and antibiotics and the frequency of infections was recorded. The safety of the product was assessed by prospectively monitoring for the following complications: death from any cause, pneumothorax or hemothorax related to central catheter placement, bacteremia, cardiac arrhythmias, pulmonary embolus, myocardial infarction, and thrombocytopenia.

Analysis. An intention to treat analysis was performed that included all enrolled patients. Missing serial measurements were interpolated based on the last and first observations bracketing the interval of the missing measure(s). If a patient ceased therapy before 72 hrs, the patient's average fever burden over the available time was used to extrapolate to 72 hrs. Incomplete temperature data were defined as ≥4 consecutive hrs of missing data or <65 total hrs of data.

Fever burden in the two groups was compared using a two-tailed Student's *t*-test for independent groups. The frequency of complications between groups was compared using the chi-square or Fisher's exact test, as appropriate. The mortality between groups was compared as a secondary end point using univariate analyses and logistic regression. The initial model included the following baseline variables: etiology (traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, and ischemic stroke), race (white vs. nonwhite), blood pressure, pulse, sex, Glasgow

Table 1. Conventional fever management protocol

If bladder temperature ≥38°C
1. Acetaminophen 650 mg every 4–6 hrs (PO, NG, or PR)
2. If fever does not resolve within 2 hrs, add or substitute ibuprofen 600 mg every 4–6 hours (PO, NG, or PR) except for patients with
Primary intracerebral hemorrhage
Subarachnoid hemorrhage without repair of aneurysm
Closed head injury with intracerebral hematoma
Subdural, epidural, or parenchymal hemorrhage with abnormal platelet counts (below institutional normal range)
Known acute gastric ulcer or bleeding or positive hemoccult test
If bladder temperature >38.5°C
1. Add cooling blanket until temperature ≤37°C
2. If fever does not resolve within 60 mins, may add
Gastric lavage
Ice packs
Extra cooling blanket

PO, by mouth; NG, nasogastric tube; PR, by rectum.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Coma Scale score (3–5, 6–8, or 9–15), age (<60, 60–75, or >75), body weight, and body mass index. In addition, interactions between treatment group and each baseline variable were included. Entry criteria into the model were $p < .1$ on a univariate analysis, and retention criteria was $p < .05$.

RESULTS

A total of 296 patients were enrolled from June 2000 to March 2002. One patient was lost to follow-up. The per-protocol population included 238 patients. Sixteen patients were excluded because they did not meet the entry criteria or because of protocol violations. One patient was withdrawn by the attending physician. An additional 53 patients with incomplete data were excluded due to early death, prolonged time out of the ICU for diagnostic tests or procedures, or incomplete data collection (Figure 2).

Baseline Characteristics. The majority of the enrolled patients had subarachnoid hemorrhage, followed by traumatic brain injury, intracerebral hemorrhage, and ischemic stroke. The two cohorts did not differ with respect to any baseline variables (Table 2). Cool Line catheters were placed in the subclavian (73%), internal jugular (15%), and femoral (12%) veins with similar distributions of insertion sites for the two cohorts.

Fever Burden. The CATH group demonstrated reduced fever burden in both the intention to treat and per-protocol populations (Table 3). There was also lower use of antipyretic agents, other means of fever management, sedatives, or narcotics (Table 4). No other clinical or demographic factors were significantly related to fever burden. The differences between treatment groups were consistent among study sites.

Infections. There was no difference in the frequency of any infection between groups (Table 5). The use of antibiotics was similar in the two groups.

Safety Analysis. The two groups did not significantly differ in mortality, major adverse events, or minor adverse events. Complications directly attributable to the placement of a central venous catheter did not differ between groups and were within Society of Cardiovascular and Interventional Radiology guidelines (27) (Table 5). One multiple-trauma CATH patient with a Glasgow Coma Scale score of 3 died after open thrombectomy for a venous clot that occurred distal to the site of femoral catheter insertion. One unanticipated adverse event was reported along with other device-related issues that resulted in design and labeling changes. This event did not involve significant patient injury.

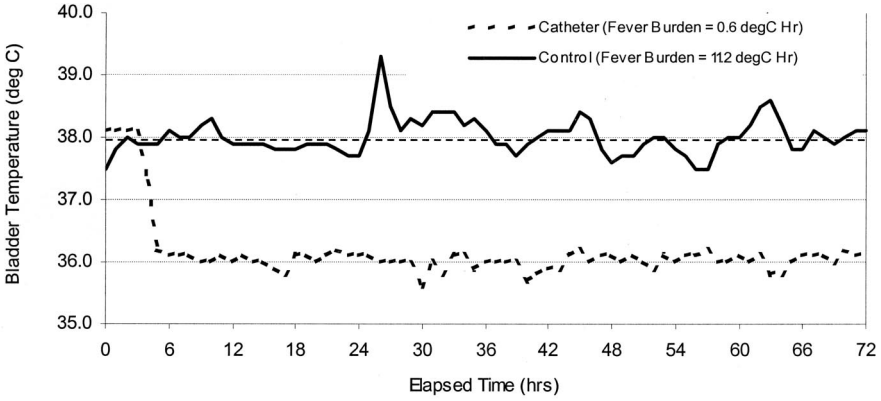

Figure 1. Example of the calculation of fever burden in individual catheter and control group patients. The graph is a time course of hourly bladder temperature measurements. The area under the fever curve that exceeds 38.0°C represents the fever burden.

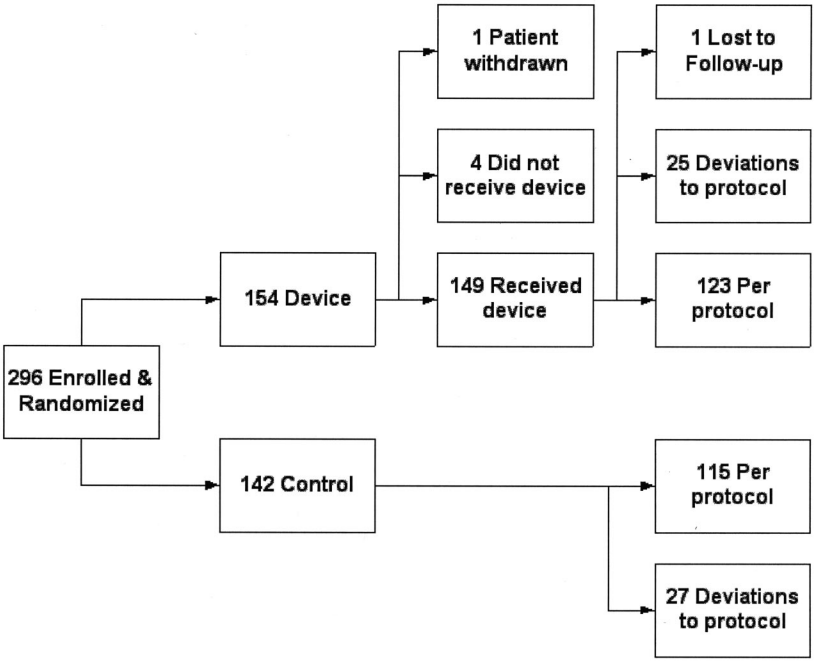

Figure 2. Participant flow.

The groups did not differ in terms of 30-day cardiovascular, gastrointestinal, pulmonary, hematologic, renal, or neurologic complications. Shivering was noted to be of concern in four patients (3.7%). In these patients, shivering was managed by primarily sedation or by manipulation of the cooling rate.

Thirty-four CATH and 21 CON patients died ($p = .14$). In none of the disease states was the difference in mortality significantly different. No deaths were judged to be device related by the reporting primary investigator or the data safety review board. The independent mortality review board determined that deaths were primarily due to the progression of the primary illness and frequently occurred as a result of the withdrawal of life-sustaining interventions (Table 6). Most patients died after the 72-hr temperature control period. No systematic causal device-related mechanism of injury was identified.

Logistic regression models were developed to determine whether the use of the catheter system was related to mortality. The variables included in the model were age, disease state, race (white vs. nonwhite), diastolic blood pressure, systolic blood pressure, pulse rate, sex, Glasgow Coma Scale score (≤7 vs. >7), body

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

weight, body mass index, and treatment group. No variables were identified within the logistic regression that predicted mortality other than age (p = .003) and baseline Glasgow Coma Scale score (p = .003).

DISCUSSION

Fever is common in the neurologic ICU, and conventional methods of cooling patients with antipyretics and surface cooling devices are not very effective. Recently, intravascular catheter-based cooling systems have been introduced as an alternative means of lowering body temperature. In this randomized, controlled trial, the use of the Cool Line/CoolGard system was more than twice as effective as conventional means in reducing fever burden.

The use of the intravascular catheter was not associated with an increase in complications greater than those associated with the use of a conventional central venous catheter. Despite concern that the use of the catheter could result in the failure to diagnose and treat infections, this was not the case. The 30-day infection rate and use of antibiotics (the catheter was used for a maximum of 7 days) was the same in both groups. It is highly unlikely that infections were missed because the protocol required the daily monitoring of the peripheral white blood cell count and collection of cultures if the peripheral white blood cell count rose by 20% or if temperature exceeded 38°C.

Shivering resulted primarily from a reduction in skin temperature. If the tubing set was not in direct contact with patient skin, shivering was uncommon in patients in the CATH group. It is important to note, however, that most of the patients in this study were intubated and sedated, which may have reduced the rate of shivering.

The primary end point chosen for this study was fever burden, not outcome. The purpose was to demonstrate the ability of the device to effectively treat fever in a broad population of neurologic ICU patients. Because of the heterogeneity of this population, the study was not powered to assess the impact of the device or of fever control on ultimate outcome. Now that an effective tool is available for treating fever in this population, an outcome study is possible and should be performed.

Although numerically higher in the catheter cohort, the mortality rates were not significantly different between groups. To assess whether there was any clinical impact of this apparent trend, an independent review panel that was blinded to treatment group reviewed each death. The panel found no relationship

Table 2. Intention to treat patient population

	Catheter (n = 154)	Control (n = 142)
Diagnosis, n (%)		
Intracerebral hemorrhage	33 (21.4)	27 (19.0)
Subarachnoid hemorrhage	61 (39.6)	63 (44.4)
Cerebral infarction	16 (10.4)	14 (9.9)
Traumatic brain injury	44 (28.6)	38 (26.8)
Age, mean ± SD yrs (n)	53 ± 18.2 (154)	53 ± 18.1 (142)
Weight, mean ± SD kg (n)	78.2 ± 16.8 (153)	79.6 ± 18.8 (140)
Height, mean ± SD cm (n)	169.8 ± 13.4 (144)	169.3 ± 13.7 (137)
Body mass index, mean ± SD (n)	28.5 ± 18.7 (144)	28.9 ± 17.4 (137)
Systolic BP, mean ± SD mm Hg (n)	152.3 ± 28.3 (154)	153.4 ± 28 (142)
Diastolic BP, mean ± SD mm Hg (n)	73.7 ± 15.8 (154)	74.1 ± 13.8 (142)
Pulse, mean ± SD beats/min (n)	91.7 ± 16.8 (154)	88.4 ± 20.9 (142)
GCS score, mode, range (n)	8, 3–15 (154)	9, 3–15 (142)
NIH Stroke Scale score, mean ± SD (n)	12.6 ± 7.3 (148)	12.8 ± 7.9 (137)
Female, n (%)	76 (49.4)	66 (46.5)
Race, n (%)		
White	92 (59.7)	92 (64.8)
Black	41 (26.6)	36 (25.4)
Asian	8 (5.2)	2 (1.4)
Hispanic	9 (5.8)	7 (4.9)
Other	4 (2.6)	3 (2.1)

BP, blood pressure; GCS, Glasgow Coma Scale; NIH, National Institutes of Health.

Table 3. Effectiveness of fever management

	Treatment Group		Reduction, %
	CATH	CON	
Fever burden (°C-hrs) for ITT population (n = 296)			
No. of patients	154	142	
Mean (raw)	2.87	7.92	64
Mean (log)	1.42	2.23	64
95% confidence interval	1.19–1.52	2.06–2.41	
p Value	<.0001		
Fever burden (°C-hrs) for per-protocol population (n = 238)			
No. of patients	115	123	
Mean (raw)	2.95	7.31	60
Mean (log)	1.41	2.19	60
95% confidence interval	1.19–1.56	2.01–2.37	
p Value	<.0001		

CATH, catheter group; CON, control group; ITT, intention to treat.

Table 4. Use of conventional cooling methods

	Treatment Group				
	CATH (n = 154)		CON (n = 142)		
	n	%	n	%	p Value
One or more topical cooling device	26	16.9	67	47.2	<.0001
Cooling blanket use	25	16.2	59	41.6	<.0001
Other device use	7	4.6	19	13.4	.008
Any antipyretic medication use	94	61.0	127	89.4	<.0001
Acetaminophen	87	56.5	124	87.3	<.0001
Ibuprofen	16	10.4	29	20.4	.02
Aspirin	18	11.7	12	8.5	.44
Sedative or narcotic use	136	88.3	125	88.0	1.00

CATH, catheter group; CON, control group.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Table 5. Complications of central venous catheters (intention to treat population)

Complications	SCVIR Expected Rate (%)	SCVIR Proposed Threshold (%)	Observed Complication Rate (%)	
			Catheter	Control
Pneumothorax	1–2	3	0.9	3.3
Hemothorax	1	2	1.9	0
Hematoma	1	2	0	0
Perforation	0.5–1	2	0	0
Air embolism	1	2	0	0
Wound dehiscence	1	2	0	0
Procedure-induced sepsis	1	2	0	0
Thrombosis	4	8	3.3	7.8
Infections	—	—	33.8	26.8
Bacteremia	—	—	1.3	4.2
Cerebral abscesses/ventriculitis	—	—	1.9	2.8
Meningitis	—	—	3.9	2.1
Pneumonia	—	—	19.5	17.6
Sepsis	—	—	3.2	2.1
Tracheobronchitis	—	—	1.3	0.7
Urinary tract infection	—	—	9.1	9.2
Antibiotic use	—	—	83.8	86.6

SCVIR, Society of Cardiovascular and Interventional Radiologists.
$p > .05$ for all variables.

Table 6. Mortality, complications, and cause of death (intention to treat population)

	Treatment Group	
	Catheter	Control
Mortality, n (%)	34 (22)	21 (15)
Possibly/probably central catheter-related complications		
Bacteremia, n	0	1
DVT, n	1	0
Pneumo/hemothorax, n	3	2
Cause of death		
Progression of primary insult, n (%)	27 (79)	17 (76)
Cardiac arrest, n	2[a]	0
Rebleeding, n	1	0
Multiple organ system failure, n	1	0
Congestive heart failure, n	1	1
Pulmonary embolus, n	0	1
Respiratory arrest, n	1	0
Hypotension, n	1	1
Unknown, n	0	1[b]
DNR/withdrawal of support, n (%)	32 (94)	19 (90)

DVT, deep venous thrombosis; DNR, do not resuscitate.
[a]Patient was randomized to Cool Line, but did not receive the Cool Line catheter; [b]patient was transferred to another hospital 6 days, and the cause of death was unknown.

between the device and cause of death. The primary cause of death in this trial was progression of the patient's presenting illness often leading to limiting interventions. In this study, >90% of patients died after having had life-sustaining interventions withheld or withdrawn, a rate that is similar to other reports in this population (28).

The CoolGard/Cool Line catheter system was not completely effective in treating fever. Sixty-five percent of patients in the CATH group exhibited period(s) of fever >38°C. This is primarily a function of the size of the catheter. Newer catheters with a greater cooling capacity are being developed that will significantly reduce this rate.

The Cool Line catheters function appropriately in terms of their capabilities as a central catheter. There were no complications related to the use of the infusion lumens on the Cool Line. The "failure to insert" rate is low (<2.8%) and within Society of Cardiovascular and Interventional Radiologists guidelines (27).

The addition of this catheter-based cooling system to conventional management significantly improves fever reduction in neurologic intensive care unit patients.

Minor adjustments have been made in the size of the dilator supplied and in the stiffness of the introducer wire as a result of feedback from the investigators.

In conclusion, this trial demonstrates that the use of the Alsius catheter-based cooling system results in a significant reduction in fever burden in febrile neurologic ICU patients with an appropriate risk profile.

ACKNOWLEDGMENTS

We thank the nursing staff of the intensive care units, without whom this study would not have been possible.

REFERENCES

1. Ginsberg MD, Busto R: Combating hyperthermia in acute stroke: A significant clinical concern. *Stroke* 1998; 29:529–534
2. Dietrich WD, Alonso O, Halley M, et al: Delayed posttraumatic brain hyperthermia worsens outcome after fluid percussion brain injury. *Neurosurgery* 1996; 38:533–541
3. Minamisawa H, Smith ML, Siesjo BK: The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. *Ann Neurol* 1990; 28:26–33
4. Busto R, Globus MYT, Dietrich WD, et al: Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in rat brain. *Stroke* 1989; 20:904–910
5. Wass CT, Lanier WL, Hofer RE, et al: Temperature changes of > or = 1 degree C alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia. *Anesthesiology* 1995; 83: 325–335
6. Reith J, Jorgensen HS, Pedersen PM, et al: Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality, and outcome. *Lancet* 1996; 347:422–425
7. Hindfelt B: The prognostic significance of subfebrility and fever in ischaemic cerebral

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

infarction. *Acta Neurol Scand* 1976; 53: 72–79
8. Terent A, Andersson B: The prognosis for patients with cerebrovascular stroke and transient ischemic attacks. *Ups J Med Sci* 1981; 86:63–74
9. Azzimondi G, Bassein L, Nonino F, et al: Fever in acute stroke worsens prognosis: A prospective study. *Stroke* 1995; 26: 2040–2043
10. Kilpatrick MM, Lowry DW, Firlik AD, et al: Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery* 2000; 47:850–855
11. Cairns CJ, Andrews PJ: Management of hyperthermia in traumatic brain injury. *Curr Opin Crit Care* 2002; 8:106–110
12. Jiang JY, Gao GY, Li WP, et al: Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma* 2002; 19: 869–874
13. Weimar C, Ziegler A, Konig IR, et al: Predicting functional outcome and survival after acute ischemic stroke. *J Neurol* 2002; 249: 888–895
14. Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al: Fever in subarachnoid hemorrhage: Relationship to vasospasm and outcome. *Neurology* 2001; 56:1299–1304
15. Mayberg MR, Batjer HH, Dacey R, et al: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Circulation* 1994; 90: 2592–2605
16. Broderick JP, Adams HP Jr, Barsan W, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1999; 30: 905–915
17. Adams HP Jr, Brott TG, Crowell RM, et al: Guidelines for the management of patients with acute ischemic stroke: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994; 25: 1901–1914
18. Guidelines for the management of severe head injury. Introduction. *J Neurotrauma* 1996; 13:643–645
19. Dippel DW, van Breda EJ, van Gemert HM, et al: Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: A double-blind, randomized phase II clinical trial. *Stroke* 2001; 32:1607–1612
20. Mayer S, Commichau C, Scarmeas N, et al. Clinical trial of an air-circulating cooling blanket for fever control in critically ill neurologic patients. *Neurology* 2001; 56: 292–298
21. Steele RW, Tanaka PT, Lara RP, et al: Evaluation of sponging and of oral antipyretic therapy to reduce fever. *J Pediatr* 1970; 77: 824–829
22. Georgiadis D, Schwarz S, Kollmar R, et al: Endovascular cooling for moderate hypothermia in patients with acute stroke: First results of a novel approach. *Stroke* 2001; 32:2550–2553
23. Lenhardt R, Negishi C, Sessler DI, et al: The effects of physical treatment on induced fever in humans. *Am J Med* 1999; 106:550–555
24. Vargas R, Maneatis T, Bynum L, et al: Evaluation of the antipyretic effect of ketorolac, acetaminophen, and placebo in endotoxin-induced fever. *J Clin Pharmacol* 1994; 34:848–853
25. Walson PD, Galletta G, Braden NJ, et al: Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther* 1989; 46:9–17
26. Matthews JN, Altman DG, Campbell MJ, et al: Analysis of serial measurements in medical research. *BMJ* 1990; 300:230–235
27. Lewis CA, Allen TE, Burke DR, et al: Quality improvement guidelines for central venous access. The Standards of Practice Committee of the Society of Cardiovascular and Interventional Radiology. *J Vasc Interv Radiol* 1997; 8:475–479
28. Diringer MN, Edwards DF, Aiyagari V, et al: Factors associated with withdrawal of mechanical ventilation in a neurology/neurosurgery intensive care unit. *Crit Care Med* 2001; 29:1792–1797

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.