Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest

The PRINCESS Randomized Clinical Trial

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IMPORTANCE Therapeutic hypothermia may increase survival with good neurologic outcome after cardiac arrest. Trans-nasal evaporative cooling is a method used to induce cooling, primarily of the brain, during cardiopulmonary resuscitation (ie, intra-arrest).

OBJECTIVE To determine whether prehospital trans-nasal evaporative intra-arrest cooling improves survival with good neurologic outcome compared with cooling initiated after hospital arrival.

DESIGN, SETTING, AND PARTICIPANTS The PRINCESS trial was an investigator-initiated, randomized, clinical, international multicenter study with blinded assessment of the outcome, performed by emergency medical services in 7 European countries from July 2010 to January 2018, with final follow-up on April 29, 2018. In total, 677 patients with bystander-witnessed out-of-hospital cardiac arrest were enrolled.

INTERVENTIONS Patients were randomly assigned to receive trans-nasal evaporative intra-arrest cooling (n = 343) or standard care (n = 334). Patients admitted to the hospital in both groups received systemic therapeutic hypothermia at 32°C to 34°C for 24 hours.

MAIN OUTCOMES AND MEASURES The primary outcome was survival with good neurologic outcome, defined as Cerebral Performance Category (CPC) 1-2, at 90 days. Secondary outcomes were survival at 90 days and time to reach core body temperature less than 34°C.

RESULTS Among the 677 randomized patients (median age, 65 years; 172 [25%] women), 671 completed the trial. Median time to core temperature less than 34°C was 105 minutes in the intervention group vs 182 minutes in the control group (P < .001). The number of patients with CPC 1-2 at 90 days was 56 of 337 (16.6%) in the intervention cooling group vs 45 of 334 (13.5%) in the control group (difference, 3.1% [95% CI, –2.3% to 8.5%]; relative risk [RR], 1.23 [95% CI, 0.86-1.72]; P = .25). In the intervention group, 60 of 337 patients (17.8%) were alive at 90 days vs 52 of 334 (15.6%) in the control group (difference, 2.2% [95% CI, –3.4% to 7.9%]; RR, 1.14 [95% CI, 0.81-1.57]; P = .44). Minor nosebleed was the most common device-related adverse event, reported in 45 of 337 patients (13%) in the intervention group. The adverse event rate within 7 days was similar between groups.

CONCLUSIONS AND RELEVANCE Among patients with out-of-hospital cardiac arrest, trans-nasal evaporative intra-arrest cooling compared with usual care did not result in a statistically significant improvement in survival with good neurologic outcome at 90 days.

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herapeutic hypothermia may increase survival with good neurologic outcome after out-of-hospital cardiac arrest. Experimental data show that therapeutic hypothermia in cardiac arrest reduces ischemic and reperfusion brain injury, with a beneficial effect of early intra-arrest cooling (ie, cooling started during cardiopulmonary resuscitation [CPR]) compared with cooling initiated at a later stage. However, the majority of clinical studies have examined the effect of therapeutic hypothermia when cooling was initiated after hospital arrival, most often at the intensive care unit (ICU), several hours after the cardiac arrest. Currently, treatment guidelines recommend hospital use of therapeutic hypothermia or temperature control at a temperature of 32°C to 36°C for at least 24 hours, with the strongest indication in patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) as first rhythm.

Clinical trials that assessed the effect of early, prehospital cooling have generally involved the use of infusions of cold fluids administered intra-arrest or soon after return of spontaneous circulation (ROSC). Cold fluids cool the patient effectively, but seem to have significant hemodynamic adverse effects. In particular, adverse effects have been observed in patients with VF as first rhythm, where intra-arrest infusion of cold fluid decreased the rate of patients achieving ROSC. Based on these findings, prehospital cooling using rapid infusion of cold intravenous fluid is not recommended.

Trans-nasal evaporative cooling is a method that does not add volume to the patient. This noninvasive cooling method can be induced intra-arrest and leads to continuous cooling, primarily of the brain. The primary objective of this study was to determine whether prehospital trans-nasal evaporative intra-arrest cooling improves survival with good neurologic outcome compared with standard practice in which cooling is initiated after hospital arrival.

Methods

Trial Design
The PRINCESS trial was an investigator-initiated, randomized clinical trial with blinded assessment of the outcome. The study was conducted in 11 emergency medical service (EMS) systems in 7 European countries between January 1, 2010, and January 31, 2018. The last patient was followed up on April 29, 2018. Ethics and institutional committees in each participating country approved the study protocol and statistical analysis plan (Supplement 1) and the rationale and design of the trial have been published. An independent data and safety monitoring committee reviewed predefined end points at interim analyses after recruitment of 200 and 500 randomized patients. After the interim analysis at 500 patients, further recruitment of patients by helicopter EMS systems was stopped because of prolonged times to inclusion, which was regarded as a safety issue. The study was conducted according to the requirements of the Declaration of Helsinki. Written informed consent was obtained from the closest relative or a legal representative of each patient after hospital admission and, at a later stage, from each patient who regained mental capacity. Neither EMS nor hospital personnel were blinded to treatment because of the nature of the intervention. However, nurses and physicians performing neurologic assessments of patients prior to discharge and at 90 days, as well as data managers and researchers, were blinded to the patients’ group assignments.

Patients
The inclusion criterion was bystander-witnessed cardiac arrest in patients at least 18 years of age. Exclusion criteria were patients aged 80 years or older; an etiology of cardiac arrest due to trauma, head trauma, severe bleeding, drug overdose, cerebrovascular accident, drowning, smoke inhalation, electrocution, or hanging; already hypothermic; an obviously anatomic barrier to placing intra-nasal catheters; an existing do-not-attempt resuscitation order; known terminal disease; known or clinically apparent pregnancy; known coagulopathy (except therapeutically induced); need for supplemental oxygen; ROSC prior to randomization; and EMS response time (ie, from collapse to EMS arrival) greater than 15 minutes.

Randomization and Trial Intervention
Patients were screened for eligibility by the advanced life support team after airway management (ie, endotracheal intubation or laryngeal mask). If the study criteria were fulfilled, patients were randomly assigned (1:1 ratio) to receive either intra-arrest cooling or standard care using sequentially numbered envelopes, which were provided by the Karolinska Institute to the participating study site. Randomization was generated in blocks of 4 without stratification. Both study groups received standard advanced life support care according to international guidelines. For patients randomized to the intervention group, intra-arrest trans-nasal evaporative cooling was initiated. The cooling method delivers a mixture of air or oxygen and a liquid coolant (perfluorohexane) via nasal catheters. When the coolant evaporates, it absorbs heat from the surrounding tissue and
rapidly cools the nasal cavity to about 2°C. The method was developed primarily to cool the brain because it takes advantage of the nasal pathways (ie, the conchal folds and turbinates) that provide a highly vascular and large, diffuse surface area that is in close proximity to the cerebral circulation. The method has previously been described in detail. If the patient achieved ROSC or was transported to the hospital during CPR, trans-nasal evaporative cooling was continued until hospital arrival, and whenever possible, until systemic hospital cooling was initiated. Patients in both study groups who were admitted to the hospital received postresuscitation treatment, including systemic hypothermia, according to current treatment guidelines. Intravenous sedation, analgesia, and neuromuscular blockade were used according to institutional cooling protocols. The targets for ventilation settings, mean arterial blood pressure, and glucose control have been described previously. The temperature was measured according to local practices in the urinary bladder, rectum, esophagus, or with intravascular probes. The target core temperature for all patients was 33°C ± 1°C and the duration of hypothermia was 24 hours. The rewarming rate was 0.2°C to 0.5°C per hour. Temperature control to avoid fever was recommended for 72 hours.

Data Collection

Data on characteristics at resuscitation (eg, age, bystander CPR, and initial rhythm) followed the Utstein template recommended by guidelines. The advanced life support team recorded prehospital event times and temperature at ROSC. Tympánic and core temperature were measured after hospital arrival and according to local protocol during the first 72 hours of hospitalization. In-hospital measures, such as coronary angiography, intra-aortic balloon pump use, and neurologic prognostic measures, were recorded. Data on adverse events were collected for 7 days following randomization. At 90 days, data on good functional recovery were reported as device-related adverse events within 24 hours and adverse events at the hospital within the first 7 days after randomization. Post hoc end points were the percentage of patients who achieved sustained ROSC and were admitted alive to the hospital, survival with CPC 1 at 90 days, and the full distribution of CPC and Modified Rankin Scale scores at 90 days.

Statistical Analyses

Power calculation was based on the preceding safety and feasibility trial that showed an absolute difference of 16% (21% vs 37%) in survival with CPC 1-2 at discharge among the patients admitted alive at the hospital. To show this absolute difference of 16% in the primary outcome, a sample size of 150 patients admitted alive to the hospital in each study group was required for 80% power (2-sided α = .05). This number would require a total sample of 650 to 800 patients to be randomized before hospital admission, depending on the number of those patients who were resuscitated and admitted to the hospital. After recommendations from the data and safety monitoring committee, the primary outcome analyses were performed in all randomized patients instead of patients who were admitted alive to the hospital.

The primary analyses were performed on all randomized patients, except patients allocated to the intervention group who did not fulfill the study criteria and never received the intervention (n = 6). Continuous variables that were not normally distributed are reported as medians and interquartile ranges (IQRs). Categorical variables are reported as numbers and percentages. The primary analysis for the efficacy end points was conducted using Pearson χ² tests for comparison of binominal proportions. As a post hoc analysis, a generalized linear mixed-effect model with study site as a random variable was used to calculate relative differences between categorical variables. Odds ratios were converted to relative risks (RRs) with 95% CIs. For continuous end points (time to core temperature <34°C), the Hodges-Lehmann estimator was used.

The secondary analysis was performed as a per-protocol analysis that was restricted to all randomized patients with adherence to the intervention (ie, patients in the intervention group who did not receive intra-arrest cooling were excluded). The secondary analysis was performed in accordance with the primary analysis.

Analyses of the primary, secondary, and exploratory end points were performed in the following prespecified subgroups: patients with VF/VT as the initial rhythm and patients for whom the EMS started CPR in less than 10 minutes. Exploratory (post hoc) end points (ie, survival with CPC 1 at 90 days and the distribution of neurologic scores) were analyzed as absolute differences in percentages with 95% CIs.
The statistical analyses were performed using R software version 3.4.3. Neurologic scores should also be considered as exploratory. Studies on survival with CPC 1 at 90 days and the distribution of points should be interpreted as exploratory. Post hoc multiple comparisons, findings for analyses of secondary endpoints were performed. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory. Post hoc analyses on survival with CPC 1 at 90 days and the distribution of neurologic scores should also be considered as exploratory. Statistical analyses were performed using R software version 3.4.3.

Results

Patients
Among 677 randomized patients, 671 (337 in the intervention and 334 in the control group) were included in the primary analysis (Figure 1). Patient characteristics, factors at the scene of the arrest, resuscitation measures, and event times prior to randomization were similar in the 2 groups (Table 1).

Event Times and Measures Before and After Hospital Admission
In patients randomly assigned to receive intra-arrest cooling, the median time to start of cooling was 19 minutes from collapse. In patients in the intervention group, median tympanic temperature at ROSC was 35.7°C vs 36.0°C in patients in the control group (P = .02). At hospital arrival, a median time of 25 minutes after ROSC, median tympanic temperatures were 34.6°C in the intervention group vs 35.8°C in the control group (P < .001) (eFigure 4 in Supplement 2). Characteristics and measures after hospital arrival were similar between the groups (Table 2).

Outcome
Primary Outcome
In the primary analysis, the number of patients who survived with good neurologic function (CPC 1-2) at 90 days was 56 of 337 (16.6%) in the intervention group vs 45 of 334 (13.5%) in the control group (difference, 3.6% [95% CI, −2.3% to 8.5%]; RR, 1.23 [95% CI, 0.86-1.72]; P = .25) (Table 3; eFigure 2 in Supplement 2). In the secondary per-protocol analysis, the number of patients with CPC 1-2 at 90 days was 56 of 328 (17.1%) in the intervention group vs 45 of 334 (13.5%) in the control group (difference, 3.6% [95% CI,
The primary outcome analysis for patients admitted to the hospital alive is presented in eTable 2 in Supplement 2.

Secondary Outcomes

Overall survival at 90 days was 60 of 337 patients (17.8%) in the intervention group vs 52 of 334 (15.6%) in the control group (difference, -2.2% [95% CI, -5.1% to 0.7%]; RR, 1.14 [95% CI, 0.81-1.57]; P = .44) (Table 3). Time to target core temperature was 105 minutes in the intervention group vs 182 minutes in the control group (P < .001). Secondary outcomes in the secondary per-protocol analysis are presented in eTable 1 in Supplement 2.

Predefined Subgroup Analyses

Among patients with VF or VT as first rhythm, 48 of 138 (34.8%) in the intervention group and 35 of 133 (25.9%) in control group had CPCR 1-2 at 90 days (difference, 8.9% [95% CI, 2.0% to 15.7%]; RR, 1.28 [95% CI, 0.90-1.81]; P = .11) (Table 3; eFigure 3 in Supplement 2). The P value for interaction was .31. For additional subgroup analyses, see Figure 2.
In the intervention group, 149 of 337 patients (44.2%) achieved sustained ROSC and were admitted alive to the hospital vs 142 of 334 patients (42.5%) in the control group (difference, 1.7% [95% CI, −5.8% to 9.2%]; RR, 1.04 [95% CI, 0.87-1.22]; P = .66).

Fifty of 337 patients (14.8%) in the intervention group vs 35 of 334 (10.5%) in the control group had CPC 1 (difference, 4.4% [95% CI, −0.7% to 9.4%]; RR, 1.40 [95% CI, 0.95-2.01]) (Figure 3). In the subgroup of patients with VF or pulseless VT, 45 of 138 (32.6%) in the intervention group vs 27 of 135 (20.1%) in the control group had CPC 1 (difference, 12.5% [95% CI, 3.7% to 21.4%]; RR, 1.49 [95% CI, 1.04-2.11]; P = .03).

Table 3. Primary and Secondary Outcomes in a Study of the Effect of Trans-Nasal Intra-arrest Cooling on Neurologic Outcome in Out-of-Hospital Cardiac Arrest

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention (n = 337)</th>
<th>Control (n = 334)</th>
<th>Difference (95% CI)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
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<tr>
<td>Survival with CPC 1-2 at 90 d, No./total (%)</td>
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<td></td>
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</tr>
<tr>
<td>All patients</td>
<td>56/337 (16.6)</td>
<td>45/334 (13.5)</td>
<td>3.1 (−2.3 to 8.5)</td>
<td>1.23 (0.86 to 1.72)</td>
<td>.25</td>
</tr>
<tr>
<td>Patients with shockable rhythm</td>
<td>48/138 (34.8)</td>
<td>35/135 (25.9)</td>
<td>8.9 (−2.0 to 19.7)</td>
<td>1.28 (0.90 to 1.72)</td>
<td>.11</td>
</tr>
<tr>
<td>Patients with nonshockable rhythm</td>
<td>8/198 (4.0)</td>
<td>10/199 (5.0)</td>
<td>−1.0 (−5.1 to 3.1)</td>
<td>0.80 (0.32 to 1.97)</td>
<td>.64</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Overall survival at 90 d, No./total (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All patients</td>
<td>60/337 (17.8)</td>
<td>52/334 (15.6)</td>
<td>2.2 (−3.4 to 7.9)</td>
<td>1.14 (0.81 to 1.57)</td>
<td>.44</td>
</tr>
<tr>
<td>Patients with shockable rhythm</td>
<td>51/138 (37.0)</td>
<td>41/135 (30.4)</td>
<td>6.6 (−4.6 to 17.8)</td>
<td>1.18 (0.83 to 1.56)</td>
<td>.25</td>
</tr>
<tr>
<td>Patients with nonshockable rhythm</td>
<td>9/198 (4.5)</td>
<td>11/199 (5.5)</td>
<td>−1.0 (−5.3 to 3.3)</td>
<td>0.82 (0.34 to 1.91)</td>
<td>.65</td>
</tr>
<tr>
<td>Sustained ROSC and admitted to hospital, No./total (%)</td>
<td>149/337 (44.2)</td>
<td>142/334 (42.5)</td>
<td>1.7 (−5.8 to 9.2)</td>
<td>1.04 (0.86 to 1.22)</td>
<td>.66</td>
</tr>
<tr>
<td>Time to core body temperature &lt;34°C, median (IQR), min</td>
<td>105 (80 to 183)</td>
<td>182 (132 to 312)</td>
<td>−70 (−100 to −44)</td>
<td>0.59 (0.49 to 0.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EMS response &lt;10 min</td>
<td>110 (80 to 192)</td>
<td>236 (158 to 415)</td>
<td>−102 (−169 to −60)</td>
<td>0.52 (0.39 to 0.65)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EMS response ≥10 min</td>
<td>99 (82 to 166)</td>
<td>152 (125 to 202)</td>
<td>−50 (−86 to −16)</td>
<td>0.66 (0.50 to 0.87)</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: CPC, Cerebral Performance Category; IQR, interquartile range; ROSC, return of spontaneous circulation.

a Ventricular fibrillation or pulseless ventricular tachycardia.

Post Hoc Analyses

In the intervention group, 149 of 337 patients (44.2%) achieved sustained ROSC and were admitted alive to the hospital vs 142 of 334 patients (42.5%) in the control group (difference, 1.7% [95% CI, −5.8% to 9.2%]; RR, 1.04 [95% CI, 0.87-1.22]; P = .66). Fifty of 337 patients (14.8%) in the intervention group vs 35 of 334 (10.5%) in the control group had CPC 1 (difference, 4.4% [95% CI, −0.7% to 9.4%]; RR, 1.40 [95% CI, 0.95-2.01]) (Figure 3). In the subgroup of patients with VF or pulseless VT, 45 of 138 (32.6%) in the intervention group vs 27 of 135 (20.1%) in the control group had CPC 1 (difference, 12.5% [95% CI, 3.7% to 21.4%]; RR, 1.49 [95% CI, 1.04-2.11]; P = .03).
(20.0%) in the control group had CPC 1 (difference, 12.6% [95% CI, 2.3%-22.9%]; RR, 1.54 [95% CI, 1.06-2.06]). The distribution of CPC categories is shown in Figure 3. Modified Rankin Scale scores at 90 days are presented in Table 6 in Supplement 2.

**Adverse Events**

Nosebleeds and nasal whitening were the most common device-related adverse events. In 4 patients, cooling had to be stopped because of relatively severe nose bleeding. In 1 patient, a computed tomographic scan showed pneumocephalus, which was seen as a serious device-related complication with probable intracerebral air leakage from the sinuses. The pneumocephalus was found to be resolved in the second computed tomographic scan after 10 days. The patient recovered and was assessed as CPC 2 at 90 days. Overall, 170 of 337 patients (50.4%) in the intervention group vs 163 of 334 (48.8%) in the control group had adverse events within 7 days of randomization, which included bleeding that required transfusion, pneumonia, recurrence of VF or VT, cardiogenic shock, pulmonary edema, and seizures. Detailed data on adverse events are presented in eTable 5 in Supplement 2.

**Discussion**

The main finding of this randomized clinical trial of 677 patients with out-of-hospital cardiac arrest was that trans-nasal intra-arrest cooling at the scene of collapse compared with standard systemic cooling at the ICU did not result in a statistically significant improvement in survival with good neurologic outcome at 90 days.

The group that received intra-arrest cooling had significantly shorter time intervals required to reach target core-body temperature. The overall adverse event rate reported within 7 days of randomization was similar between the 2 groups. These results were consistent across predefined subgroups.

In light of previous studies, the safety aspects of a prehospital cooling method are important. Cold intravenous fluid decreases coronary perfusion pressure by augmenting central venous pressure.20 This decrease in coronary perfusion pressure may partly explain the lower rate of ROSC observed in a randomized clinical trial when cold fluid was used intra-arrest in patients with VF9 and the increased number of patients with re-arrest and pulmonary edema when cold fluids have been administered after ROSC.11 Trans-nasal evaporative cooling does not add volume to the patient and could, in this trial, be initiated intra-arrest without the hemodynamic adverse events seen with cold intravenous fluids.9,11 Thus, intra-arrest cooling does not appear to lead to major harm when used in a prehospital setting among patients with cardiac arrest.

In the current study, the difference in survival with good neurologic outcome at 90 days between the groups was not statistically significant. There may be several reasons for this lack of difference. The cooling intervention might not have been effective enough to lower temperature during CPR to mitigate brain injuries secondary to the ischemia and reperfusion process. The start of cooling might have been too late to provide the benefit seen in experimental models in which such cooling was immediately applied.3,21 In this study, the cooling devices were placed in the second emergency vehicle with advanced life support capacity, which influenced the delay between the start of CPR by EMS in the first vehicle and start of cooling. When comparing the results with those of...
the previous safety and feasibility study,12 the control group performed significantly better in terms of cooling interval (ie, smaller difference between groups in time required to reach target core temperature), overall survival, and good neurologic outcome. Because power estimations were based on these findings, the current study may have been underpowered to be able to detect important clinical differences.

Patients with out-of-hospital cardiac arrest with initial rhythm of VF have the strongest recommendation for temperature management in current guidelines.6,7 The explorative findings in this subgroup of patients may be of importance to define the study population for future hypothermia trials. Survival with complete neurologic recovery without any sequelae (eg, CPC 1) is the best outcome after cardiac arrest. As a post-hoc exploratory finding, there was a higher percentage of patients with CPC 1 in the intra-arrest cooling group compared with the control group.

**Limitations**

This study has several limitations. First, prehospital and hospital personnel were not blinded to treatment. Second, the study period was long and many eligible patients with cardiac arrest were not included in the trial, which may have introduced a risk of bias. Third, the study may have been underpowered to detect a clinically important difference in the primary outcome. A larger trial might have allowed detection or rejection of such a difference.

**Conclusions**

Among patients with out-of-hospital cardiac arrest, trans-nasal evaporative intra-arrest cooling compared with usual care did not result in a statistically significant improvement in survival with good neurologic outcome at 90 days.


