

Effectiveness of an Intravascular Cooling Method Compared With a Conventional Cooling Technique in Neurologic Patients

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Abstract: Fever is common among neurologic patients and is usually treated by antipyretic drugs and external cooling. An alternative method for temperature management may be an intravascular approach. The aim of the study was to compare the effectiveness and the therapeutic costs of this new method with conventional treatment in neurologic patients. Twenty-six patients who suffered from subarachnoid hemorrhage or traumatic brain injury with febrile episodes were included the study and were randomized into 2 different groups. In the “Conventional” group, fever was treated with antipyretic drugs and/or surface cooling techniques to achieve a body core temperature of 36.5°C. In the “CoolGard” group, patients were treated with an intravascular cooling catheter (Coolgard, Alsius, CA). We compared the effectiveness of these 2 approaches by calculating the mean deviation from 36.5°C during a 48-hour period (fever burden). We found a significant difference in the fever burden [CoolGard: -0.49 to 1.22 (median -0.06) °C vs. Conventional: 1.05-2.34 (median 1.41) °C, $P < 0.05$]. Costs varied significantly between the CoolGard and the Conventional groups, with markedly higher daily costs in the CoolGard group [CoolGard: 15 to 140 US dollars (USD) (median 39 USD) vs. Conventional: 1 to 9 USD (median 5 USD), $P < 0.05$]. The effectiveness of the intravascular cooling catheter is excellent compared with conventional cooling therapies.

Key Words: temperature control, intravascular cooling catheter

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Fever is common among patients with severe neurologic illnesses, such as strokes or traumatic brain injuries (TBI). The longer the patients reside in the intensive care unit (ICU), the more likely they are to have 1 or more febrile episodes.¹ Usually, these episodes are related to

pulmonary or urinary tract infections being the most common source. However, fever can also be the result of a hypothalamic dysfunction or a subarachnoid hemorrhage (SAH). The clinical outcome tends to be worsened in patients with noninfectious hyperthermic or febrile episodes.^{2–5} In patients with spontaneous intracerebral hemorrhages, a correlation between the duration of the fever and the poor outcome was documented.⁶ Mild-to-moderate hypothermia as a treatment for brain injury provides a significant protective effect, diminishes the neural damage, reduces the rate of mortality, and improves the neurologic outcome. Therefore, the American Neurological Society recommends an aggressive temperature control in these patients.⁷

Conventional temperature control in the ICU can best be described as “reactive.” As temperature is routinely monitored in patients, increases above a certain threshold lead to the standard treatment. This may involve the administration of antipyretic drugs. However, the medical treatment usually takes up to 1 hour to show beneficial effects. Additional techniques like the cooling of the body surface are being controversially discussed. Most often cooling blankets are applied, covering only a minor part of the body. The main problem regarding the effects of the external cooling techniques of the skin surface is that the reactive thermoregulatory vasoconstriction limits the heat loss.⁸

A new alternative approach for temperature control is intravascular cooling via a specific central venous balloon catheter, which is filled with saline and is continuously cooled via an external device.⁹ This technique can be set up as a closed-loop system with the cooling efforts aimed at reaching a certain temperature on the basis of the patient’s actual body temperature. In neurologic patients, this may offer a continuous temperature control, avoiding febrile episodes during their ICU stays. The aim of our study was to compare the effectiveness and the therapeutic costs of this promising new technique of temperature control with those of conventional therapy, in neurologic patients. Furthermore, we wanted to assess the effectiveness of an automated servo feedback control system versus human interventions in the management of neurologic patients, to achieve a low normal target temperature.

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MATERIALS AND METHODS

After approval by the local ethics committee, the investigation was performed in the ICU of the Department of Anaesthesiology, Emergency and Intensive Care Medicine at the University Hospital in Goettingen, Germany. Neurologic patients with TBI or SAH and febrile episodes were included in this study, after admission to the ICU, and were randomized alternately to the "CoolGard" and to the "Conventional" group. In the Conventional group, temperature control was performed with antipyretic drugs and surface cooling techniques to achieve a body core temperature of 36.5°C.

In the CoolGard group, the patients were treated with an intravascular cooling catheter (Coolgard, Alsius, CA). Additionally, in this group we compared the cooling effectiveness by calculating the fever burden over a 48-hour period, during which the patients were not treated with the intravascular cooling catheter.

We compared the effectiveness of these 2 temperature management approaches by calculating the mean deviation from normothermia (36.5°C) during a 48-hour period (fever burden). Furthermore, we calculated the costs of these 2 different fever management approaches.

Inclusion Criteria

- Age \geq 18 years
- Neurologic patients with SAH or TBI
- Temperature $>$ 38.5°C for more than 48 hours
- Possibility of central venous access

Continuous sedation with intravenous midazolam and ketamine was provided to achieve a Ramsay score of 4-5.¹⁰ From the patients' files, the diagnoses, lengths of ICU stay, anthropometric data, and the ICU Scores (Glasgow Coma Scale,¹¹ APACHE II,¹² and SAPS II¹³) were recorded. Temperature was recorded through an intravascular urine catheter, equipped with a thermistor for continuous temperature measurement, and stored online in a patient data management system [Göttinger Informationssystem für Intensiv (GISI), Universitäts-Klinikum, Göttingen, Germany]. Infection statuses, including white blood cell counts, C-reactive proteins, fibrinogens, thrombocytes, antibiotics, and bacteria, were recorded from the clinical investigations. We calculated the costs for temperature control on the basis of the prices in our hospital list of 2005.

Fever Burden

According to our institutional guidelines, target bladder temperature was set to a low normal temperature of 36.5°C. Fever burden was calculated as the mean deviation from this target temperature during a 48-hour period. It is calculated by summing up the hourly deviations of the bladder temperature from a defined

temperature threshold and by dividing this sum by 48. We used the following formula:

$$\text{Fever burden} = \frac{\sum_{n=1}^{48} \text{Temperature}_n(^{\circ}\text{C}) - 36.5^{\circ}\text{C}}{48(\text{h})}$$

It describes the mean deviation from a defined temperature threshold (36.5°C) during this 48-hour period. Its unit is °C/h. A positive fever burden indicates febrile episodes; whereas negative values show episodes of hypothermia. Values of zero indicate that the target temperature was reached.¹⁴

Conventional Group

In the Conventional group, the fever was treated with antipyretic drugs and surface cooling techniques to achieve a body core temperature of 36.5°C. In this group, a human response on the fever episodes was necessary. Therefore, on the bedside standard monitor, the alarm limits of the temperatures were set to below 36.0°C and above 37.0°C. If there were alarm violations, the patients were continuously cooled with a surface blanket connected to a standard cooling device [Warmtouch 5800, Tyco Healthcare Deutschland GmbH, Neustadt (Donau), Germany], which delivered air of room temperature. In case of further violations of target the temperature, the attending nurses and physicians were instructed to treat the patients with antipyretic drugs, in accordance with their histories and comorbidities, to achieve the target temperature.

Antipyretic Drugs and Cooling Blankets

The costs of the antipyretic drugs and the cooling blankets [Tyco Healthcare GmbH, Neustadt (Donau), Germany] were calculated on the bases of the prices of 2005. Antipyretic drugs were administered intravenously, either as bolus or as continuous infusions. We used Metamizol (Winthrop Arzneimittel GmbH, Mülheim-Kärlich, Germany), Paracetamol (Winthrop Arzneimittel GmbH, Mülheim-Kärlich, Germany), Dihydroergotoxin (Novartis Pharma GmbH, Nürnberg, Germany), and a cocktail consisting of 50-mg Promethazin (Bayer Healthcare AG, Leverkusen, Germany), 50-mg Pethidin (Hoechst Marion Roussel Deutschland GmbH, Bad Soden, Germany), and 1.5-mg Dihydroergotoxin (Novartis Pharma GmbH, Nürnberg, Germany). The calculations of the costs of these drugs were calculated based on the prices of 2005. Apart from the costs of these antipyretic drugs, the costs of the materials needed for drug administration, like intravenous lines, crystalline or saline solutions, were calculated.

CoolGard Group Intravascular Cooling System CoolGard

The CoolGard system (CoolGard, Alsius, CA) is a device for controlling the body core temperature in patients. It consists of a temperature monitor, a temperature controller unit, a heat exchanger unit, and a roller pump. Two heat exchange circuits control the

temperature control system. The primary circuit integrates a tubing roller pump with a disposable sterile barrier heat exchanger to circulate sterile saline through the connecting tubing and the input/output temperature control lumen of the venous catheter. The secondary circuit includes the recirculating waterbath and the chiller unit with an integral circulation pump that provides a controlled temperature coolant to the sterile barrier heat exchanger. The refrigerated bath/circulator is self-contained and can be operated continuously. The objective of the 2 circuits is to circulate chilled sterile saline to the indwelling central venous catheter that is placed percutaneously in the patient. Both the circuits are closed loops and the coolant is continuously recirculated. Data from the temperature monitor are integrated into the system via software that also controls the temperature of the sterile saline that is circulated through the catheter to maintain the desired body temperature.

The central venous heat exchange catheter is a multilumen intravascular catheter. The working shaft of the catheter has a nominal useable length of 35 cm, with a diameter of 8.5 F. Two catheters with 2 or 3 cooling membranes are available. The membranes are expandable up to 5.0 or 8.0 mm. Two of the catheter's lumens are used to circulate sterile saline to exchange heat with the central venous blood supply. The inflow lumen/outflow lumen forms a closed-loop system through which the chilled saline circulates. The catheter's inflow/outflow lumen is connected to the CoolGard. Additionally, 2 or 3 lumens of the catheter are standard infusion lumens. The catheter is manufactured from biocompatible polyurethane impregnated with barium sulfate, to make the catheter radiopaque for visualization by the physician during placement of the catheter. The catheter blood contact surfaces are heparin coated (Duraflo, Baxter Deutschland GmbH, München-Unterschleißheim, Germany). The CoolGard system and its catheter system are Communauté Européenne marked and labeled for use in the cooling and warming of patients.

Statistics

Calculations were performed using the STATISTICA software package (Statistica 5.1, StatSoft Inc, Tulsa, USA). We tested the normal distribution with the Kolmogorov-Smirnov test. We presented data as minimum-maximum (median), unless stated otherwise. We applied a Wilcoxon matched-pair test or a Mann-Whitney *U* test to analyze the differences between the 2 methods. Linear regression analysis using the least square method was applied for the correlation analysis. $P < 0.05$ was considered significant for all statistical tests.

RESULTS

Altogether, we studied 26 patients, of whom we treated 13 in the CoolGard group and 13 in the Conventional Group. Figure 1 shows an example of the urine bladder temperatures of 2 patients treated either in the Conventional or in the CoolGard group. In the patient treated by CoolGard, the body temperature

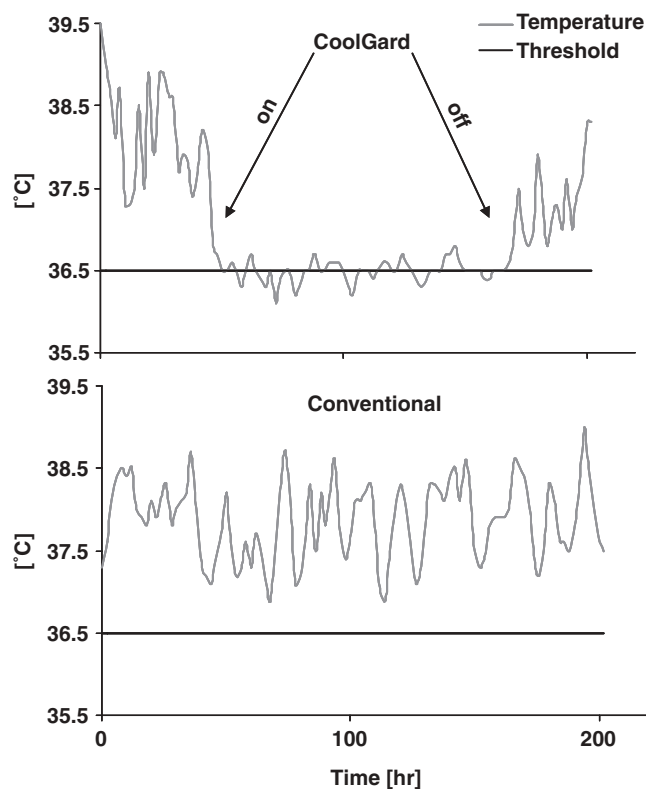


FIGURE 1. Time courses of temperatures in patients treated with the intravascular approach (CoolGard) and the conventional approach (Conventional). In the patient treated by CoolGard, the body temperature without active cooling is higher than the defined threshold. It sinks immediately to the threshold temperature after beginning the cooling with the CoolGard and remains constant during the treatment with the CoolGard. After stopping the treatment, the body temperature starts rising again over the defined threshold. In the patient treated with the conventional approach, the body temperature remains above the threshold temperature most of the time.

without cooling is higher than the defined threshold. It sinks immediately after the beginning of the cooling with the CoolGard. It reduces the threshold temperature and remains constant during the treatment with the CoolGard. After stopping the treatment, the body temperature rises again over a defined threshold. In the patient treated with the conventional approach, the body temperature most of the time remains above the threshold temperature most of the time. We found no differences in the anthropometric data, severity of illness, or severity of infections. The mean length of ICU stay was 28 days (range 6 to 80 d) and 26 days (range 19 to 71 d) in the CoolGard and the Conventional groups, respectively. Five patients had a brain-head injury. Eight patients had an SAH in the CoolGard group and all the patients had an SAH in the Conventional group. The mean ages were 48 years (range 18 to 75 y) and 47 years (range 33 to 75 y) in the CoolGard and the Conventional groups, respectively. Body weight, and height did not differ in the

2 groups. We found no differences in the severity of illness scores—APACHE II 17 (range 12 to 22) and 19 (range 15 to 27), and the SAPS II 55 (range 41 to 69) and 60 (range 46 to 70)—in the CoolGard and the Conventional groups, respectively. All the patients had their primary temperature probes located in the bladder. The intravascular cooling catheter was located mainly in the subclavian vein, except for 2 catheters, which were located in the jugular vein. The physicians attending on the study patients were familiar with central venous access. Therefore, the subjective assessment of the catheter placement was good in all the cases. The intravascular catheter induced no side effects (ie, cardiac or vascular, thromboembolism).

Infections were not observed in all the patients. Fifty-four percent in the CoolGard group and 62% in the Conventional group had infections located in the pulmonary or urinary tracts, or in the blood. Locations of infections in the 2 groups did not differ significantly (54% vs. 62%). Of these infections that were located in the lungs were 46% versus 54%, in the urinary tract, 15% versus 15%, and in the blood culture, 8% versus 8%, in the CoolGard and the Conventional group, respectively. We treated all infections with antibiotics after considering the microbiologic analysis. We found no significant differences in the severity of the infections, as measured by the C-reactive proteins (median 60 range 16 to 169 mg/L vs. median 58 range 16 to 184 mg/L), the white blood cell counts (median 12 range 8 to $15 \times 10^3/\mu\text{L}$ vs. median 11 range 8 to $17 \times 10^3/\mu\text{L}$), the thrombocytes (median 306 range 188 to $382 \times 10^3/\mu\text{L}$ vs. median 347 range 148 to $642 \times 10^3/\mu\text{L}$), and the fibrinogens (median 618 range 430 to 1007 mg/L vs. median 610 range 434 to 917 mg/L) in the CoolGard and Conventional groups, respectively. We found a higher consumption of antipyretic drugs in the Conventional group.

We found a significant difference in the fever burdens during the 48-hour observation period, defined as the period with a bladder temperature higher than 36.5°C [CoolGard -0.49 to 1.22 (median -0.06) $^\circ\text{C}$ vs. Conventional 1.05 to 2.34 (median 1.41) $^\circ\text{C}$]. Additionally, in the CoolGard group, we compared the fever burden in a 48-hour period for the patients who were either treated with CoolGard (CoolGard on) or not treated with CoolGard (CoolGard off). We found a significant difference in the observed fever burden [CoolGard on: -0.49°C to 1.22°C (median -0.06°C); CoolGard off: 0.68 to 2.49 (median 1.43) $^\circ\text{C}$]. All results are summarized in Figure 2.

The costs for the temperature control varied significantly between the CoolGard and the Conventional groups, with markedly higher costs in the CoolGard group. We found the total cost for the ICU stay to be 996 US dollars (USD) (range 739 to 1984 USD) and the daily costs to be 39 USD (range 15 to 140 USD) in the CoolGard group. In the Conventional group, total costs were 164 USD (range 44 to 381 USD) and the daily costs were 5 USD (range 1 to 9 USD). All the data are presented in Table 1.

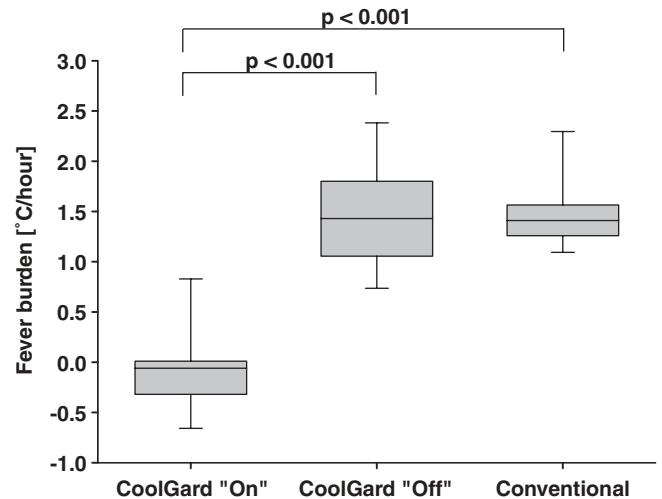


FIGURE 2. Fever burdens in the Conventional and the CoolGard groups during a 48-hour observation period. Additionally, in the CoolGard group fever burdens were calculated during a 48-hour period when the patients were treated with the CoolGard (CoolGard “on”) and without the CoolGard (CoolGard “off”). Data are presented as the 5th/95th percentiles.

DISCUSSION

Fever is common in critically ill neurosurgic patients, especially in those with a prolonged ICU stay. A large body of evidence shows that the fever worsens the neurologic outcomes in these patients. An alternative to conventional methods for fever management may be an intravascular cooling catheter that is closed-looped with the cooling efforts of the intravascular approach to the patient’s actual body temperature. This may offer a continuous temperature control in neurologic patients, avoiding febrile episodes during their ICU stays. The aims of the study were testing the effectiveness of this new technique and comparing its costs with those of conventional fever management techniques.

Until now, no study has compared the effectiveness and the costs for an intravascular cooling catheter compared with conventional therapy. The costs for temperature control varied between the CoolGard and the Conventional groups, with markedly higher total and daily costs in the CoolGard group. The markedly higher therapy costs are based on the costs of the start-up kit, which consists of a chiller unit and tubes for connection to the intravascular catheter. Additionally, costs arise from the intravascular catheter. However, this catheter has 2 or 3 lumens for infusion therapy. Therefore, in some patients an additional central intravenous line can be saved, reducing the cost of fever treatment.

We found an excellent effectiveness of the intravascular cooling catheter compared with the conventional temperature control with antipyretic drugs and cooling blankets. During the 48-hour observation period, we found a median fever burden of $-0.06^\circ\text{C}/\text{h}$ in patients treated with the intravascular cooling approach. This

TABLE 1. Anthropometric Data, Infections During 48 hours Observation Period, Fever Burden, and Costs

	CoolGard	Conventional	P
n	13	13	ns
Age (y)	18-64 (44)	33-75 (47)	ns
Weight (kg)	50-115 (72)	65-100 (76)	ns
Height (cm)	160-190 (170)	160-182 (172)	ns
Body mass index (kg/m ²)	20-40 (25)	22-31 (25)	ns
Female/male	8/5	6/7	ns
Length of ICU stay (d)	6-80 (28)	19-71 (26)	ns
Diagnosis			
TBI	5	0	
SAH	8	13	
Glasgow Coma Scale	3 (3)	3 (3)	ns
APACHE II	12-22 (17)	15-27 (19)	ns
SAPS II	41-69 (55)	46-70 (60)	ns
Infection status			
C-reactive protein (mg/L)	16.4-169.0 (60.0)	15.9-183.5 (57.8)	ns
Leukocytes (*1000/ μ L)	8.0-15.4 (12.2)	8.0-17.2 (10.7)	ns
Thrombocytes (*1000/ μ L)	188-382 (306)	148-642 (347)	ns
Fibrinogen (mg/dL)	430-1007 (618)	434-917 (610)	ns
Infection observed	7 (54%)	8 (62%)	
Pulmonary	6 (46%)	7 (54%)	
Urinary	2 (15%)	2 (15%)	
Blood	1 (8%)	1 (8%)	
Antipyretic drugs			
Metamizol (g/d)	0-2 (0)	3-7 (6)	< 0.001
Paracetamol (g/d)	0-0 (0)	0-4 (3)	< 0.001
Dihydroergotoxin (mg/d)	0-0 (0)	3-4.5 (2)	< 0.001
Lytic cocktail (n/d)	0-0 (0)	0-3 (1)	< 0.001
Fever burden ($^{\circ}$ C) 48-h	-0.49-1.22 (-0.06)	1.05-2.34 (1.41)	< 0.001
Costs			
Total per patient (USD)	739-1984 (996)	44-381 (164)	< 0.001
Daily per patient (USD)	15-140 (39)	1-9 (5)	< 0.001

Values as minimum-maximum (median).

Lytic cocktail consists of 50 mg of Promethazin, 50 mg of Pethidin, and 1.5 mg of Dihydroergotoxin.

ns indicates not significant ($P > 0.05$).

means that the target temperature of 36.5 $^{\circ}$ C was achieved predominantly during the observation period. Further evidence of the effectiveness of this system was an observation period of 48 hours in the patients equipped with an intravascular cooling catheter, in which the cooling device was not used. We observed an increase in the median fever burden of 1.43 $^{\circ}$ C. This means that the patient's temperature up to 38 $^{\circ}$ C during the times that the intravascular cooling catheter was not used. In contrast, in the conventional group, when the patients' fever management was performed with antipyretic drugs and cooling blankets, we found a significant higher fever burden (1.41 $^{\circ}$ C) compared with the intravascular cooling approach. This means that patient suffered from a body temperature of about 37.9 $^{\circ}$ C. Schmutzhard and coworker reported in a pilot study the high effectiveness of this intravascular cooling catheter, in patients with intracranial disease. This group used the CoolGard system with a target temperature also set at 36.5 $^{\circ}$ C. They concluded that it might be advisable to consider the potential use of this intravascular cooling catheter for the rapid induction and control of normothermia or mild hypothermia in cardiac arrest patients. In our study, we studied neurologic patients with brain injury and we found also a high effectiveness of this intravascular cooling catheter. Al Senani and coworkers concluded, in a study of comatose survivors of

cardiac arrests, that hypothermia via endovascular methods is safe and feasible and that target temperatures can be achieved and controlled rapidly and precisely.

Increased body temperature adds to neural damage in brain injury mainly during the early period of intracranial disease. The prevention of temperature peaks may be of importance. This is of further importance, as an animal study suggests that the neuroprotective effect of drugs cannot be expected if the body and brain temperatures are allowed to rise above normal.¹⁵ However, there is currently no evidence from randomized trials to support the routine use of physical or chemical cooling therapies in acute stroke patients. As experimental studies showed a neuroprotective effect of hypothermia in cerebral ischemia, and as hypothermia seems to improve the outcomes in patients with severe closed head injuries, these trials with cooling therapies in acute stroke patients are warranted.¹⁶

We observed no side effects, like embolism, balloon rupture, pneumothorax, or life-threatening arrhythmia, or catheter sepsis in the study patients treated with the intravascular catheter. The handling of the intravascular catheter and the cooling system was excellent. As the catheter is equipped with 2 to 3 additionally intravenous lines, it can be used for intravenous intensive care medication. These were confirmed in earlier studies.¹⁷

We estimated the brain temperature from the bladder temperature. However, bladder and rectal temperatures often underrepresented brain temperatures after TBI, especially when the patients were hyperthermic.¹⁸ It was found that in these patients, the differences in mean temperatures between the brain and the rectum were inconsistent and unpredictable, ranging between +1.8°C to -2.9°C.¹⁹ In patients with SAH, it was found that brain temperature was higher than the bladder temperature.²⁰ Therefore, according to our institutional guidelines, the target bladder temperature was set to a low normal temperature of 36.5°C. In view of the failure to recognize or even to discuss the problems of using the bladder temperature to indicate the brain temperature, more studies are needed to assess the efficacy of rapid endovascular hypothermia.²¹

In conclusion, the effectiveness of the intravascular cooling catheter is excellent compared with conventional cooling therapies with antipyretic drugs or cooling blankets. Although the expenses for the cooling catheter are higher compared with conventional cooling therapies, the poor outcome in patients with febrile episodes promotes this intravascular cooling approach.

REFERENCES

- Kilpatrick MM, Lowry DW, Firlik AD, et al. Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery*. 2000;47:850-855.
- Jorgensen HS, Reith J, Pedersen PM, et al. Body temperature and outcome in stroke patients. *Lancet*. 1996;348:193.
- Azzimondi G, Bassein L, Nonino F, et al. Fever in acute stroke worsens prognosis. A prospective study. *Stroke*. 1995;26:2040-2043.
- Yu CG, Jagid J, Ruenes G, et al. Detrimental effects of systemic hyperthermia on locomotor function and histopathological outcome after traumatic spinal cord injury in the rat. *Neurosurgery*. 2001;49:152-158.
- Oliveira-Filho J, Ezzeddine MA, Segal AZ, et al. Fever in subarachnoid hemorrhage: relationship to vasospasm and outcome. *Neurology*. 2001;56:1299-1304.
- Schwarz S, Hafner K, Aschoff A, et al. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology*. 2000;54:354-361.
- Consensus Conference. Rehabilitation of persons with traumatic brain injury. NIH Consensus Development Panel on Rehabilitation of Persons With Traumatic Brain Injury. *JAMA*. 1999;282:974-983.
- 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.
- Aiyagari V, Diringner MN. CoolGard/Cool Line catheter system. *Neurocrit Care*. 2004;1:209-211.
- Ramsay MA. Measuring level of sedation in the intensive care unit. *JAMA*. 2000;284:441-442.
- Jennett B, Teasdale G, Braakman R, et al. Predicting outcome in individual patients after severe head injury. *Lancet*. 1976;1:1031-1034.
- Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818-829.
- Castella X, Artigas A, Bion J, et al. A comparison of severity of illness scoring systems for intensive care unit patients: results of a multicenter, multinational study. The European/North American Severity Study Group. *Crit Care Med*. 1995;23:1327-1335.
- Schmutzhard E, Engelhardt K, Beer R, et al. Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients: a prospective pilot study. *Crit Care Med*. 2002;30:2481-2488.
- Memezawa H, Zhao Q, Smith ML, et al. Hyperthermia nullifies the ameliorating effect of dizocilpine maleate (MK-801) in focal cerebral ischemia. *Brain Res*. 1995;670:48-52.
- Correia M, Silva M, Veloso M. Cooling therapy for acute stroke. Cochrane Database. *Syst Rev*. 2000;CD001247.
- Broessner G, Beer R, Franz G, et al. Case report: severe heat stroke with multiple organ dysfunction—a novel intravascular treatment approach. *Crit Care*. 2005;9:R498-R501.
- Henker RA, Brown SD, Marion DW. Comparison of brain temperature with bladder and rectal temperatures in adults with severe head injury. *Neurosurgery*. 1998;42:1071-1075.
- Childs C, Vail A, Protheroe R, et al. Differences between brain and rectal temperatures during routine critical care of patients with severe traumatic brain injury. *Anaesthesia*. 2005;60:759-765.
- Otawara Y, Ogasawara K, Kubo Y, et al. Brain and systemic temperature in patients with severe subarachnoid hemorrhage. *Surg Neurol*. 2003;60:159-164.
- Al Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the CoolGard System and Icy catheter following cardiac arrest. *Resuscitation*. 2004;62:143-150.