Clinical paper

Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest

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A B S T R A C T

Aim of the study: Hypothermia treatment with cold intravenous infusion and ice packs after cardiac arrest has been described and used in clinical practice. We hypothesised that with this method a target temperature of 32–34 °C could be achieved and maintained during treatment and that rewarming could be controlled.

Materials and methods: Thirty-eight patients treated with hypothermia after cardiac arrest were included in this prospective observational study. The patients were cooled with 4 °C intravenous saline infusion combined with ice packs applied in the groins, axillae, and along the neck. Hypothermia treatment was maintained for 26 h after cardiac arrest. It was estimated that passive rewarming would occur over a period of 8 h. Body temperature was monitored continuously and recorded every 15 min up to 44 h after cardiac arrest.

Results: All patients reached the target temperature interval of 32–34 °C within 279 ± 185 min from cardiac arrest and 216 ± 177 min from induction of cooling. In nine patients the temperature dropped to below 32 °C during a period of 15 min up to 2.5 h, with the lowest (nadir) temperature of 31.3 °C in one of the patients. The target temperature was maintained by periodically applying ice packs on the patients. Passive rewarming started 26 h after cardiac arrest and continued for 8 ± 3 h. Rebound hyperthermia (>38 °C) occurred in eight patients 44 h after cardiac arrest.

Conclusions: Intravenous cold saline infusion combined with ice packs is effective in inducing and maintaining therapeutic hypothermia, with good temperature control even during rewarming.

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1. Introduction

The outcome among patients admitted to hospital after out-of-hospital cardiac arrest is still relatively poor. However, induced mild hypothermia can improve survival and the neurological outcome. Hypothermia treatment is recommended for witnessed cardiac arrest with initial ventricular tachycardia/ventricular fibrillation (VT/VF) and should be considered in other initial ECG rhythms according to current cardiopulmonary resuscitation (CPR) guidelines. The effect of hypothermia on the neurological outcome would seem to be most beneficial when the treatment is initiated as early as possible after restoration of spontaneous circulation (ROSC) and maintained for 12–24 h. Despite its recommendation in current CPR guidelines, therapeutic hypothermia after cardiac arrest is not used in clinical practice in all hospitals caring for these patients, for reasons based on scientific, technical, logistical and economic issues.

The ideal method for inducing and maintaining therapeutic hypothermia is not known. Different cooling methods and devices are described for administration of this therapy, such as surface cooling, cooling with endovascular catheters, use of cooling caps/helmets, and cool intravascular fluid. Among these methods, surface cooling is generally considered the least expensive and is the most widely used. However, these methods are often combined with induction of hypothermia by cold infusion. Cold infusion alone is effective for such induction but is inadequate for maintaining hypothermia. In a study by Bernard et al., the use of cold, 4 °C, intravenous crystalloid infusion was combined with ice packs applied in the groins, axillae and along the neck. In that study induction to the target temperature of hypothermia treatment was achieved, but maintenance of hypothermia and the length of the rewarming phase were not reported.

The aim of the present study was to further evaluate the temperature control with cold, 4 °C intravenous crystalloid infusion
combined with ice packs for hypothermia treatment not only during induction but also during maintenance and rewarming.

We hypothesised that with this method a target temperature of between 32 and 34 °C can be achieved and maintained during treatment, and that rewarming can be controlled.

2. Methods

This was a prospective observational study comprising patients treated with hypothermia at the Intensive Care Unit (ICU) of Uppsala University Hospital, Uppsala, Sweden, after cardiac arrest between December 2004 and June 2007. The study was reviewed and approved by the local human ethics committee in Uppsala. Consent to participation was obtained from a legal next of kin, and later from survivors when they were considered competent. The patients were eligible for inclusion if they were still comatose with a Glasgow Coma Scale (GCS)20 <8 or a Reaction Level Scale (RLS 85)21 ≥3 after successful ROSC with a systolic arterial blood pressure ≥80 mmHg > 5 min. Patients were excluded if they were under 18 years of age, if hypothermia treatment was started more than 6 h after cardiac arrest, if the temperature was below 34 °C on admission to the ICU, or if the cardiac arrest was a consequence of trauma. Before cooling, all patients were intubated and sedated. In patients admitted after out-of-hospital cardiac arrest, the hypothermia treatment was started in the emergency department. Patients with in-hospital cardiac arrest were transferred to the ICU before hypothermia treatment was initiated.

2.1. Cooling methods

To induce hypothermia, the patient was given a 4 °C intravenous saline infusion, in a planned volume of 30 ml/kg at a rate of 100 ml/min via two peripheral intravenous catheters. Simultaneously, ice packs were applied in the groins, axillae and along the neck and were changed when necessary to allow continuous cooling. The ice packs used were saline infusion bags of 250 ml which were stored in the freezer of the emergency department or the ICU, and they were covered with a pillowcase to prevent cold injury on the patient’s skin. If the temperature started to rise above 33.5 °C the ice packs were applied, and if it fell below 32.5 °C they were removed. The planned duration of hypothermia treatment was 24 h, and it was estimated that the first two hours after the cardiac arrest would be taken up by transportation to hospital and decision about hypothermia treatment. The target temperature of 32–34 °C was therefore maintained for up to 26 h after the estimated time of cardiac arrest. Passive rewarming at 0.5 °C/h started after 26 h and it was expected that a temperature of 36 °C, which was considered the normal core temperature, would be reached within 8 h. If the temperature increased too rapidly, the patient was given a bolus injection of a sedative, the blankets were removed, and the ice packs were applied again.

2.2. Treatment protocol

The patients were sedated with a propofol infusion given at a dose of 0.3–4 mg/kg/h and fentanyl infusion at 1–3 μg/kg/h. In the event of shivering, the patient first received additional sedation and then if necessary, muscle relaxation with rocuronium as a bolus injection of 0.6 mg/kg and subsequently, if required, infusion at 0.15 mg/kg/h. The goal was to discontinue administration of muscle relaxant when the target temperature of the hypothermia treatment was reached. After rewarming, the sedation was terminated.

The treatment protocol had defined goals for factors that are generally considered important for critically ill/cardiac arrest patients, but was adjusted for therapeutic hypothermia. The target for blood pressure was defined as a mean arterial pressure ≥60 mmHg, and if required, vasoactive (norepinephrine) or inotropic (dobutamine) medication was administered. Ventilation was set to maintain a PaO2 ≥ 12 kPa (>90 mmHg) and PaCO2 of 5.0–5.5 kPa (38–41 mmHg). Diuresis was expected to be >1 ml/kg/h and a decrease was treated primarily with additional crystalloids. The electrolyte magnesium, calcium and phosphate were maintained in a high-normal range and potassium at ≥ 4.0 mmol/l. The target blood glucose was 5–8 mmol/l and a titrated insulin infusion was administered if required. For nutrition, the patients received an intravenous infusion of glucose 50 mg/ml, 1–1.5 l/24 h with simultaneous enteral nutrition at 10–20 ml/h. All patients were given ulcer prophylaxis with ranitidine 50 mg × 3 and thrombosis prophylaxis with enoxaparin sodium 40 mg × 1. Antibiotics were only used if there was an indication of ongoing infection.

2.3. Monitoring

Core temperature was measured continuously in the urinary bladder (Curity silicon thermistor 400 series catheter, Tyco Healthcare, United Kingdom) and recorded on the patient’s chart every 15 min up to 44 h after the cardiac arrest.

All patients received an arterial line in the radial or femoral artery and a central venous catheter as soon as possible. Arterial and central venous pressures, ECG, oxygen saturation and body temperature were continuously monitored (Marquette, Solar 8000, Hellige Systems, Freiburg Germany or Delta Infinity®. Drägermedical, Lübeck, Germany). Patients were monitored for arrhythmia, signs of acute heart failure, electrolyte disturbances, infection and coagulopathies. Every 90–120 min, arterial blood samples were drawn for measurement and analysis of blood gases, including PaO2, PaCO2 and electrolytes (Na, K, Ca, Cl), and also glucose and lactate (ABL 700, Radiometer Triolab AB, Copenhagen, Denmark). Serum magnesium and phosphate were measured on arrival and again 12, 18, 24, 36, 48 and 72 h after cardiac arrest. Complete blood counts were taken on admission and were repeated every 24 h during the remainder of the patient’s stay at the ICU. Markers for myocardial infarction were measured according to hospital routines. Transthoracic echocardiography was performed 12 and 48 h after cardiac arrest. Neurological evaluation was carried out with RLS 85 or GCS on arrival, after rewarming at 36 h from cardiac arrest and every 12 h during the ICU stay. The neurological outcome was assessed with Pittsburgh cerebral performance categories (CPC)22 at discharge from the ICU and 6 months after cardiac arrest. The categories were defined as: (1) good recovery, (2) moderate disability, (3) severe disability, (4) vegetative state, and (5) death.

2.4. Statistical analysis

Data were analysed with a spreadsheet application (Excel, Microsoft, Redmond, WA). All data collected were treated confidentially. Descriptive statistics and demographic data are presented as mean, standard deviation, range, percentages and numbers. An independent statistician at the Uppsala Clinical Research Center evaluated all data.

3. Results

During the 30-month period of the study, 38 of the 45 patients treated with hypothermia after cardiac arrest were included. In five of the seven patients not included in the study the temperature protocol was not filled in by the staff. In one patient, hypothermia treatment was begun >6 h after cardiac arrest. One patient with cardiac arrest due to trauma was not included in the study, but the patient received hypothermia treatment. Patients were cooled after
both out-of-hospital and in-hospital cardiac arrest (Table 1). All cardiac arrest patients were treated irrespective of the first recorded ECG rhythm if a decision on further active ICU treatment was taken. The first recorded ECG rhythm was VF in 16 patients (42%), asystole in 12 patients (32%), pulseless electrical activity (PEA) in 6 patients (16%), and other recorded rhythms in 4 patients (10%) (Table 1).

The mean age was 60 years (range 22–82 years), and 25 patients were men (Table 1). The mean weight was 81 kg (range 49–104 kg).

### Temperature control

In all patients the target temperature range of 32–34 °C was attained and this was reached within 279 ± 185 min from the estimated time of cardiac arrest (Table 2 and Fig. 1).

After the induction of cooling, the target temperature of ≤34 °C was reached in 216 ± 177 min (Table 2 and Fig. 1). The temperature before initiation of cooling was known in 11 patients and the mean initial temperature in these patients was 36.3 °C. The cooling rate in these 11 patients was calculated to be 0.6 °C/h. The actual volume of 4 °C intravenous saline infused before attainment of the target temperature was 42 ± 12 ml/kg (Table 2).

In nine patients (24%) the temperature dropped below 32 °C during a period ranging from 15 min to 2.5 h. The nadir temperature in seven patients was 31.7–31.9 °C, and in one patient it was 31.3 °C. No patients exceeded the upper limit of 34 °C of the target temperature range during hypothermia treatment.

Two patients died during hypothermia treatment, one of whom 9 h after cardiac arrest; however, the target temperature of 32–34 °C was achieved in both patients and they were included in the analysis.

Passive rewarming started 26 h after cardiac arrest and continued for 8.2 ± 3.2 h (Table 2 and Fig. 1). Rebound hyperthermia (>38 °C) occurred in eight patients (21%), and the mean temperature in these patients 44 h after cardiac arrest was 38.5 ± 0.6 °C (38.1–39.8 °C).

### Table 1
Demographic characteristics of cooled patients (n = 38).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (range)</td>
<td>60 (22–82)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (66)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Weight, kg (n = 38), mean (range)</td>
<td>81 (57–104)</td>
</tr>
<tr>
<td>CA out-of-hospital, n (%)</td>
<td>30 (79)</td>
</tr>
<tr>
<td>Witnessed CA, n (%)</td>
<td>28 (74)</td>
</tr>
<tr>
<td>First recorded ECG rhythm</td>
<td></td>
</tr>
<tr>
<td>VF, n (%)</td>
<td>16 (42)</td>
</tr>
<tr>
<td>Asystole, n (%)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>PEA, n (%)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>ICU stay in days, mean (range)</td>
<td>4.4 (1–12)</td>
</tr>
</tbody>
</table>

### Table 2
Temperature profiles of cooled patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from cardiac arrest to target temperature (n = 38)</td>
<td>279 min (±185) 60–650</td>
</tr>
<tr>
<td>Time from start of cooling to target temperature (n = 38)</td>
<td>216 min (±177) 10–570</td>
</tr>
<tr>
<td>Time for rewarming (started 26 h after cardiac arrest until patient reached 36 °C (n = 36)</td>
<td>8.2 h (±3.2) 12–16.5</td>
</tr>
<tr>
<td>Infused saline 4 °C (n = 28)</td>
<td>42 ml/kg (±12) 20–70</td>
</tr>
</tbody>
</table>

### Table 3
Outcome at discharge from ICU and after 6 month.

<table>
<thead>
<tr>
<th>Category</th>
<th>CPC 1–2</th>
<th>CPC 3–4</th>
<th>CPC 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome at discharge from ICU</td>
<td>n = 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 (26)</td>
<td>16 (42)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>First recorded ECG VF (n = 16)</td>
<td>6 (37)</td>
<td>7 (44)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>First recorded ECG asystole, PEA (n = 18)</td>
<td>3 (17)</td>
<td>7 (39)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Outcome after 6 month</td>
<td>n = 38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>17 (45)</td>
<td>2 (5)</td>
<td>19 (50)</td>
</tr>
<tr>
<td>First recorded ECG VF (n = 16)</td>
<td>10 (63)</td>
<td></td>
<td>6 (37)</td>
</tr>
<tr>
<td>First recorded ECG asystole, PEA (n = 18)</td>
<td>5 (28)</td>
<td>2 (11)</td>
<td>11 (61)</td>
</tr>
</tbody>
</table>

Values are reported as numbers with percentages in parenthesis. CPC = cerebral performance categories: 1, good recovery; 2, moderate disability; 3, severe disability; 4, vegetative state, and 5, death. ICU = intensive care unit.

### Section 3.2

At the neurological outcome evaluation on discharge from ICU, 10 of the patients (26%) had a CPC score of 1–2, 16 patients (42%) had a score of 3–4, and 12 patients (32%) had a score of 5 (Table 3). Six months after cardiac arrest, 17 patients (45%) had a CPC score of 1–2, 2 patients (5%) had a score of 3–4, and 19 patients (50%) had a score of 5 (Table 3). Six patients with a CPC score of 3–4 when they left ICU died after discharge from this unit. Eight patients with a CPC score of 3–4 on discharge from ICU improved to a score of 1–2 after 6 months. One patient with a CPC score of 2 died after discharge from ICU after suffering a new, refractory cardiac arrest on day 4 after the first cardiac arrest episode.

Six months after cardiac arrest, 10 patients (63%) of the group of 16 patients whose first recorded ECG rhythm was VF recovered to a CPC score of 1–2, and the other 6 patients (37%) died. After 6 months, two patients with asystole and three patients with PEA as the first recorded ECG rhythm had improved to CPC 1–2.

### Section 4

In this study of cardiac arrest patients, cold saline infusion combined with ice packs was found to be effective in inducing and maintaining therapeutic hypothermia and also in controlling rewarming. However, close monitoring of the body temperature was required to achieve this.

All patients in the study (n = 38) reached the target temperature of 32–34 °C, on average 4.4 h from cardiac arrest and 3.4 h after initiation of hypothermia treatment, results which are comparable to those with external and endovascular methods (Table 4).1,2,7,12,14,23–25 The target temperature remained stable during maintenance of hypothermia treatment with only minor interventions, consisting either of application of ice packs when the temperature started to rise above 33.5 °C or removal of the ice packs when it fell below 32.5 °C. Unfortunately no recordings were made of how often the ice packs were applied or removed during treatment.

The infusion of cooled saline solution was targeted to a volume of 30 ml/kg and a rate of 100 ml/min to induce hypothermia, which is in line with other reports.5,18 In this study, the patients received 42 ml/kg (20–70 ml/kg). The reason for infusing more cooled saline was that the target temperature was not reached, necessitating a greater volume. This did not result in any clinical signs of right heart failure or pulmonary oedema in any of the patients.

Cooling below the target temperature range did occur but was not a major problem in this study. In nine patients (24%) the temperature dropped below 32 °C, and the lowest temperature of 31.3 °C was noted in one patient. This low temperature might have been avoided if ice packs had been removed at a higher temperature than the 32.5 °C planned in our protocol. Occurrence of a temperature below the target has been reported from a study in which patients...
received surface cooling, when the temperature was below 32 °C for >1 h in 63%.26 In the current study the temperature was monitored continuously and recorded every 15 min during hypothermia treatment and rewarming. Early information was thus obtained if the body temperature was drifting out of range. We therefore consider that careful monitoring of the body temperature during hypothermia treatment is necessary to achieve good temperature control with the present method.

In this study passive rewarming started 26 h after the estimated time of cardiac arrest and the median time taken to reach 36 °C, which was considered the normal core temperature, was 8.2 h (Table 2 and Fig. 1). It is recommended today that rewarming should take place at a rate of 0.2–0.5 °C/h.19,27 The goal in our study was not to exceed a rewarming rate of 0.5 °C/h. With the method we used, careful monitoring of the body temperature was also required during rewarming in order to control the rate of temperature elevation. Additional sedation was given or ice packs re-applied in an effort to prevent too fast rewarming in our patients. The time taken for rewarming was comparable to that reported from other studies (Table 4).2,7,12,14,23,25 Problems with too fast rewarming and rebound hyperthermia have been described.23,25,28 In our study, passive rewarming was followed by fever of >38 °C 44 h on average after cardiac arrest in eight patients (21%). This problem, however, seems to be independent of the cooling method used and occurs especially in awake patients after extubation.25,26,28

The method applied in the present study could be initiated early and did not interfere with other interventions, which most frequently consisted of an immediate transfer from the emergency ward for coronary angiography or CT scan of the brain. The method is inexpensive and the cost of the infusion and ice packs used per treated patient will not exceed €30.

All comatose patients with ROSC after cardiac arrest and receiving active treatment in the ICU were cooled regardless of the first recorded ECG rhythm. Asystole was the first recorded ECG rhythm in 11 patients (32%) and PEA in 6 patients (18%). The study was not designed to compare the outcome either between methods of cooling or between first recorded ECG rhythms. The high rates of PEA and asystole possibly contributed to a slightly lower survival in the study population in comparison with the two previously published studies by the Hypothermia after Cardiac Arrest Study Group (HACA) and Bernard.1,2 The present study showed a higher proportion of VF patients with a good outcome (63%) than in the HACA study2 (55%) and in the study by Bernard et al.1 (49%).

It has been debated whether or not patients with asystole or PEA should or should not be treated with hypothermia. In the small population of such patients in the present study, after six months one patient with asystole as the first recorded ECG rhythm had improved to a CPC score of 1–2, and three patients with PEA as the first recorded rhythm had also improved to a CPC score of 1–2. In spite of guideline recommendations,3,4 the limited total number of patients studied and the fact that the survival was lower in patients with asystole or PEA as the presenting rhythm, we considered that these patients deserved to be treated with hypothermia.

It is noteworthy that in this study many patients made a recovery after discharge from ICU. The treatment should not therefore be discontinued too early, and patients might need different lengths of time to achieve neurological recovery.

### 4.1. Limitations

This was an observational study without comparisons with normal temperature controls and other established cooling devices.

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**Table 4**

Comparison of studies regarding time to target temperature and duration of rewarming.

<table>
<thead>
<tr>
<th></th>
<th>Time to target temperature</th>
<th>Duration of rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>From cardiac arrest</td>
<td>From start of cooling</td>
</tr>
<tr>
<td>Present study (n = 38)</td>
<td>279 min, 60–650 (mean, range)</td>
<td>216 min, 10–570 (mean, range)</td>
</tr>
<tr>
<td>Bernard et al.1(n = 43)</td>
<td>150 min, 65–240 (mean, range)</td>
<td>8 h, 8, 12 (median, interquartile range)</td>
</tr>
<tr>
<td>HACA1(n = 137)</td>
<td>480 min, 240–960 (mean, range)</td>
<td>11 h, 8, 14 (median, interquartile range)</td>
</tr>
<tr>
<td>Wolff et al.7(n = 49)</td>
<td>410 min, 271–544 (median, interquartile range)</td>
<td>137 min, 96–168 (median, interquartile range)</td>
</tr>
<tr>
<td>Haugk et al.15(n = 27)</td>
<td>284 min (median)</td>
<td>219 min, 80, 315 (mean, interquartile range)</td>
</tr>
<tr>
<td>Al-Senani14(n = 13)</td>
<td>284 min (median)</td>
<td>300 min 180, 420 (median, interquartile range)</td>
</tr>
<tr>
<td>Oddo et al.21(n = 55)</td>
<td>330 min (mean)</td>
<td>187 min, 30–600 (mean, range)</td>
</tr>
<tr>
<td>Sunde et al.26(n = 40)</td>
<td>296 min, 110–805 (mean, range)</td>
<td>13.5 h, 7–30 (mean, range)</td>
</tr>
</tbody>
</table>

a Compared with present study concerning cooling time to target temperature.
b Compared with present study concerning both cooling time and duration of rewarming.
The small sample size precluded any major assessment of the effect of this technique on the outcome. As already mentioned, there were unfortunately no recordings of how often the ice packs were applied or removed during the treatment. Five patients were excluded because the temperature protocol was not completed, and this may have biased our results.

Chlorpromazine was not part of the treatment protocol but was administered in four cases after a decision by the clinician in charge, when given intravenously, this drug can reduce the core temperature. It is not known whether the administration of chlorpromazine or any other additional intervention in these patients would have been necessary to reach the target temperature or avoid rebound hyperthermia.

5. Conclusion

Use of cold intravenous saline infusion (4°C) together with ice packs placed in the groins, axillae and along the neck is an effective method for inducing and maintaining therapeutic hypothermia after cardiac arrest with good temperature control even during the rewarming phase. The method is feasible in clinical practice at low cost and should be considered as an alternative to other methods of planned hypothermia treatment.

Conflict of interest

There is no conflict of interest.

Acknowledgements

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