



Clinical paper

Prehospital cooling to improve successful targeted temperature management after cardiac arrest: A randomized controlled trial[☆]



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ARTICLE INFO

Article history:

Received 16 May 2017

Received in revised form

25 September 2017

Accepted 2 October 2017

Keywords:

Targeted temperature management

Out-of-hospital cardiac arrest

Quality improvement

Randomized controlled trial

Knowledge translation

Critical care

Prehospital intervention

Safety

ABSTRACT

Rationale: Targeted temperature management (TTM) improves survival with good neurological outcome after out-of-hospital cardiac arrest (OHCA), but is delivered inconsistently and often with delay.

Objective: To determine if prehospital cooling by paramedics leads to higher rates of 'successful TTM', defined as achieving a target temperature of 32–34 °C within 6 h of hospital arrival.

Methods: Pragmatic RCT comparing prehospital cooling (surface ice packs, cold saline infusion, wristband reminders) initiated 5 min after return of spontaneous circulation (ROSC) versus usual resuscitation and transport. The primary outcome was rate of 'successful TTM'; secondary outcomes were rates of applying TTM in hospital, survival with good neurological outcome, pulmonary edema in emergency department, and re-arrest during transport.

Results: 585 patients were randomized to receive prehospital cooling (n = 279) or control (n = 306). Prehospital cooling did not increase rates of 'successful TTM' (30% vs 25%; RR, 1.17; 95% confidence interval [CI] 0.91–1.52; p = 0.22), but increased rates of applying TTM in hospital (68% vs 56%; RR, 1.21; 95%CI 1.07–1.37; p = 0.003). Survival with good neurological outcome (29% vs 26%; RR, 1.13, 95%CI 0.87–1.47; p = 0.37) was similar. Prehospital cooling was not associated with re-arrest during transport (7.5% vs 8.2%; RR, 0.94; 95%CI 0.54–1.63; p = 0.83) but was associated with decreased incidence of pulmonary edema in emergency department (12% vs 18%; RR, 0.66; 95%CI 0.44–0.99; p = 0.04).

Conclusions: Prehospital cooling initiated 5 min after ROSC did not increase rates of achieving a target temperature of 32–34 °C within 6 h of hospital arrival but was safe and increased application of TTM in hospital.

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Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; DSMC, Data Safety and Monitoring Committee; EMS, emergency medical services; GCS, Glasgow Coma Scale; ILCOR, International Liaison Committee on Resuscitation; MRS, Modified Rankin Scale; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, relative risk; SPARC Network, Strategies for Post Arrest Care Network; TTM, targeted temperature management.

[☆] A Spanish translated version of the abstract of this article appears as Appendix in the final online version at <https://doi.org/10.1016/j.resuscitation.2017.10.002>.

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<https://doi.org/10.1016/j.resuscitation.2017.10.002>

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Background

Targeted temperature management applied after hospital arrival has been shown to improve survival with good neurologic outcome and is recommended for patients resuscitated from out-of-hospital cardiac arrest (OHCA) following a return of spontaneous circulation (ROSC) [1,2]. Although its mechanism is not completely understood, a reduction in core body temperature likely reduces the inflammatory response that occurs following ischemia-reperfusion injury, directly diminishes cellular injury, and increases cerebral neuronal healing by reducing cerebral oxygen demand and intracranial pressure [3].

The American Heart Association, International Liaison Committee on Resuscitation, and other international agencies now strongly recommend TTM for eligible patients following resuscitation from cardiac arrest [4,5]. Despite these recommendations, TTM is delivered inconsistently, incompletely, and often with delay [6–9]. Reasons cited to explain this incomplete adoption include lack of awareness of recommended practice, perceptions of poor prognosis, limited time and resources, and staffing shortages [10–14]. Hospital-based knowledge translation interventions designed to increase use of TTM have been only modestly successful [15].

We hypothesized that prehospital cooling by emergency medical services (EMS) providers (paramedics) could act as a catalyst to encourage more timely application of TTM by in-hospital clinicians, and that earlier cooling might also improve clinical outcomes [16]. We tested this hypothesis by conducting an open-label pragmatic randomized controlled trial (RCT) to answer the following question: Does prehospital cooling using surface ice packs, infusion of intravenous cold saline, and application of a wristband reminder – compared to no prehospital cooling – lead to higher rates of ‘successful TTM’ in OHCA patients, defined as achieving a target temperature of 32–34 °C within 6 h of hospital arrival? (Initiation of Cooling by Emergency medical services to Promote the Adoption of in-hospital therapeutic hypothermia in Cardiac arrest Survivors, the ICEPACS RCT).

Methods

Participants and setting

The study was conducted by 4 large EMS systems (Halton Paramedic Services, Peel Paramedic Services, Toronto Paramedics Services, and York Paramedic Services) serving the Greater Toronto Area and their 24 receiving hospitals in the Strategies for Post-Arrest Care Network [17]. Patients were eligible if they had an EMS-treated OHCA; age ≥ 18 years; sustained ROSC of ≥ 5 min and had systolic blood pressure ≥ 100 mmHg; and were unresponsive to verbal stimuli or required endotracheal intubation. Patients were ineligible if the etiology of cardiac arrest was trauma, burn, or exposure hypothermia; or if they had clinical evidence of active severe bleeding, severe sepsis, known coagulopathy, known do-not-resuscitate (DNR) order, known pregnancy, or prisoner status.

Randomization

We randomized (1:1) eligible patients into 2 groups using sequential, numbered, opaque, sealed envelopes and variable (4–6) block sizes [18]. This approach has been shown to be an acceptable method for maintaining allocation concealment, and has been successfully used in the past by participating EMS systems [19,20].

Study intervention

Ambulances in participating EMS systems were stocked at the beginning of each 12-h paramedic shift with a cooler containing

cold saline and ice packs [22,23]. Patients randomized to receive prehospital cooling had ice packs applied to their neck, axillae, and both groins and infusion of up to 2L of cold saline (0.9% sodium chloride solution at approximately 4 °C) via a pressure infusion bag and standard intravenous line during transport to hospital. Patients were given a single dose of midazolam 5 mg, and a second dose (maximum 10 mg) if needed to prevent shivering. The paramedics fastened a wristband to the patient with the following message: “Cardiac Arrest Survivor – Therapeutic Hypothermia Initiated – Consider Continuation of Cooling”. Patients randomized to the control arm received conventional post-resuscitative supportive care but no prehospital cooling or wristband reminders.

In both study groups, all in-hospital procedures including the application of TTM were left to the discretion of the treating clinical team. All destination hospitals were involved in our previous implementation study, the Strategies for Post-Arrest Care (SPARC) stepped wedge cluster RCT [15]. This previous study ensured that all hospitals had implemented protocols and order sets for delivering targeted temperature management, typically using surface cooling measures, in the emergency department and in coronary care units and intensive care units.

Data collection

All consecutive OHCA patients who were treated by participating EMS systems and transported to a participating destination hospital were identified and entered into a regional clinical registry called Rescu Epistry [21,22]. Rescu Epistry is a web-based data management interface that links electronic ambulance call report data from EMS systems and Fire Services with in-hospital data to identify all OHCA patients in the City of Toronto and adjacent regions (Halton, Peel, Simcoe, Muskoka, Toronto, York, and Durham). Rescu Epistry incorporates comprehensive and automated searching of EMS records that results in negligible rates of missed cases. Trained data abstractors blinded to treatment allocation collect in-hospital data from these OHCA patients, including elements of in-hospital post-arrest care, and clinical outcomes until hospital discharge. These data are entered manually with point of entry logic and error checks to minimize errors. Duplicate data abstraction occurs on a random sample of 10% of abstracted charts for each in-hospital data collector [22].

Outcomes

The primary outcome was ‘successful TTM’, defined as achieving a target temperature of 32–34 °C within 6 h of emergency department (ED) arrival [15]. Secondary outcomes included rates of (ever) applying TTM in-hospital; survival to hospital discharge with good neurological outcome, defined as a score of 0, 1, or 2 on the Modified Rankin Scale [23]; survival to 6 h and to hospital discharge; re-arrest during transport to hospital; pulmonary edema identified in the ED; first temperature recorded in-hospital; and time to achieve target temperature among patients ever reaching target temperature.

Analyses

We summarized baseline characteristics using descriptive statistics. The primary outcome and all secondary outcomes were analysed accounting for the stratified randomization (by EMS system) [24]; all relative risks comparing dichotomous variables were estimated using modified Poisson regression with robust standard error and fixed effects for the EMS system. Rates of survival and survival with good neurological outcome were also compared after adjustment for age, sex, EMS system, and shockable rhythm [ventricular tachycardia (VT) or ventricular fibrillation (VF) vs other

rhythm] [25]. We used *t*-tests to compare total fluid infused and first temperature recorded in ED and Wilcoxon rank-sum tests to compare times to achieve successful TTM. Scores on the Modified Rankin Scale at hospital discharge were compared using Fisher's exact test.

Sample size estimate

During the 28 months of our SPARC in-hospital hypothermia study, there were 4399 OHCA patients who were treated by EMS systems in participating regions and 1737 (40%) achieved ROSC [15]. Of these, 934 (22%) survived transport to hospital and were deemed eligible for TTM. Based on these rates, we anticipated that paramedics would screen approximately 4000 patients after OHCA during the ICEPACS trial and approximately 900 eligible patients would be randomized and also survive to hospital admission. This sample size would provide sufficient (>80%) power to detect a 30% relative improvement in the primary outcome of 'successful TTM' from a baseline event rate of 30% (i.e. an absolute increase to 39%). This sample size would also provide sufficient power (>80%) to detect absolute improvements from 20% to 28% in rates of survival with good neurological outcome.

Interim analyses

We planned to conduct 2 interim analyses after randomization of one-third ($n=300$) and two-thirds ($n=600$) of the total sample size. The trial could be stopped early for harm according to the early stopping criteria of Haybittle-Peto at a significance level of $p<0.001$, for differences in either of the following 2 pre-specified endpoints: mortality during transport to hospital and survival with good neurological outcome at hospital discharge [26].

At the first scheduled interim analysis after enrolment of 315 patients, it was determined that the trial was unlikely to achieve the planned sample size of 900 patients due to lower than expected recruitment rates. The Data Safety and Monitoring Committee (DSMC) recommended that enrolment should continue until the study operating funds were depleted (revised final sample size, approximately 500 patients). When making this recommendation, the DSMC also considered the impact of 2 studies that were published after the launch of the ICEPACS RCT. The first was a RCT of prehospital cooling for patients with OHCA, which detected no survival benefit but a higher re-arrest rate associated with prehospital cooling [27]. However, at the interim analysis, no excess in re-arrest rates was observed for either group in the ICEPACS trial. The second study was a RCT that showed similar clinical outcomes when in-hospital TTM was applied to achieve either a target temperature of 33 °C or 36 °C [28], raising the concern that the primary outcome of 'successful TTM' (i.e. achieving a target temperature of 32–34 °C within 6 h of ED arrival) could become infeasible. The DSMC noted, however, that prehospital cooling might still affect clinically important secondary endpoints, for example rates of (ever) applying TTM in-hospital or survival with good neurological outcome at hospital discharge and safety endpoints of pulmonary edema or re-arrest.

Patient involvement

Patients were not involved in the development of the research question or the design of this RCT.

Ethics

The trial was reviewed and approved by the Research Ethics Boards of Sunnybrook Health Sciences Centre and Lakeridge Health and was conducted under exception from informed consent in

emergency research. All enrolled patients (or their surviving relatives) were sent a letter of notification that explained their inclusion in the trial using a waiver of consent. The research ethics boards of all participating destination hospitals approved the necessary chart reviews to obtain relevant clinical outcomes for the trial. The trial was registered with the U.S. National Institutes of Health (ClinicalTrials.gov NCT01528475).

Results

Patients and measurements

Between July 3, 2012 and Jan 8, 2016, 17,940 patients were treated by participating EMS systems, and 3312 achieved ROSC (Fig. 1). Of these, 700 patients satisfied eligibility criteria and 585 were randomized. Eligible but non-randomized patients were younger and had shorter transport times, but were otherwise similar to randomized patients (Table A1 in Supplementary material). The identity of 3 patients in the control group could not be obtained and thus could not be linked to hospital records, leaving 582 patients for the final intention-to-treat analysis (Table 1).

Primary outcome

Rates of 'successful TTM' were not increased among patients randomized to receive prehospital cooling compared to controls [85 (30%) vs 77 (25%); RR 1.17 (95%CI 0.91–1.52), $p=0.22$; Table 2]. Similar results were obtained in a sensitivity analysis that was restricted to the period prior to the publication of the in-hospital TTM trial (Table A2 in Supplementary material) [28].

Secondary outcomes

Patients in the prehospital cooling group were more likely to (ever) receive TTM in hospital [190 (68%) vs 170 (56%); RR 1.21, $p=0.003$] than patients in the control group. Rates of survival to hospital discharge and survival with good neurological outcomes were similar in both groups (Table 2 and Fig. 2), even after adjusting for age, sex, presence of a shockable rhythm, and EMS system [survival to hospital discharge, RR 1.01 (95%CI 0.83–1.23), $p=0.93$; survival with good neurological outcomes RR 1.11 (95%CI 0.88–1.39), $p=0.38$]. No increase in rates of re-arrest during transport [7.5% vs 8.2%; RR 0.94 (95%CI 0.54–1.63), $p=0.83$] was observed among patients receiving prehospital cooling, and rates of pulmonary edema in ED were lower than in control patients [12% vs 18%, RR 0.66 (95% CI 0.44–0.99), $p=0.04$; Table 3].

Cooling process measures

The majority (239, 86%) of patients randomized to receive prehospital cooling received either surface cooling or infusion of cold saline, but application of both was not consistent (Table 4). The mean volume of total fluid infused during transport was greater in the prehospital cooling group (640 vs 470 ml, $p<0.0001$), and the mean volume of cold saline infused during prehospital cooling was 490 ml (SD 420 ml). Three patients in the control group received infusions of cold saline as protocol violations. The first temperature measured in the ED was not different between groups (35.1 °C in patients receiving prehospital cooling vs 35.2 °C in control patients, $p=0.53$; Table 3). Among patients who ever received TTM in hospital (and who ever reached the target temperature), the time to achieve the target temperature was similar in the prehospital cooling group versus the control group [median (IQR) 5.4 h (3.0–8.2) vs 4.8 h (2.8–7.7), $p=0.45$].

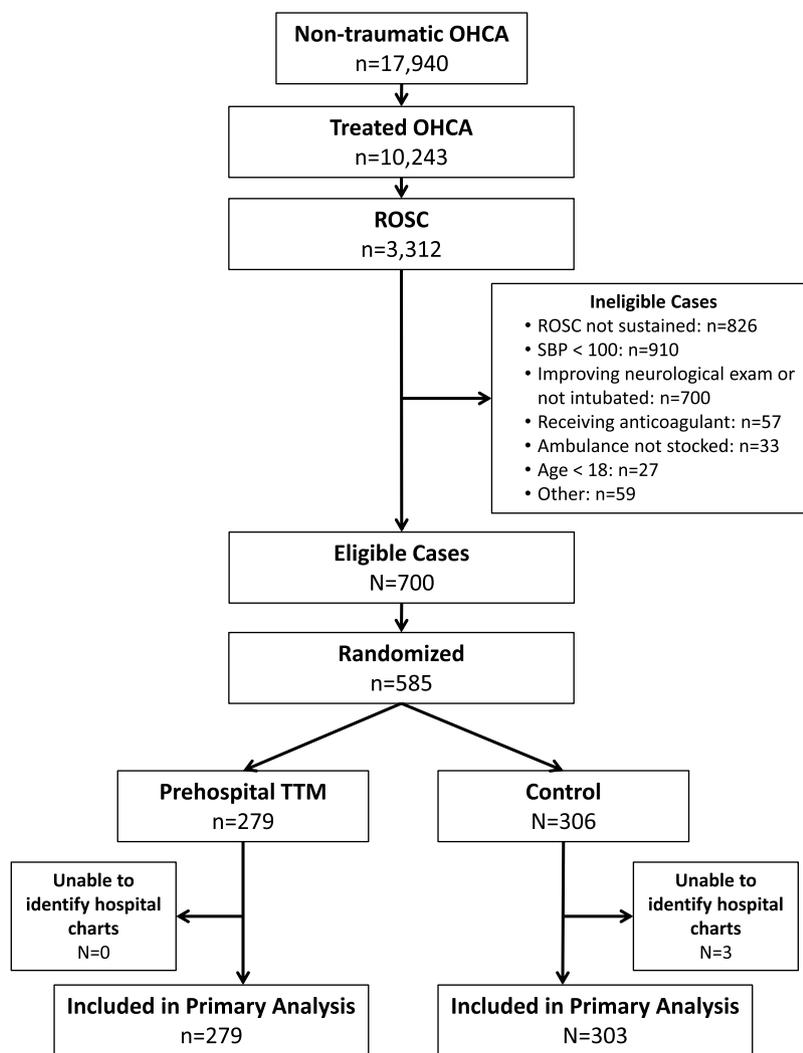


Fig. 1. Patient Flow.

Fig. 1 shows screening and enrolment of patients during the trial.

Table 1
Characteristics of Patients.

Patient Characteristics	Prehospital Cooling (n = 279)	Control (n = 303)
Age – mean (SD)	68 (15)	69 (16)
Men, No. (%)	196 (70%)	184 (61%)
Public arrest, No. (%)	61 (22%)	66 (22%)
Bystander witnessed, No. (%)	163 (58%)	188 (62%)
Bystander CPR, No. (%)	124 (44%)	146 (48%)
PAD applied, No. (%)	13 (4.7%)	17 (5.6%)
Initial rhythm VF/VT, No. (%)	124 (45%)	134 (44%)
Time from 911 call to EMS arrival – mean (SD), minutes	6.0 (2.6)	6.2 (2.5)
Time from EMS arrival to ED arrival – mean (SD), minutes	45 (12)	46 (12)
Time from first ROSC to ED arrival – mean (SD), minutes	29 (10)	29 (11)
GCS score recorded post ROSC – mean (SD)	3.3 (1.6)	3.3 (1.4)
Systolic blood pressure pre-randomization, mmHg (SD)	137 (42)	138 (42)
Comorbidities		
Coronary artery disease or previous MI	44 (16%)	34 (11%)
Congestive heart failure	13 (4.7%)	11 (3.6%)
Previous aortocoronary bypass surgery	20 (7.2%)	13 (4.3%)
Hypertension	103 (37%)	126 (42%)
Diabetes	55 (20%)	66 (22%)
From nursing home or long-term care facility	10 (3.6%)	15 (5.0%)

Footnotes:

Abbreviations: TTM = Targeted Temperature Management; SD = standard deviation; CPR = cardiopulmonary resuscitation; PAD = public access defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia; EMS = Emergency Medical Services; ED = Emergency Department; ROSC = Return of Spontaneous Circulation; GCS = Glasgow Coma Scale; mmHg = millimeters of Mercury; MI = myocardial infarction.

Table 2
Outcomes.

	Prehospital Cooling (n = 279)	Control (n = 303)	RR (95% CI)	p-value
TTM reaching 32–34 °C within 6 hours, No. (%)	85 (30%)	77 (25%)	1.17 (0.91–1.52)	0.22
TTM applied in hospital (ever), No. (%)	190 (68%)	170 (56%)	1.21 (1.07–1.37)	0.003
Survival to hospital discharge, No. (%) ^b	92 (33%)	98 (32%)	1.02 (0.81–1.29)	0.88
Survival to 6 hours after ED admission, No. (%)	223 (80%)	233 (77%)	1.15 (0.84–1.56)	0.39
Survival to hospital discharge – patients presenting with VT/VF, No. (%)	79 (64%)	74 (55%)	1.16 (0.95–1.41)	0.16
Good neurological outcome ^a at hospital discharge, No. (%) ^b	82 (29%)	76 (26%)	1.13 (0.87–1.47)	0.37
Neurological status at discharge ^{b,c}				0.77
No symptoms (mRS 0), No. (%)	46 (16%)	45 (15%)		
No significant disability (mRS 1), No. (%)	26 (9.3%)	23 (7.8%)		
Slight disability (mRS 2), No. (%)	10 (3.6%)	8 (2.7%)		
Moderate disability (mRS 3), No. (%)	4 (1.4%)	4 (1.4%)		
Moderately severe disability (mRS 4), No. (%)	1 (0.4%)	5 (1.7%)		
Severe disability (mRS 5), No. (%)	5 (1.8%)	5 (1.7%)		
Dead (mRS 6), No. (%)	187 (67%)	205 (69%)		

Footnotes:

Abbreviations: RR = Relative Risk; CI = confidence interval; TTM = Targeted Temperature Management; ROSC = return of spontaneous circulation; VT/VF = pulseless ventricular tachycardia/ventricular fibrillation; mRS = Modified Rankin Scale

^a Good neurological outcome defined as a score of 0, 1, or 2 on the Modified Rankin Scale.

^b Neurological status at hospital discharge could not be obtained for 8 (2.6%) of patients in the control group and vital status at hospital discharge could not be obtained for 1 patient (0.3%) in the control group.

^c p-value based on Fisher's exact test of scores on the Modified Rankin Scale by treatment assignment.

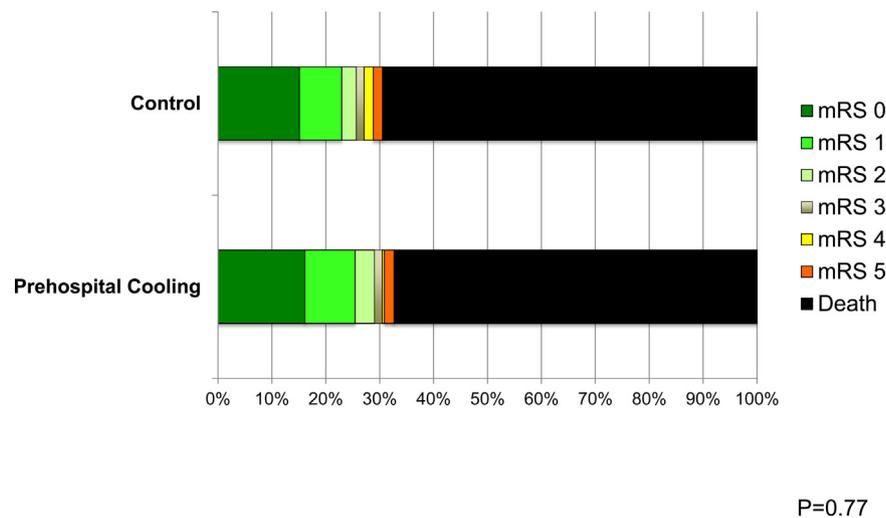
**Fig. 2.** Neurological Outcomes at Hospital Discharge.

Fig. 2 shows distribution of patients' neurological outcomes at hospital discharge by treatment group according to Modified Rankin Scale.

Table 3

Prehospital and In-hospital Process Data.

	Prehospital Cooling (n = 279)	Control (n = 303)	RR (95% CI)	p-value
Re-arrest during transport, No. (%)	21 (7.5%)	25 (8.2%)	0.94 (0.54–1.63)	0.83
Sustained ROSC at ED arrival	250 (90%)	258 (85%)	1.05 (0.99,1.12)	0.10
Fluid infused total (ml), mean (SD) ^a	640 (470)	470 (330)	N/A	<0.0001
First temperature (°C) recorded in ED, mean (SD) ^b	35.1 (1.8)	35.2 (1.7)	N/A	0.53
Temperature (°C) recorded at 6 hours, mean (SD) ^{b,c}	34.6 (1.9)	34.7 (1.8)	N/A	0.44
Pulmonary edema in ED, No. (%)	33 (12%)	54 (18%)	0.66 (0.44–0.99)	0.04
Use of vasopressors during first 24 hours, No. (%)	150 (54%)	188 (62%)	0.87 (0.75–1.00)	0.04
PCI during first 72 hours, No. (%)	58 (21%)	61 (20%)	1.03 (0.75–1.41)	0.87
Implantable defibrillator during admission, No. (%)	34 (12%)	26 (8.6%)	1.40 (0.86–2.28)	0.18
Deaths due to WLST during first 72 hours, No. (%)	44 (16%)	47 (16%)	1.00 (0.69–1.46)	0.98
Brain Death, No. (%)	18 (6.4%)	10 (3.3%)	1.98 (0.93–4.22)	0.08

Footnotes:

Abbreviations: TTM = Targeted Temperature Management; RR = Relative Risk; CI = confidence interval; IQR = interquartile range; SD = Standard Deviation; ED = Emergency Department; °C = ° Celsius; PCI = percutaneous coronary intervention; WLST = withdrawal of life-sustaining therapy; N/A = Not applicable

^a Total fluid infused was not documented for 98 (35%) patients who received Prehospital Cooling and 121 (40%) control patients.

^b No temperature measurement was recorded for 58 (21%) patients who received Prehospital Cooling and 60 (20%) control patients.

^c Refers to last temperature recorded in chart prior to 6 h.

Discussion

We conducted a pragmatic RCT in a large metropolitan area to compare prehospital cooling by paramedics of patients resuscitated

after OHCA, to usual care with no TTM applied until hospital. The main hypothesis was that a prehospital cooling bundle including

Table 4
Prehospital Cooling.

	Prehospital Cooling (n = 279)
Any prehospital cooling documented	239 (86%)
Cold ice-packs applied, No. (%)	186 (67%)
Cold fluid infused, No (%)	201 (72%)
Cold fluid infused total (ml), mean (SD) ^a	490 (420)

Footnotes:

Abbreviations: RR = Relative Risk; CI = confidence interval; SD = Standard Deviation.

^a Total volume of cold fluid infused was not documented for 79 (28%) of patients in the prehospital cooling group.

surface ice packs, infusion of cold saline, and wristband reminders would promote more efficient use of in-hospital TTM, by starting the cooling process earlier and acting as a powerful reminder to in-hospital clinicians. The primary outcome of ‘successful TTM’ – achieving a target temperature of less than 34 °C within 6 h of ED arrival – was not significantly different comparing groups. However, prehospital cooling resulted in increased application (ever) of in-hospital TTM compared to controls (68% vs 56%, $p=0.003$). This finding confirms the hypothesis that a prehospital intervention can directly influence the application of evidence-based recommendations by in-hospital clinicians, as suggested by observational research [29].

Most previous trials examining prehospital cooling have been small single-centred RCTs or feasibility studies [30,31]. However, two other large trials of prehospital cooling have been published. A RCT conducted by the EMS system in Seattle randomized 1359 patients to receive usual care or prehospital cooling initiated immediately after ROSC by infusion of cold intravenous saline (75% of patients received ≥ 1 l), 7–10 mg of intravenous pancuronium, and 1–2 mg of intravenous diazepam [27]. The trial showed no difference in the primary outcomes of survival and neurological status at hospital discharge, but detected more episodes of re-arrest (26% vs 21%) and pulmonary edema on first chest x-ray (41% vs 30%) among patients in the prehospital cooling group. A recent RCT from Australia randomized 1198 patients to usual care or prehospital cooling by infusion of up to 2 L of cold saline (mean 1193 ml) initiated during the delivery of CPR [32]. This trial was stopped early due to concerns that TTM management in receiving hospitals had changed following publication of the Nielsen TTM trial [28]; no differences were observed in the primary outcome of survival at hospital discharge. However, ROSC was less frequent among patients receiving prehospital cooling compared to control patients (41% vs 51%). Together, these 2 large trials suggested that cooling during resuscitation or immediately following ROSC may be harmful. In contrast, our trial detected no excess of adverse events when prehospital cooling was delayed until 5 min after successful ROSC. We intentionally delayed the initiation of prehospital cooling in our trial to reduce the risk of re-arrest, which occurs most frequently in the minutes immediately following ROSC [33,34]. Patients randomized to prehospital cooling in our RCT also received less intravenous cold saline during transport than was administered in these other trials, which may have further decreased the potential for prehospital cooling to induce recurrent arrhythmias or pulmonary edema.

Our trial has several limitations. The trial did not achieve the anticipated sample size due to slower than expected enrolment, and may have been underpowered to detect small but clinically important differences in primary or secondary outcomes. Not all eligible patients were enrolled by participating paramedics, and this may affect the generalizability of our findings. The main reason for not randomizing 16% of eligible patients was that individual paramedics declined to participate in research. Randomized patients had slightly longer transport times and younger age, but were otherwise similar to eligible but non-randomized patients with no clear evidence of sampling bias. Our primary outcome of

‘successful TTM’ – achieving a target temperature of 32–34 °C – was chosen as a feasible process endpoint that would capture more efficient and timely delivery of TTM. However, it remains unknown whether achieving a target temperature sooner is associated with improved outcomes after cardiac arrest [35]. The optimal endpoint for prehospital trials remains a topic of debate [36,37]. In particular, striving to measure plausible increases in rates of survival to hospital discharge may require enormous sample sizes [38,39]. Our primary outcome directly measured the effectiveness of prehospital cooling as an implementation strategy, but alternate endpoints that could be considered in future research include improving physiology, limiting disability, alleviating discomfort, and improving patient satisfaction [40].

The publication of the in-hospital TTM trial in 2013 may also have caused many clinicians to only target a temperature of 36 °C after cardiac arrest, making our primary outcome of ‘successful TTM’ – cooling to a target of 32–34 °C – less relevant. However, the results of our primary outcome comparison were unchanged when analyses were restricted to the period prior to the publication of the TTM trial. Nevertheless, prehospital cooling was still associated with higher rates of applying in-hospital TTM overall, confirming the hypothesis that prehospital treatment decisions can influence delivery of recommended practices in receiving hospitals. Our trial evaluated the effectiveness of a prehospital cooling bundle that included intravenous cold fluids, surface ice packs, and wristband reminders; we are unable to determine which component of this bundle was most effective at influencing in-hospital clinician behavior. Patients randomized to receive prehospital cooling had this intervention incompletely delivered; only two-thirds of patients had cold ice packs applied and about three-quarters received infusions of cold saline. Despite the use of pressure infusion bags, the mean volume of cold fluid infused was only 490 ml, suggesting that transport times may not have been sufficiently long to facilitate effective intravenous cooling, or that the saline for infusion was not uniformly maintained at 4 °C while stored in the cooler. This likely explains why initial temperatures measured in EDs were similar comparing groups, but may also explain the apparent safety of our protocol compared to other studies of prehospital cooling.

Conclusion

In conclusion, prehospital cooling initiated 5 min after ROSC did not lead to higher rates of achieving a target temperature of 32–34 °C within 6 h of hospital admission after OHCA, but was safe and increased the application of TTM in hospital.

Transparency declaration

Damon Scales affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. Ruxandra Pinto and Damon Scales had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors' contribution

Conception of Study: DCS
 Design of Study: DCS, SCB, SC, KND, MM, KET, PRV, LJM
 Implementation: DCS, DA, SC, KG, PRV, LJM
 Analytical Plan/Analyses: DCS, RP
 Drafting of Manuscript: DCS

Editing of Manuscript for intellectual content: DCS, DA, SDB, SC, KND, KG, RP, MM, KET, PRV, LJM.

Source of funding

This trial (Initiation of Cooling by Emergency medical services to Promote the Adoption of in-hospital therapeutic hypothermia in Cardiac arrest Survivors, the **ICEPACS RCT**) was funded by a grant from the Canadian Institute of Health Research. Dr. Scales was the recipient of the Graham Farquharson Knowledge Translation Fellowship from the Physicians Services Incorporated Foundation. Dr. Morrison holds the Robert and Dorothy Pitts Chair in Acute Care and Emergency Medicine, Li Ka Shing Knowledge Institute, St Michael's Hospital, University of Toronto. The SPARC Network is also funded by a Center for Resuscitation Science and Knowledge Translation grant from the Laerdal Foundation for Acute Medicine – Centre Support Program and a grant from the Heart and Stroke Foundation of Canada and Canadian Institute of Health Research.

Conflicts of interest

S.C. received speaking honoraria from Zoll Medical Corporation and Physio-Control Corporation for providing educational talks on CPR quality.

Strategies for Post Arrest Care – ICEPACS network participating institutions (www.sparcnetwork.ca)

1. Halton Healthcare – Georgetown Hospital, Georgetown, Ontario, Canada
2. Halton Healthcare – Milton District Hospital, Milton, Ontario, Canada
3. Halton Healthcare – Oakville Trafalgar Memorial Hospital, Oakville, Ontario, Canada
4. Humber River Hospital – Church Site, York, Ontario, Canada
5. Humber River Hospital – Finch Site, York, Ontario, Canada
6. Joseph Brant Hospital, Burlington, Ontario, Canada
7. Lakeridge Health – Oshawa, Oshawa, Ontario, Canada
8. Mackenzie Health, Richmond Hill, Ontario, Canada
9. Markham Stouffville Hospital, Markham, Ontario, Canada
10. Michael Garron Hospital, Toronto, Ontario, Canada
11. Mount Sinai Hospital, Toronto, Ontario, Canada
12. North York General Hospital, Toronto, Ontario, Canada
13. Rouge Valley Health System – Centenary Site, Scarborough, Ontario, Canada
14. Royal Victoria Regional Health Centre, Barrie, Ontario, Canada
15. The Scarborough Hospital – General Campus, Scarborough, Ontario, Canada
16. St. Joseph's Health Centre, Toronto, Ontario, Canada
17. St. Michael's Hospital, Toronto, Ontario, Canada
18. Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
19. Trillium Health Partners – Credit Valley Hospital, Mississauga, Ontario, Canada
20. Trillium Health Partners – Mississauga Hospital, Mississauga, Ontario, Canada
21. University Health Network – Toronto General Hospital, Toronto, Ontario, Canada
22. University Health Network – Toronto Western Hospital, Toronto, Ontario, Canada
23. William Osler Health System – Brampton Civic Hospital, Brampton, Ontario, Canada
24. William Osler Health System – Etobicoke General Hospital, Etobicoke, Ontario, Canada

ICEPACS participating emergency medical services

Halton Paramedic Services
Peel Regional Paramedic Services
Toronto Paramedic Services
York Paramedic Services

Acknowledgements

Michelle Gaudio, Kate Byrne, Aarthi Kamath, and Toula Gonadelles for trial support; Sedigheh Shaeri for record reviews; Cathy Zhan for data analysis and Adam Byers for data management. All of the aforementioned individuals were salaried employees on the grant.

For operational and implementation support at each EMS system: Toronto Paramedic Services: Chief Paul Raftis, Gary Mcauley, Deputy Chief Garrie Wright, Erin Royal, Rachel Edwards, Kris Staley, Scott Gorsline, Alan Craig; Peel Paramedic Services: Chief Peter Dundas, Priya Kakar, Gordon Nevels; Halton Paramedic Services: Chief Greg Sage, Roman Nowickyj; York Paramedic Services: Chief Norm Barrette, Deputy Chief Chris Spearen, Natalie Kedzierski, Steve Darling, Kyle Grant, Louise Lorenc, Andy Benson.

As collaborators at receiving hospitals: Dr. Philip Moran (Lakeridge Health); Dr. Donna McRitchie (North York General Hospital); Dr. Joey Butchey (Rouge Valley Health System); Dr. Robert Cirone (St. Joseph's Health Centre); Dr. Tom Chan (The Scarborough Hospital); Dr. Angie Stone (Michael Garron Hospital); Dr. Janos Pataki and Dr. Eric Letovsky (Trillium Health Partners); Dr. Niall Ferguson and Dr. Eyal Golan (Mount Sinai Hospital and University Health Network); Dr. Michelle Welsford (Hamilton Health Sciences).

The Data Safety and Monitoring Committee was comprised of 3 experts in critical care and emergency medicine, clinical trial methodology, and biostatistics: H. Tom Stelfox MD PhD (Chair; expert in critical care, clinical trials, and clinical epidemiology); George A. Wells, MSc, PhD (methodological and statistical expertise in the conduct of clinical trials); Brian H. Rowe, MD, MSc (expert in emergency medicine, clinical trials, and clinical epidemiology).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2017.10.002>.

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