Hypothermia in Comatose Survivors From Out-of-Hospital Cardiac Arrest : Pilot Trial Comparing 2 Levels of Target Temperature

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Circulation. published online November 6, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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Pilot Trial Comparing 2 Levels of Target Temperature

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Background—It is recommended that comatose survivors of out-of-hospital cardiac arrest should be cooled to 32° to 34°C for 12 to 24 hours. However, the optimal level of cooling is unknown. The aim of this pilot study was to obtain initial data on the effect of different levels of hypothermia. We hypothesized that deeper temperatures will be associated with better survival and neurological outcome.

Methods and Results—Patients were eligible if they had a witnessed out-of-hospital cardiac arrest from March 2008 to August 2011. Target temperature was randomly assigned to 32°C or 34°C. Enrollment was stratified on the basis of the initial rhythm as shockable or asystole. The target temperature was maintained during 24 hours followed by 12 to 24 hours of controlled rewarming. The primary outcome was survival free from severe dependence (Barthel Index score ≥60 points) at 6 months. Thirty-six patients were enrolled in the trial (26 shockable rhythm, 10 asystole), with 18 assigned to 34°C and 18 to 32°C. Eight of 18 patients in the 32°C group (44.4%) met the primary end point compared with 2 of 18 in the 34°C group (11.1%) (log-rank $P=0.12$). All patients whose initial rhythm was asystole died before 6 months in both groups. Eight of 13 patients with initial shockable rhythm assigned to 32°C (61.5%) were alive free from severe dependence at 6 months compared with 2 of 13 (15.4%) assigned to 34°C (log-rank $P=0.029$). The incidence of complications was similar in both groups except for the incidence of clinical seizures, which was lower (1 versus 11; $P=0.0002$) in patients assigned to 32°C compared with 34°C. On the contrary, there was a trend toward a higher incidence of bradycardia (7 versus 2; $P=0.054$) in patients assigned to 32°C. Although potassium levels decreased to a greater extent in patients assigned to 32°C, the incidence of hypokalemia was similar in both groups.

Conclusions—The findings of this pilot trial suggest that a lower cooling level may be associated with a better outcome in patients surviving out-of-hospital cardiac arrest secondary to a shockable rhythm. The benefits observed here merit further investigation in a larger trial in out-of-hospital cardiac arrest patients with different presenting rhythms.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT01155622.

(*Circulation*. 2012;126:00-00.)

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ induced mild hypothermia ■ resuscitation ■ trials

The pathophysiology of cerebral injury after successful resuscitated cardiac arrest is the subject of extensive research, and it is currently thought to be multifactorial. The initial damage is directly related to the time elapsed from the onset of cardiac arrest to the return of spontaneous circulation (ROSC). Cerebral anoxia not only causes the death of cerebral tissue and neurons but also primes the brain for further injury during the reperfusion phase. Experimental and clinical evidence have confirmed the neuroprotective effect of moderate to mild (30°C to 35°C) therapeutic hypothermia (TH), probably by acting on multiple deleterious pathways.[1–4]

Editorial see p ●●●
Clinical Perspective on p ●●●

On the basis of 2 randomized clinical trials,[3,4] the American Heart Association and the European Resuscitation Council recommended TH for adults who remained comatose after initial resuscitation from out-of-hospital ventricular fibrillation or pulseless ventricular tachycardia as the initial cardiac rhythm of circulatory arrest.[5] The panel also stated that TH might possibly be beneficial for treatment of other heart rhythms and for in-hospital cardiac arrest. The target temper-

Received August 10, 2012; accepted October 13, 2012.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.136408**

ature recommended is 32°C to 34°C for 12 to 24 hours.[5] However, it is unknown which target temperature is more efficacious. Different clinical trials have compared normothermia with mild TH, but none have compared different levels of TH. Theoretically, lower temperatures should provide more protection. Experimental models suggest that for every 1°C reduction in body core temperature, the cerebral metabolic rate decreases by 6%.[6] However, only 1 registry analyzed different levels of TH, raising concerns when patients reached 32°C.[7] In addition, although TH is recommended, there is no information derived from clinical trials on the effect of TH in out-of-hospital cardiac arrest (OHCA) with asystole as first rhythm. Even some investigators consider the efforts for resuscitation in asystolic OHCA futile.[8] The aim of this pilot, randomized, single-center study was to obtain initial data on the effect of different levels of TH in comatose survivors of OHCA. We hypothesized that colder temperatures would be associated with better survival and neurological outcome.

Methods

Patients

Patients admitted consecutively between March 2008 and August 2011 to the acute cardiac care unit of the Hospital Universitario La Paz, Madrid, Spain, were potentially eligible for the study if they had a witnessed OHCA apparently related to heart disease and an interval of ≤60 minutes from collapse to ROSC. Additional inclusion criteria were age >18 years and initial registered rhythm of a shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) or asystole. Exclusion criteria were known pregnancy, Glasgow Coma Scale score after ROSC >8, cardiogenic shock (a systolic blood pressure of <80 mm Hg despite inotrope infusion >30 minutes), other nonshockable rhythms (pulseless electric activity), a terminal illness present before the OHCA, or possible causes of coma other than cardiac arrest (drug overdose, head trauma, or cerebrovascular accident).

Study Design and Treatment Protocol

Because there are no clinical trials in humans studying the effect of different levels of TH after OHCA, this pilot study was conducted as a preliminary investigation designed to generate data to assess whether there is likely to be a treatment effect in a main study, to assess safety, and for sample size calculations.

The protocol and consent procedure were approved by the institutional ethics review committee in accordance with European guidelines for good clinical practice. Next of kin were informed about the trial, and written consent was obtained before inclusion. Treatment assignments to 32°C or 34°C were randomly generated by computer, and enrollment was stratified on the basis of the initial rhythm (shockable rhythm or asystole), with instructions to use the sealed opaque envelopes in numeric order according to the initial rhythm. Immediately after a patient had been enrolled, an envelope was opened, and the patient was assigned to the specified group.

Personnel involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments. However, the physicians responsible for assessing the neurological outcome within the first 6 months after the arrest were unaware of the treatment assignment.

All patients received standard care according to a detailed protocol. On arrival, the patients underwent routine initial assessment and treatment. After an evaluation of neurological status, sedation was induced by the intravenous administration of midazolam (bolus of 5–10 mg followed by 1.5 μg/kg per minute initially) and remifentanil (0.1 μg/kg per minute initially), and the doses were adjusted as needed for the management of mechanical ventilation. To prevent shivering, paralysis was induced by the intravenous administration of cisatracurium (1 μg/kg per minute initially) during TH. Ventilation was set to maintain an arterial oxygen saturation ≥95%, thereby maintaining normoxemia as well as normocapnia. Positive end-expiratory pressure up to 5 mm Hg was used to reduce FiO_2. Mean arterial blood pressure objective was between 85 and 100 mm Hg measured by an arterial line; any decrease was treated with crystalloids and/or colloids, and vasopressors were used only if blood pressure could not be controlled with fluid therapy alone. To minimize hyperglycemia, no glucose infusions were used, and insulin was administered to maintain the blood glucose level at <180 mg/dL (10 mmol/L). Patients with ST-segment elevation on ECG underwent immediate cardiac catheterization, and percutaneous coronary intervention was performed if indicated. The head of the bed was elevated at 30°; a bladder catheter with a temperature probe was inserted routinely to monitor urinary output and core temperature.

All patients were cooled on admission with the intravenous infusion of <8°C cold saline at a rate of 1000 mL/h followed by the implantation of the Icy 9.3F 38-cm catheter (ZOLL Medical Corporation, Chelmsford, MA) placed in the inferior vena cava through a femoral vein connected to the Thermogard XP Temperature Management System (ZOLL Medical Corporation). The system consists of a pump that circulates refrigerated sterile saline (to a minimum temperature of 4°C to 5°C) from the external device through balloons coaxially mounted on the catheter, enabling direct cooling of the blood. Cooling was set at a maximum rate with a target temperature of 32°C or 34°C according to randomization. Cold saline infusion was maintained at the discretion of the attending physician but always terminated when target temperature was achieved. The target temperature was maintained during 24 hours, and afterward a controlled rewarming was started at a set rate of 0.1°C to 0.3°C per hour to reach 37°C in 12 to 24 hours after the start of rewarming. All other aspects of patient management were at the discretion of the treating physicians.

For patients who remained deeply comatose after 5 days of evolution, limitation of active advanced life support was decided in agreement with their representatives. Patients with an uncertain prognosis underwent tracheostomy and were discharged from the acute cardiac care unit when life support measures could be withdrawn.

Data on cardiac arrest for individual patients were recorded in the Utstein style.[9] Laboratory tests were performed at least at baseline and 24 and 48 hours after OHCA and as clinically indicated. Risk factors for an unfavorable outcome were documented.

Outcome

The primary outcome measure was to examine the effect on survival free from severe dependence at 6 months between 2 levels of TH after OHCA. Independence was defined as a Barthel Index score ≥60 points. A specialist in rehabilitation medicine evaluated the surviving patients after discharge and 6 months. The Barthel Index is a 10-item ordinal scale that measures functional independence in the domains of personal care and mobility. Specifically, it measures self-care, sphincter management, transfers, and locomotion.[10] Individuals are scored on 10 activities, which are summed to give a score of 0 (totally dependent) to 100 (fully independent). In practical terms, a score of ≥60 indicates that the patient is independent for essential personal care. The neurological outcome was determined without knowledge of the patient's treatment assignment. Testing was prespecified to be analyzed in the whole population and according to the initial rhythm. Secondary end points were overall mortality at 6 months and favorable neurological outcome at 6 months, defined as the best cerebral class as determined by a Pittsburgh cerebral performance category of 1 or 2 (good or moderate disability) on a 5-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (brain death).[11]

Safety end points were the rate of complications during the first 72 hours and 7 days after OHCA. The complications analyzed were bleeding (bleeding causing fatality, intracranial bleeding, and other bleeding that required transfusion); infection (sepsis, pneumonia, urinary tract infection) with positive culture; renal impairment (increase in serum creatinine of ≥0.5 mg/dL or 25% over their

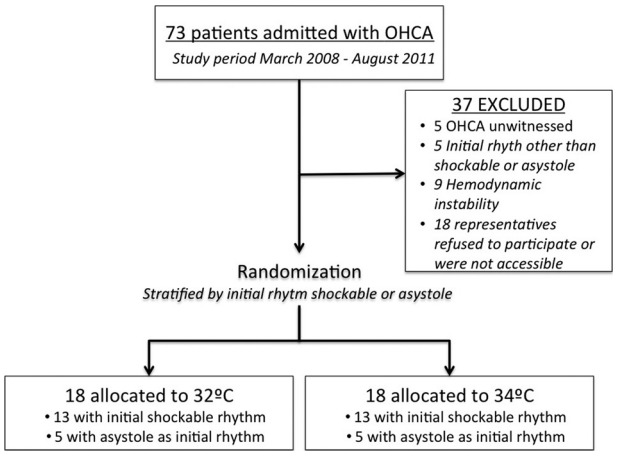

Figure 1. Flow chart for patients admitted to Hospital Universitario La Paz who were comatose survivors of an out-of-hospital cardiac arrest (OHCA) during the study period.

baseline value); hypokalemia (<3.5 mEq/L); and arrhythmia (ventricular fibrillation, ventricular tachycardia, bradycardia <40 bpm, atrial flutter, atrial fibrillation, need for pacing, new cardiac arrest) at different hypothermia levels. Other adverse events, such as the incidence of clinically recognized seizures or hyperthermia (≥38°C within 7 days), were also analyzed.

Statistical Analysis

Continuous variables are presented as mean±SD and were compared with the use of the Student *t* test; variables that were not normally distributed were described as medians and interquartile ranges, and differences were analyzed with the Kruskal-Wallis method. Categorical variables were compared by the χ^2 test or Fisher exact test. Survival curves for time to event of the primary objective were summarized by treatment group and stratum of initial rhythm, and event rates were expressed with Kaplan-Meier estimates at 6 months and were compared with the use of the log-rank test. The interaction between target temperature and initial rhythm was tested with the Cox proportional hazards model including the temperature level, initial rhythm, and the crossed covariate of temperature level×initial rhythm. Variables such as bystander cardiopulmonary resuscitation and dichotomized variables of age (aged >65 years or not), minutes from collapse to ROSC (<30 minutes or not), and Glasgow Coma Scale score (3 or 4–8) were tested with the Cox proportional hazards model with the assigned temperature and survival free from severe dependence at 6 months. An adjusted odds ratio for survival free from severe dependence at 6 months was calculated by multivariate logistic regression including the variables with $P<0.05$ in the Cox model. The statistical significance of these variables in the multivariate models was evaluated by a likelihood ratio χ^2 test. Statistical analysis was performed with the JMP 9.01 statistical package (SAS Institute Inc, Cary, NC).

Results

Characteristics of the Patients

During the study period, 73 patients were assessed for eligibility; 36 patients were enrolled in the trial, with 18 assigned to 34°C and 18 to 32°C. Thirty-seven patients were not enrolled in the study; 19 of them were ineligible, 5 because the arrest was unwitnessed, 5 because the documented initial rhythm was other than asystole or a shockable rhythm, and 9 because of hemodynamic instability at admission; the remaining 18 patients were not randomized because their representatives refused to participate in the trial or were not accessible at admission (Figure 1). Patients not enrolled in the trial were treated with TH at target temperature of 33°C. Baseline features of the patients enrolled are presented in Table 1, showing the characteristics according to the assigned temperature. All enrolled patients reached the target temperature and completed the assigned cooling treatment. The mean temperature during the 24-hour period of target cooling was 32.11±0.23°C and 34.09±0.20°C in those assigned to 32°C and 34°C, respectively. Only 1 patient assigned to 32°C and who had a body mass index of 38.1 kg/m^2 was difficult to maintain at the target temperature. Two patients assigned to 32°C died during rewarming and did not achieve 37°C. Data on primary outcome at 6 months were available in all patients.

Outcomes

Eight of 18 patients in the 32°C group (44.4%) were alive free from severe dependence at 6 months compared with 2 of 18 in the 34°C group (11.1%) (Figure 2; log-rank $P=0.12$). All randomized patients whose initial rhythm was asystole died before 6 months in both groups of assigned temperature (Figure 3A; log-rank $P=0.24$). In patients whose initial rhythm was ventricular fibrillation, there was a higher survival rate free from severe dependence at 6 months in those patients assigned to 32°C (61.5%) compared with those assigned to 34°C (15.4%) (Figure 3B; log-rank $P=0.029$). The Cox model showed that there was a significant interaction of target temperature and initial rhythm (target temperature, $P=0.49$; initial rhythm, $P=0.003$; target temperature× initial rhythm, $P=0.039$).

In the whole study population, the Cox model identified 2 variables significantly related to the primary outcome: an initial shockable rhythm (risk ratio, 0.35; 95% confidence interval, 0.15–0.84; $P=0.02$) and Glasgow Coma Scale score at admission of 4 to 8 (risk ratio, 0.0000007; 95% confidence interval, 0.0–0.58; $P=0.01$), confirmed with multivariate logistic regression analysis ($P=0.015$ and $P=0.01$, respectively). In patients with shockable initial rhythm, the Cox model identified 3 variables significantly related to the primary outcome: age <66 years (risk ratio, 0.28; 95% confidence interval, 0.09–0.82; $P=0.02$); Glasgow Coma Scale score at admission of 4 to 8 (risk ratio, 0.0000007; 95% confidence interval, 0.0–0.91; $P=0.04$); and assignment to a target temperature of 32°C (risk ratio, 0.31; 95% confidence interval, 0.09–0.94; $P=0.04$), confirmed with multivariate logistic regression analysis ($P=0.006$, $P=0.046$, and $P=0.03$, respectively).

Secondary end points are shown in Table 2. Twenty-six patients (72.2%) died 6 months after OHCA: all patients with an initial rhythm of asystole (100%) and 16 (61.5%) of those patients with a shockable initial rhythm. At 6 months, there was only 1 patient alive with a cerebral performance category of 3 (the only patient with Barthel Index score <60) who was assigned to 34°C. Among 26 patients who died, 17 perished after limitation of the therapeutic effort due to encephalopathy, 3 of multiorgan failure, 3 because of new cardiac arrest with unsatisfactory response, 1 of hepatic rupture, and 1 of acute respiratory distress syndrome. Neurological outcome could not be assessed in 4 patients because they died before sedation was withdrawn: 2 with initial rhythm of asystole and

Table 1. Clinical Characteristics of the 36 Patients Randomized to Different Levels of Temperature

	32°C (n=18)	34°C (n=18)	*P*
Age, mean±SD, y	64.7±14.5	63.1±13.1	0.7
Female sex, n (%)	3 (16.7)	1 (5.6)	0.3
Diabetes mellitus, n (%)	5 (27.8)	3 (16.7)	0.4
Hypertension, n (%)	7 (38.9)	12 (66.7)	0.09
Dyslipemia, n (%)	7 (38.9)	1 (5.6)	0.01
Current smoker, n (%)	9 (50.0)	11 (61.1)	0.5
Previous heart failure, n (%)	2 (11.1)	3 (16.7)	0.6
Previous myocardial infarction, n (%)	6 (33.3)	4 (22.2)	0.5
Previous revascularization, n (%)	3 (16.7)	5 (27.8)	0.4
ST-segment elevation myocardial infarction, n (%)	4 (22.2)	6 (33.3)	0.5
Bystander CPR, n (%)	13 (72.2)	12 (66.7)	0.7
Initial rhythm, VF-VT/asystole	13/5	13/5	
Time to arrival of ALS, mean±SD, min	9.6±5.2	9.8±4.2	0.9
Time to ROSC, mean±SD, min	21.2±13.0	31.9±22.0	0.09
GCS score on admission, median (25% to 75% IQR)	3 (3–3)	3 (3–3)	0.08
Body mass index, mean±SD	27.2±3.7	28.1±3.2	0.5
MAP at admission, mean±SD, mm Hg	97.0±25.7	81.9±24.2	0.08
Primary PCI, n (%)	4 (22.2)	6 (33.3)	0.6
Time since ROSC to start of TH, mean±SD, min	140.6±94.5	100.8±72.1	0.2
Time since start of TH to 34°C, mean±SD, min	303.9±238.9	270.2±151.4	0.6
Time since start of TH to target, mean±SD, min	491.2±324.1	270.2±151.4	0.01
Time ≤34°C, mean±SD, min	1944.7±351.3	1461.1±85.8	<0.0001
Time on target temperature, median (25% to 75% IQR), min	1440 (1316–1440)	1440 (1403–1477)	0.09

CPR indicates cardiopulmonary resuscitation; VF-VT, ventricular fibrillation/ventricular tachycardia; ALS, advanced life support; ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale; IQR, interquartile range; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; and TH, therapeutic hypothermia.

2 with shockable rhythm, all of them assigned to 32°C. A favorable neurological outcome was achieved in 8 of the 14 patients (57.1%) in the 32°C group compared with 5 of the 17 (29.4%) in the 34°C group before death or discharge from hospital (risk ratio, 2.06; 95% confidence interval, 0.86–4.92). In patients whose initial rhythm was asystole, only 1 patient assigned to 34°C had a favorable neurological outcome before dying of acute respiratory distress syndrome. In patients whose initial rhythm was a shockable rhythm, a favorable neurological outcome was reached in 4 of the 11 patients (36.3%) in the 32°C group compared with 4 of the 13 (30.8%) in the 34°C group before death or discharge from hospital (risk ratio, 2.36; 95% confidence interval, 0.97–5.77; $P=0.059$).

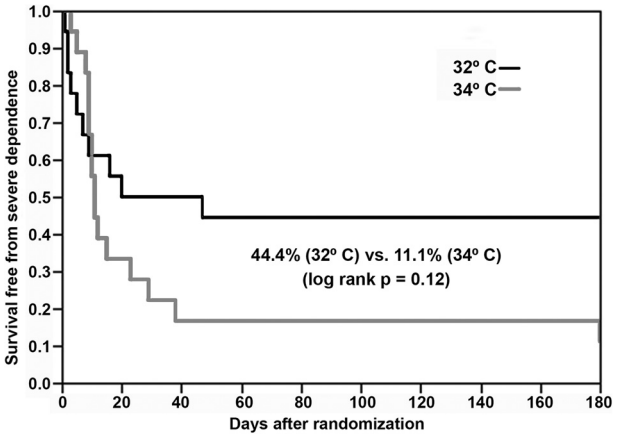

Figure 2. Cumulative survival free of severe dependence at 6 months in the 32°C and 34°C groups.

Safety Issues

Adverse events and complications that occurred during the first 7 days are presented in Table 3. The incidence of clinical seizures was lower (1 versus 11; $P=0.0002$) in patients assigned to 32°C than in those assigned to 34°C. On the contrary, there was a trend of higher incidence of bradycardia (7 versus 2; $P=0.054$) in patients assigned to 32°C. Although potassium levels decreased in a greater degree among patients assigned to 32°C, the incidence of hypokalemia was similar in both groups.

Discussion

The results of this pilot, randomized trial suggest that TH with a target of 32° may yield better protection than cooling at 34°C, resulting in a better short- and long-term outcome.

Target Temperature

TH has become a standard of care for patients who remain comatose after OHCA. However, there is a lack of informa-

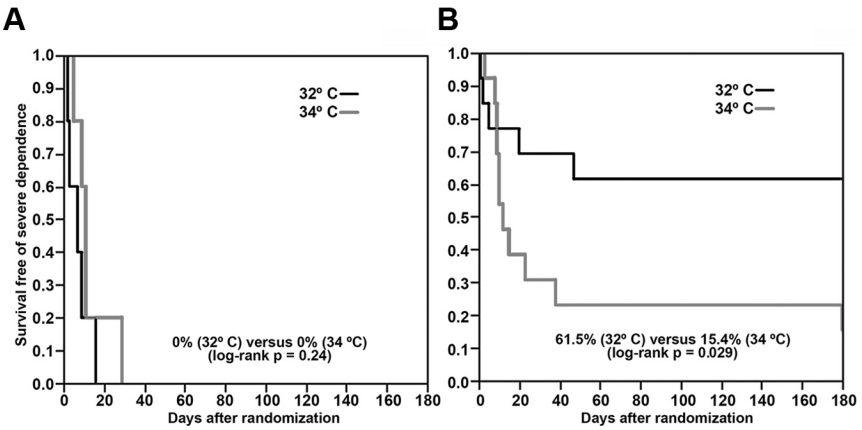

Figure 3. Cumulative survival free of severe dependence at 6 months according to initial rhythm in the 32°C and 34°C groups. **A**, Outcomes in patients with asystole as initial rhythm. **B**, Outcomes in patients with ventricular fibrillation or pulseless ventricular tachycardia as initial rhythm.

tion regarding many of the temperature management components, including the following: optimal target temperature, duration of cooling, and optimal methodology for cooling and rewarming. The early use of TH included target body temperatures <30°C; these were associated with cardiac arrhythmias, coagulopathy, and elevated infection rates. Animal studies suggest that there is better protection when a lower temperature is reached.[1] To reduce these adverse side effects, some studies at the beginning of the last century focused on the efficacy of lowering body temperature to ≈33±1°C after successful resuscitation, referred to as mild TH.[3,4] Most clinical studies to date have used conventional surface-based cooling techniques (ice bags and cool air or water blankets), which are controlled manually and are generally slow and imprecise in achieving and maintaining target temperature. Endovascular cooling and other surface automatic devices have proved to be more accurate methods for temperature regulation than conventional surface cooling techniques.[12] This has generated the need to determine the optimum level of cooling in this situation, particularly when there is a possibility of maintaining the target temperature at a stable level within a narrow margin. At the time when this pilot study was designed, no data were available in humans that would aid in choosing between 32° and 34°C. As a result, most attending physicians decided to treat patients at 33°C. Recently, a registry analyzed the results of different target temperatures in which the target temperature was chosen according to the preference of the attending physician.[7] No significant differences were found between different cooling temperatures with respect to mortality and neurological out-

Table 2. End Points According to Different Levels of Temperature

	32°C, No./ Total No. (%)	34°C, No./ Total No. (%)	*P*
Primary end point			
All patients	8/18 (44.4)	2/18 (11.1)	0.12
Initial rhythm asystole	0/5 (0)	0/5 (0)	0.24
Initial rhythm VF/VT	8/13 (61.5)	2/13 (15.4)	0.029
Death at 6 mo			
All patients	10/18 (55.6)	16/18 (88.9)	0.03
Initial rhythm asystole	5/5 (100)	5/5 (100)	
Initial rhythm VF/VT	5/13 (38.5)	11/13 (84.6)	
Best neurological status in 6 mo (all)*			0.08
CPC 1–2	9/18 (50)	4/18 (22.2)	
CPC 3–5	9/18 (50)	14/18 (77.8)	
Best neurological outcome in 6 mo (asystole)*			0.2
CPC 1–2	0/5 (0)	1/5 (20.0)	
CPC 3–5	5/5 (100)	4/5 (80.0)	
Best neurological outcome in 6 mo (VF/VT)*			0.02
CPC 1–2	9/13 (69.2)	3/13 (23.1)	
CPC 3–5	4/13 (30.8)	10/13 (76.9)	

FV/VT indicates ventricular fibrillation/pulseless ventricular tachycardia; CPC, cerebral performance category.

*Neurological outcome could not be assessed in 2 patients with initial rhythm of asystole and 2 with shockable rhythm because they died before evaluation and were considered to have a best neurological outcome in 6 mo of CPC 3–5.

Table 3. Complications During the First Week According to the Assigned Target Temperature

	32°C (n=18), n (%)	34°C (n=18), n (%)	*P*
Bleeding	6 (33.3)	3 (16.7)	0.2
Hyperthermia	12 (66.7)	16 (88.9)	0.1
Any infection (positive culture)	8 (44.4)	6 (33.3)	0.5
Renal impairment	2 (11.1)	1 (5.6)	0.5
Renal replacement therapy	2 (11.1)	0 (0.0)	0.2
Hypokalemia	9 (50)	5 (27.8)	0.2
Ventricular malignant arrhythmia	2 (11.1)	1 (5.6)	0.5
Atrial fibrillation/flutter	5 (27.8)	1 (5.6)	0.3
Bradycardia	7 (38.9)	2 (11.1)	0.054
Temporary cardiac pacing	2 (11.1)	0 (0.0)	0.2
Need of inotropes	13 (72.2)	16 (88.9)	0.2
IABP	4 (22.2)	1 (5.6)	0.1
Incidence of clinical seizures	1 (5.6)	11 (61.1)	0.0002
Pressure sores	0 (0)	0 (0)	1
Deep venous thrombosis	0 (0)	1 (5.6)	0.3
Pulmonary embolism	0 (0)	1 (5.6)	0.3

IABP indicates intra-aortic balloon pump.

comes. Conversely, many authors consider that the existing evidence is inconclusive. There is nevertheless a large ongoing trial that compares 2 different target temperatures (33°C versus 36°C) and is attempting to define which is the paramount mechanism of protection is avoidance of hyperthermia or hypothermia per se.[13] The main objective of the study was to obtain preliminary data to explore whether it could be reasonable to undertake a new study with different levels of TH and not to demonstrate the superiority of one temperature over the other. Because of the concern about possible complications, temperature <32°C was not explored in this pilot trial. Studying temperatures >34°C would not help for future research. If there were differences between 32°C and temperatures >34° suggestive of any effect, they would probably be attributed to the lack of allocation of one group to a level of TH without proven efficacy (>34°C). On the contrary, a lack of differences between 32°C and >34°C would only generate uncertainties in regard to the effectiveness of TH on the basis of a small trial not powered to analyze treatment effects. For this reason, we have selected temperatures within the limits established by current recommendations. Different levels of TH had been evaluated previously in animal studies, suggesting that neurological recovery is enhanced with 30°C of cranial temperature compared with outcome with 34°C or 27°C.[14] On the contrary, another study did not find differences in outcome between 33°C and 35°C.[15] With the results obtained, it is now probably justified to also explore the effect of achieving levels <32°C.

Endovascular cooling devices seem to be superior for rapid induction of TH, and they maintain a more stable temperature than cooling techniques with blankets and ice bags.[16] Similar results probably could be obtained with the use of automatic surface cooling devices, but with these classic methods it would not be possible to maintain the temperature within the narrow margins achieved with automatic devices. Recently, it has been reported that there are no differences in temperature management between automatic surface and core cooling devices.[17]

Another factor that may have had an impact on the better results in patients assigned to 32°C was that this group of patients remained cooled for a longer period of time than those assigned to 34°C. Although the duration at target temperature was similar in both groups, patients assigned to 32°C required more time to reach the target temperature, as well as a longer rewarming time. Longer exposure to TH may have a better impact on prognosis, as was observed in a series of patients treated with TH in which those patients maintained at a stable core temperature of 33°C over 18 hours had a more favorable neurological outcome than those patients cooled for a shorter time.[18]

Rewarming is an issue that often has been ignored in clinical trials. This pilot trial was only designed to address a possible effect between 2 target levels of cooling. For this reason, it was decided that rewarming should last between 12 and 24 hours. Although rewarming was controlled at a rate of 0.1°C to 0.3°C per hour, which is within the general recommendations, it could have had an impact on the results. It is noteworthy that 4 patients assigned to 32°C died, 2 during rewarming and 2 shortly after finishing rewarming as a result of hemodynamic instability, whereas none assigned to 34°C died. Some data suggest that higher rewarming rates may have a deleterious effect.[19] Future research in this field should also focus on this issue and probably set rewarming at a similar rate or explore different rewarming rates.

Initial Rhythm

In this small series, the outcome was worse in patients with asystole as initial rhythm. The apparent benefit observed in patients with shockable initial rhythm assigned to 32°C was not apparent in patients with asystole. The benefit observed in shockable rhythm may be due to multiple factors other than the effect of lower target temperature. Although characteristics between the 2 groups were not statistically different, poor prognostic factors were present in a higher proportion in patients assigned to 34°C, which may have had an impact on the results. Patients assigned to 34°C received fewer resuscitation attempts by bystanders, required longer time to ROSC, and had a tendency to have a worse admission Glasgow Coma Scale score compared with patients assigned to 32°C. Adjusted multivariate analysis showed an independent effect of assigned target temperatures. Moreover, some factors that can affect prognosis have not been taken into account in this pilot study, as well as in most trials, such as quality of resuscitation attempts, comorbidities, and etiology of arrest. On the other hand, small samples containing subgroups with unanticipated results are difficult to interpret and can only be considered suggestive.

Safety

The choice of a target temperature of 32°C apparently is as safe as that of 34°C. In the previously mentioned registry,[7] hypotension was more frequent in the 32°C group ($P=0.023$). The present study suggests that heart rate may decrease more with lower temperatures, but otherwise no differences were found in the incidence of other secondary effects, with the exception of the incidence of seizures, which were more common in the 34°C group. Seizures are common after OHCA. It remains unclear whether they contribute to poor neurological outcomes or are simply a marker of irreversible brain damage. Acute clinical seizures occur in between 15% and 44% of postarrest patients.[20] Although continuous electroencephalography has been recommended for patients who remain comatose after OHCA, it was not used routinely in this trial. Clinically recognized seizures were less frequent in patients assigned to 32°C; whether cooling to this lower temperature has an impact on seizures that are not recognized at the bedside is unknown.

Potassium levels decreased to a greater extent in patients assigned to 32°C, but there were no statistical differences in the incidence of hypokalemia between both groups, as documented in trials of TH.[21] Despite the findings of this pilot study, safety may be biased because knowledge of the assigned temperature by attending physicians and the routine blood samples obtained could have prevented the manifestation of many of the complications associated with TH.[21]

Although outcomes from OHCA resulting from nonshockable rhythms are poor when compared with shockable rhythm presentations, a significant improvement after implementa-

tion of resuscitation guideline changes has been documented previously.[22] This group of patients is more heterogeneous than that of patients with shockable rhythms. Nonshockable rhythms include asystole, pulseless electric activity, and extreme bradycardia, which are associated with different prognoses. Our results suggest a very poor overall outcome in these patients, but this pilot study is inconclusive in determining whether there could be some effect in OHCA due to asystole. For this reason, treatment in this situation remains a subject of debate.[23]

Estimation of Sample Size

In this study, we used the Barthel Index in an attempt to better discriminate the possible neurological sequelae rather than the cerebral performance category scale, which is subjective. In this trial, the number of patients with a cerebral performance category of 1 or 2 was similar to that of patients with Barthel Index score ≥ 60. Therefore, it is not possible to know whether this index is better than that commonly used in patients with traumatic brain injury or OHCA in future research. If we consider that the relative risk of 6-month survival free of dependence is 1.86 with a cooling level of 32°C compared with 34°C in the entire population enrolled in the trial, a forthcoming clinical trial would need a sample size of 137 patients in each group on the basis of a 2-tailed analysis with a significance threshold (α) of 0.025 and a statistical power ($1-\beta$) of 0.95, with the assumption of an exponential survival distribution, a linear recruitment rate, and no dropout.

Study Limitations

The present study has a number of limitations. The small sample size and the inherent variability of the prognosis of these patients lead to the presence of multiple confounding factors with possible influence on the outcomes, and therefore the results should be interpreted with caution. In particular, post hoc multiple comparisons of subgroup analysis may yield spurious false-positive results. Nevertheless, the aim of the study was not to provide information to change clinical practice but to offer a basis for future research. The absence of blinding of the target temperature may have introduced a bias in the monitoring and management of patients. However, it is known that to avoid complications, these patients need invasive monitoring of blood pressure and periodic blood samples for adjustment of ventilator parameters and electrolyte reposition on an individual basis, not directed by the temperature reached.

Conclusions

The findings of this pilot trial suggest that a cooling target of 32°C may improve outcomes of OHCA secondary to ventricular fibrillation or pulseless ventricular tachycardia. Further investigation is needed to address the optimal target level of hypothermia in this challenging clinical setting.

Sources of Funding

This study was funded by the Hospital Universitario La Paz, Madrid, Spain.

Disclosures

None.

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CLINICAL PERSPECTIVE

Comatose survivors from an out-of-hospital cardiac arrest present very high mortality, and survivors frequently recover with severe neurological disabilities. Early studies suggest that therapeutic hypothermia may reduce cerebral damage in this setting. However, the optimal level of cooling remains controversial. With classic cooling methods, it was very difficult to maintain a stable temperature at a particular level, which is now possible with the use of devices with automatic temperature feedback control. To further investigate the optimal target temperature during hypothermia, we conducted a pilot trial comparing cooling at 32°C versus 34°C in comatose survivors of out-of-hospital cardiac arrest. The results suggest that the lower temperature level is safe and may be associated with a better outcome in patients surviving an arrest secondary to a shockable rhythm. This observation merits further investigation in a large clinical trial with different initial rhythms.