Cooling for Acute Ischemic Brain Damage (COOL AID)

A feasibility trial of endovascular cooling

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Abstract—*Objective:* To report results of a randomized pilot clinical feasibility trial of endovascular cooling in patients with ischemic stroke. *Methods:* Forty patients with ischemic stroke presenting within 12 hours of symptom onset were enrolled in the study. An endovascular cooling device was inserted into the inferior vena cava of those randomized to hypothermia. A core body temperature of 33 °C was targeted for 24 hours. All patients underwent clinical assessment and MRI initially, at days 3 to 5 and days 30 to 37. *Results:* Eighteen patients were randomized to hypothermia and 22 to receive standard medical management. Thirteen patients reached target temperature in a mean of 77 ± 44 minutes. Most tolerated hypothermia well. Clinical outcomes were similar in both groups. Mean diffusion-weighted imaging (DWI) lesion growth in the hypothermia group (n = 12) was 90.0 ± 83.5% compared with 108.4 ± 142.4% in the control group (n = 11) (NS). Mean DWI lesion growth in patients who cooled well (n = 8) was 72.9 ± 95.2% (NS). *Conclusions:* Induced moderate hypothermia is feasible using an endovascular cooling device in most patients with acute ischemic stroke. Further studies are needed to determine if hypothermia improves outcome.

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Reperfusion reduces infarct size during acute ischemic stroke. Several challenges exist, however, including the short therapeutic time window,[1] the risk of reperfusion injury,[2] and hemorrhage.[3] In animal models of middle cerebral artery (MCA) occlusion, hypothermia consistently decreases infarct volume.[4-6] Studies of postischemic hypothermia have also shown a benefit in the immediate postischemic period.[4,7] Recently, hypothermia has been shown in two randomized trials to improve outcomes after cardiac arrest.[8,9] Despite the promise of hypothermia, several problems have limited its use in acute stroke. Surface cooling is slow and cumbersome and requires general anesthesia to counteract shivering. Endovascular cooling using a counter-current heat exchange catheter is a new method to induce hypothermia and precisely control temperature. Recently, the combination of meperidine, buspirone, and surface warming was found to reduce shivering during endovascular cooling.[10,11] We tested whether endovascular cooling combined with meperidine, buspirone, and surface warming could achieve hypothermia rapidly in patients with acute ischemic stroke.

Materials and methods. From March 2001 to March 2002, patients with acute ischemic stroke were randomized to receive endovascular cooling or standard medical management. Patients were enrolled at five centers in the United States (The Cleveland Clinic Foundation, Erlanger Medical Center, Massachusetts General Hospital), Germany (Justus Liebing University, Giessen), and Australia (Royal Melbourne Hospital). The study protocol was approved by each institutional review board, and informed consent was obtained from all patients or designated surrogates. Randomization was done by opening sealed randomization envelopes. Patients were older than 18 years, had anterior circulation territory ischemic stroke, had an NIH Stroke Scale (NIHSS) score of ≥8 and ≤25, and presented within 12 hours of symptom onset. Exclusion criteria included recent sepsis; contraindication to MRI; platelet count of <75,000/mm^3; known coagulopathy; significant ventricular cardiac dysrhythmias or QTc interval of >450 milliseconds; pregnancy; intolerance to buspirone or meperidine; treatment with monoamine oxidase inhibitors; life expectancy of <6 months; baseline modified Rankin Scale (mRS) score of >2; rapidly improving symptoms; intracerebral hemorrhage, mass, or aneurysm by brain CT scan; hypersensitivity to hypothermia; height of <1.5 m; inferior vena cava filter in place; and renal insufficiency. Patients returned for a clinical assessment at 30 + 7 days including mRS and NIHSS scores (the NIHSS score was corrected for side of stroke by adding 5 to the NIHSS score in patients with right hemispheric strokes).[12] Adverse events were predefined, monitored through 30 + 7 days, and reviewed by an independent Clinical Events Committee (Harvard Clinical Research Institute, Boston, MA). A Data Safety Monitoring Board was also convened for the study (see the Appendix).

Endovascular cooling. Endovascular cooling was initiated using the Reprieve Endovascular Temperature Management System (Radiant Medical, Redwood City, CA), which consists of a proprietary triple-lobed, helically wound, heat-exchange balloon catheter that is placed in the inferior vena cava via the femoral vein and a microprocessor-driven controller. The catheter is inserted through a 10F femoral introducer sheath until the distal tip is at the level of the diaphragm and is connected to a cassette with a

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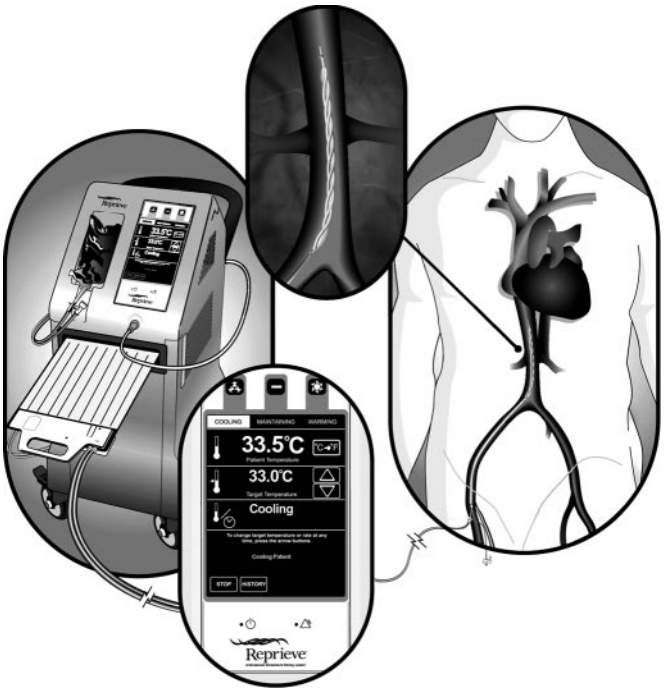

Figure 1. The Reprieve Endovascular Temperature Management System.

***Table 1** Reasons for exclusion from study**

No. (%)	Reason
47 (15.1)	Symptom onset >12 h
45 (14.4)	Patient improved
38 (12.2)	Nonqualifying NIHSS score
30 (9.6)	Unknown
30 (9.6)	Nonanterior territory stroke
19 (6.1)	No informed consent
18 (5.8)	mRS score >2
15 (4.8)	Hemorrhagic stroke
13 (4.2)	Primary physician refused
12 (3.9)	Unknown onset time
11 (3.5)	Competing trial
7 (2.2)	Respiratory compromise
6 (1.9)	Transferred to outside hospital/no bed available
5 (1.6)	Contraindication to MRI
4 (1.3)	Cardiac dysrhythmia (QTc >450 ms)
3 (1.0)	Renal insufficiency

* Nine patients were excluded for miscellaneous reasons.

NIHSS = NIH Stroke Scale; mRS = modified Rankin Scale.

pump that circulates cold or warm saline (figure 1). The target core body temperature was 33 °C (monitored with an esophageal probe). Cooling was maintained for 24 hours. Controlled rewarming was performed using the same catheter by setting the target temperature to 36.5 °C. Rewarming was performed at a rate of 0.2 °C/h. Shivering was suppressed using a forced-air warming blanket (BairHugger; Augustine Medical, Eden Prairie, MN), oral buspirone (60 mg), and IV meperidine (50- to 75-mg loading dose followed by an IV infusion at 25 to 35 mg/h).

All patients received standard medical treatment, including thrombolytic therapy if indicated. Hematologic variables and electrolytes were measured every 8 hours in the hypothermia group and daily in the control group. Esophageal temperatures were monitored every 15 minutes during active cooling or warming and every 30 minutes during temperature maintenance in the hypothermia group. Bladder or rectal temperatures were monitored hourly in the control group.

Brain imaging. After randomization but before cooling, all patients had baseline diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and MR angiography (MRA) performed. Those who received thrombolytic therapy underwent a brain CT scan after 24 hours. DWI, PWI, and MRA were repeated on days 3 to 5. Follow-up T2-weighted and fluid-attenuated inversion recovery (FLAIR) MR images were obtained to measure final infarct volumes at day 30. In patients who died before day 30, the DWI from days 3 to 5 was used to measure infarct volumes. DWI lesion growth was calculated by comparing the baseline DWI with the day 3 to 5 DWI. All imaging analysis was performed by Perceptive Informatics (Bethesda, MD), which was blinded to treatment assignment.

Results. *Demographics.* Three hundred fifty-two patients with acute ischemic stroke were screened, and 40 were randomized. Table 1 lists the reasons for exclusion. Eighteen patients were assigned to the hypothermia group and 22 to the control group. One patient assigned to the control group had a normal DWI after randomization and was diagnosed with a TIA; this patient was excluded from analysis.

Baseline patient characteristics are summarized in table 2. The distribution of gender differed between the two groups: 72% men in the hypothermia group and 71% women in the control group ($p = 0.02$). In the hypothermia group, 61% had right hemispheric infarcts vs 43% in the control group (NS). The corrected NIHSS score (mean ± SD) in the hypothermia group was 18.2 ± 4.4 and in the control group 16.7 ± 5.5 (NS).[12] Cardioembolism was the most common mechanism of stroke (72% in the hypothermia group and 67% in control group). Large artery disease was found in one hypothermia patient (5.6%) and dissection in two (11%). Large artery disease was found in four control patients (19%). The cause was undetermined in two hypothermia patients (11%) and three control patients (14%). Rates of thrombolytic therapy were similar between the two groups. The mean admission oral temperatures were also similar (36.3 ± 0.6 °C in the hypothermia group and 36.3 ± 0.5 °C in the control group).

Cooling feasibility. The mean time from stroke onset to presentation was slightly shorter in the hypothermia group (3 hours 27 minutes ± 2 hours 46 minutes) compared with the control group (4 hours 16 minutes ± 1 hour 58 minutes) (NS). The mean time to IV thrombolytic therapy was 130 ± 43 minutes in the hypothermia group and 150 ± 23 minutes in the control group. The mean time from stroke onset to initiation of cooling was 8 hours 59 minutes ± 2 hours 52 minutes. The main reason for delay was the time needed to obtain baseline MRI. Catheter placement was well tolerated in all patients. Cooling was also generally well tolerated, with no case being discontinued because of patient discomfort. Significant shivering occurred in two patients (Patients H3 and H13). Of the 18 patients in the hypothermia group, 13 cooled with a mean time to target temperature of 77 ± 44 minutes, the most rapid reaching target in 15 minutes. These 13 patients achieved a core temperature of at least 35.0 °C in 37 ± 26 minutes, with 9 of them achieving at least 35.0 °C in 22 ± 11 minutes. There was no overshoot. Cooling was less effi-

Table 2 *Baseline patient characteristics*

	Hypothermia, n = 18	Control, n = 22
Patient characteristics		
Age, y	60.9 ± 12.1	67.3 ± 12.5
Gender	13 male	6 male*
Race	18 white	19 white
Presenting NIHSS score	15.2 ± 4.4	14.6 ± 5.6
Corrected NIHSS score	18.2 ± 4.4	16.7 ± 5.5
Risk factors		
Hypertension	12 (66.7)	15 (71.4)
Hyperlipidemia	4 (22.2)	8 (38.1)
Diabetes mellitus	5 (27.8)	4 (19.0)
Myocardial infarction	4 (22.2)	3 (14.3)
Arrhythmia	3 (16.7)	6 (28.6)
Valvular dysfunction	1 (5.6)	2 (9.5)
Congestive heart failure	3 (11.1)	2 (9.5)
Cardiomyopathy	1 (5.6)	1 (4.5)
Peripheral vascular disease	2 (11.1)	2 (9.5)
Cerebrovascular disease	4 (22.2)	6 (28.6)
Therapy		
Received thrombolysis	13 (72.2)	15 (71.4)
Received IV rt-PA	10 (55.6)	12 (57.1)
Received intra-arterial rt-PA	3 (16.7)	3 (14.3)

Values in parentheses are percentages.

* $p = 0.02$.

NIHSS = NIH Stroke Scale; rt-PA = recombinant tissue plasminogen activator.

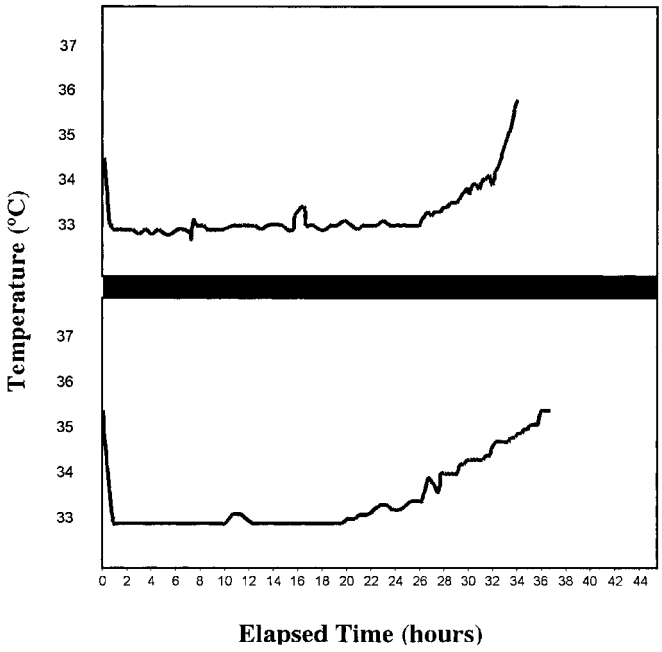

Figure 2. Examples of temperature curves of patients undergoing endovascular cooling. Patient H3: Time to target temperature = 20 minutes; Patient H4: time to target temperature = 35 minutes.

cient in five patients; target temperature was not reached in four and reached after several hours in one. Reasons included incorrect catheter placement (the catheter was not advanced far enough into the inferior vena cava) in three patients (one of whom also shivered), kinking of the catheter outside the body in one patient, and shivering in one patient. Examples of temperature curves of patients undergoing endovascular cooling are shown (figure 2).

Safety. Endovascular cooling was generally well tolerated. There were no significant differences in hemodynamic variables or laboratory values between the two groups. There was a slight increase in mean systolic blood pressure and heart rate during induction of cooling and a slight decrease in respiratory rates. During the maintenance phase, systolic blood pressures came back to baseline and heart and respiratory rates dropped slightly below baseline (figure 3). There were 16 complications that occurred in 11 patients in the hypothermia group and 14 complications in 10 patients in the control group (table 3). In general, patients with complications had higher NIHSS scores (median 17.0 ± 4.6) than those without complications (median 10.5 ± 4.7) ($p = 0.009$).

Mortality. There were five deaths in the hypothermia group and four in the control group. None of the deaths was considered by the Data Safety Monitoring Board to be related to the device or to hypothermia. In the hypothermia group, three of the five patients died from complete MCA territory strokes, brain swelling, and herniation. One patient died from a large stroke with hemorrhagic transformation, and another died from multiorgan system failure. This man (Patient H2), with a history of ischemic cardiomyopathy, hypertension, and chronic renal failure, developed cardiogenic shock 24 hours after rewarming. A DNR/comfort care order was written following a long intensive care unit stay, and he died on day 30. The mean NIHSS score of hypothermia patients who died was 19.2 ± 1.9. In the control group, all four deaths occurred in patients with massive strokes. One woman (Patient C14) with ischemic cardiomyopathy developed cardiogenic shock on day 4 and died of a cardiac arrest on day 24. The mean NIHSS score of control patients who died was 20.3 ± 4.5.

Neurologic events. Two patients in the hypothermia group developed symptomatic hemorrhagic transformation. Neither received thrombolysis, and one had a hemorrhage present on the baseline MRI but not seen on CT scan. This patient (H7) was very hypertensive, had recanalized at the time of angiography, and was loaded with clopidogrel and begun on aspirin. Both patients had relatively late initiation of cooling (13 hours 29 minutes after stroke onset in one and 10 hours after stroke onset in another). One patient in the control group had a second ischemic stroke 4 days after the index stroke following carotid endarterectomy.

Cardiac events. In the hypothermia group, one patient (H2), as mentioned, developed cardiogenic shock 24 hours after rewarming and wide complex tachycardia later during the hospitalization. One patient developed new-onset atrial fibrillation thought to be the source of his stroke. In the control group, one patient developed cardiogenic shock

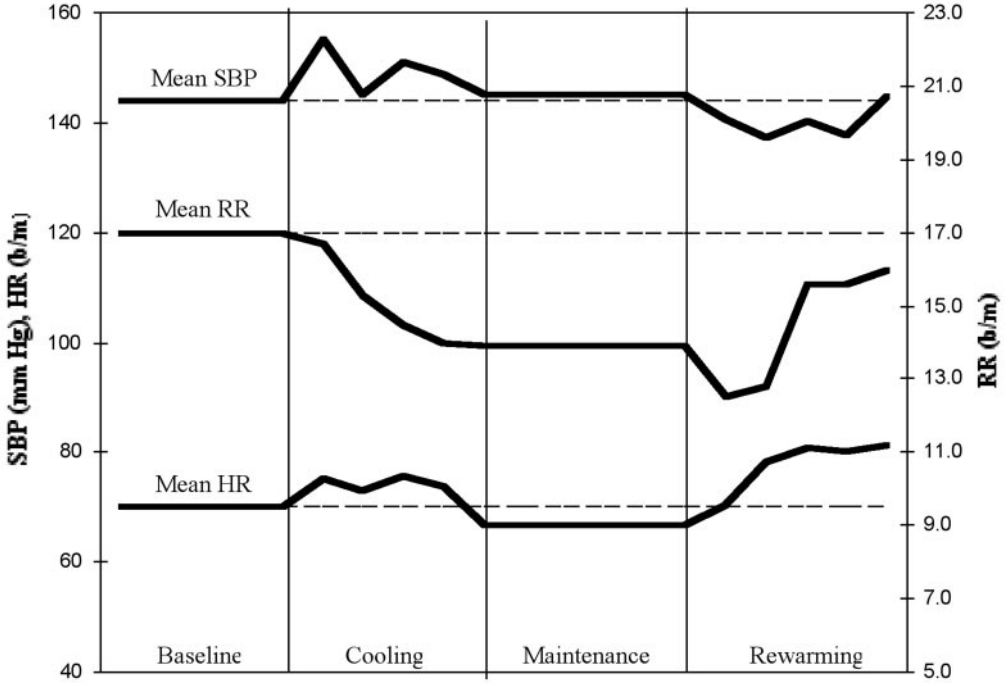

Figure 3. Hemodynamic data. SBP = systolic blood pressure; RR = respiration rate; HR = heart rate.

on day 4, another developed new-onset angina pectoris, and a third developed wide complex tachycardia.

Pulmonary events. Pulmonary events occurred in five patients in the hypothermia group and three in the control group. Two of the five hypothermia patients developed pneumonia, and three developed pulmonary edema. One developed radiographic signs of pulmonary edema, though clinically was asymptomatic. A second patient developed pulmonary edema and a pleural effusion following a retroperitoneal hemorrhage. A third patient (H10) developed pulmonary edema on day 1 that resolved with diuresis. On day 13, he developed bilateral infiltrates vs pulmonary edema and was treated with antibiotics and diuresis. On day 27, he was intubated for an adult respiratory distress syndrome-like pattern and to facilitate bronchoscopy. In the control group, two patients developed pneumonia and one developed pulmonary edema.

Eight patients in the hypothermia group required intubation during their hospitalization ($p = 0.002$). Four of the eight were patients with massive strokes who were intubated for airway protection. Only one was intubated during the maintenance phase of hypothermia, and the other three were intubated 48 to 72 hours after stroke onset. The other four patients were intubated for cardiopulmonary reasons at a mean of 9.5 ± 10 days after stroke onset. These reasons included cardiogenic shock (Patient H2 with an ejection fraction of 20%), pulmonary edema/pleural effusion (Patient H4 following retroperitoneal hemorrhage), worsening aspiration pneumonia present on admission (Patient H5), and pulmonary edema (Patient H10). The median age (71.0 ± 11.1 years) and NIHSS score (18.5 ± 3.5) of those requiring intubation were greater than the median age (54.5 ± 11.2 years; $p = 0.05$) and NIHSS score (14.5 ± 4.0; $p = 0.08$) of those who were not intubated. Only one patient in the control group was intubated: a woman with an NIHSS score of 23 who developed cardiogenic shock. The median NIHSS score of the remaining 18 nonintubated patients in the control group (excluding 3 who were DNR) was 11 ± 5.1. In the hypothermia group, the mean total meperidine dose was similar for intubated (12.5 ± 4.0 mg/kg) and nonintubated (12.2 ± 7.1 mg/kg) patients, but the mean duration of meperidine infusion was longer in patients who were intubated (33 hours 51 minutes ± 7 hours 9 minutes) than in those who were not intubated (26 hours 40 minutes ± 10 hours 14 minutes) (NS).

Peripheral vascular events. Vascular events occurred in four patients in the hypothermia group and two in the control group. One patient in the hypothermia group developed a retroperitoneal hemorrhage on the side of the femoral vein introducer sheath on day 6 while fully anticoagulated with heparin. She had just received intra-arterial thrombolysis for an MCA occlusion and was on aspirin and clopidogrel at the time of the initial femoral venous puncture. She was transfused 2 units of packed red blood cells and remained hemodynamically stable. Three patients had lower extremity deep vein thromboses (DVTs) detected by routine Doppler examinations. This surveillance Doppler monitoring was performed only in treatment patients and not control subjects. In one patient, the DVT was detected 9 days after enrollment and 3 days after a venogram showed no thrombosis. The DVT occurred at the previous site of access for both the device and the venogram. In a second patient, the DVT was detected 13 days after enrollment and 1 day after a central line was placed at the same site (and was still in place when the routine Doppler ultrasound was performed). In a third patient, the DVT was detected 2 days after enrollment; the catheter and introducer had just been removed, and manual pressure and a sandbag had been used at the site within hours of the examination. Routine surveillance Doppler monitoring was performed only in treatment patients. In the control group, one patient had a pulmonary embolism and another had a lower extremity DVT.

Table 3 *Complications*

Hypothermia, n = 18			Control, n = 21		
Event	Patient	Day	Event	Patient	Day
Neurologic			Neurologic		
Symptomatic HT	H7	Day 3	Repeat stroke	C20	Day 4
	H17	Day 3			
Cardiac			Cardiac		
Cardiogenic shock	H2	Day 3	Cardiogenic shock	C14	Day 4
Ventricular arrhythmia	H2	Day 21	Ventricular arrhythmia	C12	Day 2
Atrial fibrillation	H1	Day 2	Angina pectoris	C15	Day 4
Pulmonary			Pulmonary		
Pulmonary edema	H4	Day 7	Pulmonary edema	C12	Day 2
	H9	Day 2			
	H10	Day 1			
Pneumonia	H5	Day 1	Pneumonia	C2	Day 3
	H7	Day 3			
Vascular			Vascular		
Lower extremity DVT	H2	Day 10	Lower extremity DVT	C14	Day 6
	H7	Day 14			
	H8	Day 3			
Retroperitoneal hematoma	H4	Day 6	Pulmonary embolism	C4	Day15
Other			Other		
UTI	H11	Day 5	UTI	C3	Day 8
				C6	Day 8
				C9	Day 4
				C1	Day 2
Positive blood culture	H13	Day 3	Hematuria	C2	Day 3
16 events in 11 patients			14 events in 10 patients		

HT = hemorrhagic transformation; DVT = deep vein thrombosis; UTI = urinary tract infection.

Infections and other events. In the hypothermia group, one patient developed a urinary tract infection and another had a positive blood culture that probably was a contaminant (one of two bottles). In the control group, four patients developed urinary tract infections. Finally, in the control group, one patient developed hematuria on heparin that resolved once the heparin was stopped.

Efficacy. NIHSS and mRS scores at days 30 to 37 were similar between the two groups. Comparative MRI data were available in only 23 of the 40 patients. Comparing the initial image with the day 3 to 5 image, the DWI lesion growth in the hypothermia group was 90.0 ± 83.5% (n = 12) and in the control group 108.4 ± 142.4% (n = 11) (NS). The mean DWI lesion growth in patients who cooled well (n = 8) was 72.9 ± 95.2%. The mean DWI lesion growth in patients who cooled poorly (n = 4) was 124.4 ± 45.5% (NS).

Discussion. In this pilot trial, we found that endovascular cooling was feasible in patients with moderate to severe anterior circulation territory ischemic stroke. The heat-exchange catheter could be inserted quickly and easily, and we achieved a core body temperature of 33 °C in 14 of 18 patients (78%). Reduction in core temperature was rapid in 13 patients with a mean time to target temperature of 77 ± 44 minutes. In recent surface cooling trials, >4 hours was required to cool patients with severe brain injury[13] and 8 hours to cool patients after cardiac arrest.[9] In our previous surface cooling pilot trial, we were able to reach target temperature (32 °C) on average 3.5 hours after induction with considerable effort. We experienced no overshoot of target temperature with endovascular cooling in contrast to surface cooling.[14] In a few patients, the target temperature of 33 °C was not achieved, mainly because of mechanical reasons. Only one patient with a massive stroke was intubated during active cooling. All other 17 patients (94.4%) remained awake and responsive during hypothermia.

The safety of mild to moderate hypothermia has been demonstrated in several clinical settings, including traumatic brain injury,[13] cardiac arrest,[8,9] and myocardial infarction.[11] Although deep hypothermia may cause ventricular arrhythmia, coagulopathy, or immunosuppression, mild to moderate hypothermia has not been associated with these complications. All patients remained hemodynamically stable throughout hypothermia. The frequency of complications was similar in the hypothermia and control groups. In both groups, patients with complications were older and had more severe strokes. Endovascular cooling is invasive, however, and complications can occur. The one retroperitoneal hemorrhage was directly related to the initial femoral puncture when inserting the venous sheath. This occurred in a patient who had received

intra-arterial thrombolysis, followed by aspirin, clopidogrel, and heparin. Three patients had DVTs in the treatment group that may have been related to the endovascular cooling device, although there were several other confounding factors in these patients. Other studies using the Reprieve[11,15] and other endovascular cooling devices[16] have not demonstrated an increased incidence of DVT. Four patients in the hypothermia group with massive strokes were intubated for airway protection (only one during active cooling), and another four were intubated later for cardiopulmonary reasons. Intubated patients were older and had more severe strokes than nonintubated patients. They also had longer durations of meperidine infusions, however, and it is possible that this contributed to the need for intubation. As anticipated, given the small size, there were no differences in clinical outcomes. Infarct volume growth was less in the hypothermia group, but this was not significant.

We sought to evaluate the feasibility of induced moderate hypothermia in patients with acute ischemic stroke using an endovascular cooling device coupled with meperidine, buspirone, and surface warming to suppress shivering. The results suggest that this approach is feasible; moderate hypothermia can be induced in patients with ischemic stroke quickly and effectively and maintained for 24 hours in most patients. Endovascular cooling is generally safe and well tolerated in most patients. Some elderly patients with severe strokes and those with comorbidities treated for >24 hours developed pulmonary compromise, however. The medications used to suppress shivering induce sedation and need to be titrated carefully. This may be especially important in the elderly stroke patient with compromised airway control or with propensity toward sedative-induced hypoventilation and atelectasis. We believe that the best target population for induced hypothermia includes younger patients and those with moderate strokes. Although the optimal duration is not clear, treatment for ≤24 hours may reduce the risks. Larger clinical trials are needed to determine whether endovascular cooling improves clinical outcomes in patients with acute ischemic stroke.

Appendix

Data Safety Monitoring Board Allan Ropper, MD (St. Elizabeth's Medical Center, Boston, MA); Jennifer J. Gassman, PhD (Cleveland Clinic Foundation, OH).

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