Surface Cooling for Rapid Induction of Mild Hypothermia After Cardiac Arrest: Design Determines Efficacy

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Abstract

Objectives: Recently, a novel cooling pad was developed for rapid induction of mild hypothermia after cardiac arrest. The aim of this study was to evaluate the cooling efficacy of three different pad designs for in-hospital cooling.

Methods: Included in this prospective interventional study were patients with esophageal temperature (Tes) > 34°C on admission. The cooling pad consists of multiple cooling units, filled with a combination of graphite and water, which is precooled to −18°C (design A) or to −9°C (designs B and C) before use. The designs of the cooling pad differed in number, shape, and thickness of the cooling units, with weights of 9.7 kg (design A), 5.3 kg (design B), and 6.2 kg (design C). All three designs were tested in sequential order and were changed according to the results found in the previous trial. Cooling was started after admission until Tes = 34°C, when the cooling pad was removed. The target temperature of Tes = 32–34°C was maintained for 24 hours. Data are presented as medians and interquartile ranges (IQRs = 25%–75%) or proportions.

Results: Cooling rates were 3.4°C/hour (IQR = 2.5–3.7) with design A (n = 12), 2.8°C/hour (IQR = 1.6–3.3) with design B (n = 7), and 2.9°C/hour (IQR = 1.9–3.6) with design C (n = 10; p = 0.5). To reach 34°C, the cooling pad had to be exchanged with a new one due to melting and therefore depleting cooling capacity in three patients with design A, in five patients with design B, and in no patient with design C (p = 0.004).

Conclusions: With adequate design and storage temperature, the cooling pad proved to be efficient for rapid in-hospital cooling of patients resuscitated from cardiac arrest.

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Sudden cardiac arrest is still a major cause of death, with limited emergency care strategies. Therapeutic mild hypothermia (32–34°C) is currently the most advanced medical concept to improve neurologic outcome in patients after cardiac arrest and is recommended in the 2005 resuscitation guidelines of the European Resuscitation Council and the American Heart Association. The main challenge remains the immediate induction of mild hypothermia. Animal and human data suggest that early and rapid induction of therapeutic mild hypothermia is crucial to exert its beneficial effect. Recently, a simple-to-use, noninvasive cooling pad, independent of energy source during use, was developed. In the out-of-hospital setting, this cooling pad was applied within 12 minutes after successful resuscitation, and mild hypothermia of 33°C was achieved within 90 minutes. For future use in the out-of-hospital setting as well as in-hospital setting, the volume, weight, and storage temperature of the cooling pad are of crucial importance. The aim of this study was to evaluate in-hospital cooling performance and possible adverse effects of a cooling pad design, which...
was modified twice in terms of storage temperature, size, and weight, in patients resuscitated from cardiac arrest.

METHODS

Study Design
This was a prospective interventional study of a convenience sample of comatose patients, admitted to the emergency department (ED) of a tertiary care university hospital. In the event the patient became competent during the trial period, then he or she was approached as soon as feasible by research personnel for notification of enrollment and to obtain informed consent. The study procedures were approved by the local hospital ethics committee. For all patients, the informed consent requirement was waived in accordance with the ethical standards of the local institutional review board and the guidelines for Good Clinical Practice of the International Conference of Harmonisation (ICH).

Study Setting and Population
Our tertiary care university hospital has a catchment area population of 2 million and an annual census of 87,000 visits. Included in the study were patients older than 18 years of age with sustained return of spontaneous circulation (ROSC) after witnessed or nonwitnessed cardiac arrest, irrespective of initial rhythm, with no reaction to verbal commands at the time of inclusion. Exclusion criteria were cardiac arrest due to trauma or intracranial bleeding, suspected pregnancy, known pre-existing coagulopathy, terminal disease that would not lead to further intensive care therapy, and esophageal temperature (Tes) below 34°C.

Study Protocol
The Cooling Pad. The cooling pad (EMCOOLSpad, Emcools AG, Vienna, Austria) consisted of multiple cooling units made of latex, each filled with a mixture of graphite and water. The inner layer was a biocompatible hydro-gel that adheres to the patient’s skin on application and provides direct pad-to-skin contact for efficient heat transfer. The three different designs of the cooling pad were tested in sequential order.

Design A consisted of 11 units, each 15 mm thick, in different predefined shapes for the head, back, chest, abdomen, and thighs. The entire cooling pad weighed 9.7 kg, with a total surface area of 0.6 m² and was stored at –9°C before use. Based on our former experimental and clinical experience, the development of final design C has evolved (Figure 1).

In design C, the cooling pad consisted of 10 units, with a thickness of 11 mm, but filled with more graphite and water to a weight of 6.2 kg. All units had the same size (21.5 × 30 cm) without predefined shapes for different body parts, with a total surface area of 0.65 m², and stored at –9°C before use. Based on our former experimental and clinical experience, the development of final design C has evolved (Figure 1).

Temperature Measurement. Before the start of cooling, measurement of Tes was started. To avoid coiling of the temperature probe in the oral cavity, a lubricated tracheal tube (7.5 mm) was fully advanced into the esophagus up to 30-cm lip level, through which the temperature probe (Mon-a-therm General Purpose, 12 Fr, Mallinckrodt Medical Inc., St. Louis, MO) was fully inserted. Thus it was ensured that the tip of the temperature probe was in the distal esophagus, 5 cm below the end of the tube. After insertion, the temperature probe was connected to a generic temperature monitoring device (Emcoolstemp, Emcools AG) for continuous monitoring and recording of Tes and also to a standard monitor (Hewlett Packard CMS Monitor, Hewlett Packard Ges.m.b.H, Vienna, Austria) as a backup system to avoid any data loss.

Patient Management. Once the patient fulfilled the inclusion criteria, sedation, analgesia, and paralysis were started with a midazolam bolus of 5 mg, followed by continuous infusion (250 mg/50 mL midazolam, started at 3 mL/hour and adjusted as needed); a fentanyl bolus of 0.1 mg, followed by continuous infusion (2.5 mg/50 mL fentanyl, started at 5 mL/hour and adjusted as needed); and a rocuronium bolus of 0.5 mg/kg, followed by continuous infusion of 0.5 mg/kg/hour. The cooling pad was applied on the patient’s back, thorax, abdomen, and thighs (Figure 1) until Tes reached 33.9°C, when the entire cooling pad was removed. During cooling, the cooling capacity and melting process of each pad was controlled by touching and feeling the surface of the pads. If Tes dropped
below 32.3°C, a heating blanket (Bair Hugger Augustin Medical, Inc., Eden Prairie, MN) was applied until Tes reached 32.4°C, when the heating blanket was removed. Target Tes 33°C (range = 32–34°C) was maintained for 24 hours. During maintenance cooling, single cooling units (21.5 × 30 cm each) were applied on the thorax and abdomen according to the algorithm shown in Figure 2. If Tes increased to 33.5°C, 2 units were applied and removed when Tes reached 33°C. At 24 hours after reaching the target temperature of Tes = 33°C, the patient was covered with a regular blanket and allowed to rewarm, with a rewarming rate of approximately 0.4°C/hour. At Tes = 35°C, sedation, analgesia, and paralysis were discontinued, if possible. No additional cooling techniques were applied. Postresuscitation care was provided according to established guidelines using a standardized treatment protocol at our institution.14

12-month Follow-up. All follow-up interviews were arranged by telephone by a trained study nurse using a standardized form. Mortality data were collected by reviewing the citywide hospital register.

Data Analysis
The primary endpoint of this study was efficacy in terms of cooling rate in °C/hour. The secondary endpoints of this study were safety in terms of serious and nonserious device-related adverse events and functional recovery at 12 months after the event. Data were recorded according to the recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest.15

The safety of the cooling pad was evaluated by documenting all serious and nonserious adverse events, defined as any unfavorable or unintended sign, symptom, or disease that was associated with the use of the cooling pad until 12 months after the event. Good neurologic recovery was defined as conscious, alert, and sufficient cerebral function for activities of daily life, equivalent to cerebral performance categories 1 or 2.16,17

Continuous variables are given as means with standard deviations (±SDs) or as medians and interquartile ranges (IQRs; between the 25th and 75th quartiles), if not normally distributed. Nominal data are given as counts and percentages. The sample size was not based on estimated effect size. The goal was simply a pilot/feasibility study for making point estimates of effect size and safety assessments. Group comparisons were performed with the chi-square test, analysis of variance, or the Kruskal-Wallis-test, if indicated. We were interested only in differences between all groups, rather then between pairwise group comparisons; thus, no post hoc analysis was performed. A two-sided p-value of <0.05 was considered statistically significant.

All calculations were performed with SPSS for Windows 14.0 (SPSS Inc., Chicago, IL).

RESULTS
From September 2005 until May 2007, of 360 postcardiac arrest patients admitted to the ED, 170 were treated with different invasive and noninvasive techniques to induce mild hypothermia. During the three study periods (total 17 months), of 170 patients, 129 patients were cooled with different techniques. The cooling pad (EMCOOLSpad, Emcools AG) was used in 31 patients and modified two times to find the optimal design (design A = September 2005–February 2006, 12 patients; design B = May 2006–August 2006, nine patients; design C = October 2006–May 2007, 10 patients). With design A, in one patient with sepsis, temperature drop was less than 1°C/hour, and an additional cooling method was applied; the cooling rate for this patient was calculated until start of the additional cooling method. With design B, two patients were excluded from the study because cooling had to be stopped before reaching the target temperature: in one patient, three-vessel disease was diagnosed during angiography with the immediate need of aortocoronary bypass surgery; in the other patient, subarachnoidal bleeding was diagnosed. In one patient, cooling was stopped after 9 hours due to retroperitoneal hematoma and hemoglobin drop after percutaneous coronary intervention; data on cooling performance of this patient are included into the study. With design C, all patients were cooled for a period of 24 hours (Table 1); thus, 29 patients were available for final analysis.
Primary Endpoint
Time from ROSC to start of cooling, and cooling rate for all three designs, are shown in Table 2, as well as other time intervals related to cooling. Cooling started at medians of 65 (IQR = 45–115) minutes, 78 (IQR = 35–140) minutes, and 40 (IQR = 29–65) minutes after admission for designs A, B, and C, respectively (p = 0.08). The median Tes at cooling start was 35.9°C (IQR = 35.2–36.3), 36.5°C (IQR = 35.8–37.1), and 35.8°C (IQR = 35.3–36.0°C (p = 0.3). Target Tes of 33°C was reached after a median of 53 (IQR = 42–63) minutes, 90 (IQR = 41–147) minutes, and 49 (IQR = 39–79) minutes after cooling start (p = 0.05), with a median cooling rate of 3.4°C/hour, 2.8°C/hour, and 2.9°C/hour (p =
After reaching the target temperature range, seven (24%) patients remained in the range of $\text{T}_{\text{es}} = 32$–34°C without the need of further active cooling. To maintain the temperature within the target temperature range, two single cooling units ($0.12 \text{ m}^2$) had to be reapplied on the thorax and abdomen during 24 hours, with a median frequency of 3 (IQR = 2–6) times in design A, 8 (IQR = 4–9) times in design B, and 3 (IQR = 1–5) times in design C ($p = 0.1$). During maintenance cooling, temperature remained between 32 and 34°C in all patients (Figure 3 and 4).

**Secondary Endpoints**

After the cooling pad was removed, minimal skin erythema was observed in all patients, which resolved within minutes. With design A, superficial frostbite wounds were observed in three patients; all healed without scars. After increasing the storage temperature to $-9^\circ$C, and lowering the thickness of the cooling pad in designs B and C, no further frostbite wounds were observed. During induction of cooling, no hemodynamic instabilities or arrhythmias were observed. No serious device-related adverse events were reported.

At 12 months after cardiac arrest, 12 patients (41%) were alive, all with good neurologic recovery (design A = three patients, design B = five patients, design C = four patients). The median survival time of the patients who died was 3 (IQR = 2–12) days. Causes of death were severe cerebral dysfunction with no indication for further intensive care in 10 patients, intractable cardiogenic shock in five patients, and multiorgan failure in two patients.
DISCUSSION

The cooling pad with design C, stored at $-9^\circ C$, proved to be an effective noninvasive surface cooling method for rapid in-hospital induction of therapeutic mild hypothermia in patients resuscitated from cardiac arrest. In addition, the cooling pad was also a sufficient method to maintain mild hypothermia in a range of 32–34°C for 24 hours without the need for an additional cooling method.

The deleterious cascades of neuronal death start during cardiac arrest, but are boosted with start of reperfusion.18 Hypothermia might be initiated immediately after resuscitation to interfere as soon as possible with the pathophysiologic mechanisms leading to neuronal death. Recently, a retrospective human study showed that any hour delay until reaching the target temperature tended to worsen the likelihood for a favorable outcome by approximately 31%.12 Three studies proved the feasibility of immediate induction of hypothermia in the out-of-hospital setting, either by rapid infusion of approximately 2,000 mL of cold (4°C) crystalloids19,20 or by surface cooling.13 In one study, cooling by rapid infusion of cold crystalloids was started during chest compressions.21 Additional prospective randomized controlled trials are needed to determine the importance of early induction of hypothermia to improved neurologic outcomes from cardiac arrest.

In recent years, several invasive6,7,22–24 as well as noninvasive2,3,5,7,13,24–28 cooling techniques for induction of mild hypothermia were investigated in patients after cardiac arrest. The cooling rate of these devices ranged from 0.25 to 1.2°C/hour. With the final design C, cooling was started a median of 83 minutes after ROSC, and the median temperature lagged behind Tes during fast cooling,13 observed was 31.6°C, but no arrhythmias or hemodynamic instabilities were observed. The overshoot in temperature might be deleterious in patients in the out-of-hospital setting, where monitoring of vital signs is not as accurate as in the ED, and no rewarming devices are available. However, in a previous study,13 using this device in the out-of-hospital setting, time from ROSC to arrival in the ED was 45 minutes, and median temperature at arrival was 35.4°C (IQR = 34.6–35.9°C). In this study,13 no patient showed a temperature below 32°C at arrival in the ED.

Once the target temperature range of Tes = 32–34°C was achieved in all patients, seven (24%) patients remained in this range without the need for recooling. To maintain the target temperature range we used a simple algorithm for temperature management as described under Methods (Figure 2) and a patient monitor with alarm signals for certain temperature levels to facilitate accurate temperature control. In all patients, two single cooling units (0.12 m²) had to be reapplied on the thorax and abdomen three (IQR = 1–6) times during 24 hours to keep the target temperature range of Tes = 32–34°C. During maintenance cooling, all patients remained in the target temperature range (Figure 4), as opposed to the study describing ice packs as a method for manual temperature control.30 Even if not compared to other invasive and noninvasive cooling techniques, the pads have shown to be an efficacious and convenient technique for cooling.

In preliminary studies13 we observed that the bladder temperature lagged behind Tes during fast cooling, showing a temperature difference of up to 1.5°C at a given time point. Therefore, Tes was used as the target temperature site in this study.

LIMITATIONS

One limitation was the preliminary nature of the study, as only a small number of patients were included. The small sample size of this feasibility trial had its main focus in optimizing a cooling pad with regards to efficacy. Therefore, we had no intention to make any comparisons with a historic control group in regard to the impact of fast cooling on neurologic outcome in patients resuscitated from cardiac arrest. Because this was a convenience sample, the potential for selection bias exists. This cooling system is not actively monitored. Therefore, this device could produce severe hypothermia or could provide inadequate cooling if staff are not vigilant. This may be much less likely to occur with systems that actively monitor themselves. This danger of overshoot may be especially likely when this device is combined with lower starting temperatures after iced saline infusion.

The nurses and physicians participating in this study were not being evaluated concerning user-friendliness and practicability of the cooling pad. However, when this device was tested in the out-of-hospital setting, paramedics and emergency physicians were satisfied with the final design C of the cooling pad, a warming blanket had to be used after initial cooling in all 10 patients to avoid a drop of Tes = $<32^\circ C$. Despite the use of the warming blanket, Tes dropped below 32°C in four patients; the lowest Tes observed was 31.6°C, but no arrhythmias or hemodynamic instabilities were observed.
with user-friendliness and practicability. Also, the
generalizability of this study may be limited by the fact
that the authors practiced with a team of highly moti-
vated staff that are well trained in the use of hypother-
mia. A team that is less familiar or less motivated might
not be able to obtain similar results. This study focused
on cooling efficiency during 24 hours of cooling, and
therefore we did not collect data during the rewarming
phase. Furthermore, the investigator assessing the out-
come and complications was not blinded to study popu-
lation.

CONCLUSIONS

With adequate design and storage temperature, nonin-
vasive surface cooling with this cooling pad is efficient
for rapid in-hospital induction of mild hypothermia in
patients resuscitated from cardiac arrest. A prospective,
randomized clinical trial is needed to determine
whether early and fast induction of mild hypothermia
improves neurologic outcome.

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