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Clinical paper

Pediatric out-of-hospital cardiac arrest: Time to goal target temperature and outcomes☆

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Abstract

Aim: Although recent out-of-hospital cardiac arrest (CA) trials found no benefits of hypothermia versus normothermia targeted temperature management, preclinical models suggest earlier timing of hypothermia improves neuroprotective efficacy. This study investigated whether shorter time to goal temperature was associated with better one-year outcomes in the Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital Trial.

Methods: Patients were classified by tertiles of time to attain assigned goal temperature range (32–34 °C or 36–37.5 °C) following ROSC. Outcomes in the first tertile ("earlier") Group 1 were compared with second and third tertiles ("later") Group 2. Separate analyses were, additionally, completed for hypothermia and normothermia intervention groups. Three one-year outcomes were examined: survival; Vineland Adaptive Behavior Scale (VABS-II) score ≥ 70; and decrease in VABS-II ≤ 15 points from baseline.

Results: In the entire cohort (n = 281), median time from ROSC to goal temperature was 7.4 [IQR 6.2–9.7] hours: Group 1, 5.8 [IQR 5.2, 6.2] and Group 2, 8.8 [IQR 7.4, 10.4] h. Outcomes did not differ between these groups. For hypothermia subgroup, survival was lower in Group 1 than 2, [10/49(20%) versus 47/99(47%), $p < 0.002$], with a trend toward fewer with VABS-II scores ≥ 70 and change in VABS-II ≤ 15 points ($p = 0.07$–0.08). For normothermia subgroup, there was a trend toward higher survival in Group 1 than 2 [18/42(43%) versus 21/83(25%), $p = 0.065$], but no differences in VABS-II-related measures. In multivariable logistic regression models, no difference in earlier and later groups or temperature intervention was observed.

Conclusion: We found no evidence that earlier time to goal temperature was associated with better outcomes.

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Introduction

In animal models of CA, therapeutic hypothermia (TH) improves survival and functional outcome when administered within 1 h of return of spontaneous circulation (ROSC).[1] In a rat model, Jia et al. showed that the efficacy of TH was optimal if treatment was implemented immediately after ROSC, rather than after a one-hour delay.[2] A subsequent study found that in a rat model, delayed onset of TH (33 °C ± 1 °C) up to 4 h after ROSC, coupled with sustained temperature interventions for 24 or 48 h, improved survival and rates of good neurological outcome, compared with normothermia controls; these benefits were lost if TH onset was delayed to 8 h after ROSC.[3] These pre-clinical studies illustrated that timing to begin hypothermia and to attain target temperature, as well as duration of TH, are potent variables that influence efficacy of this intervention.

One of the initial clinical trials that evaluated adults who were comatose after ROSC and were treated with hypothermia reported benefit, despite the long time interval (median 8 h) required to achieve the goal temperature and inclusion of 14% of cases who never achieved the goal temperature range.[4] Another trial in adults, reported that early initiation of cooling in the field versus in-hospital resulted in shorter time to goal temperature range of 34 C [4.2 vs 5.5 h] but found no survival or neurological outcome benefit.[5] In contrast, shorter time to target temperature has been reported in an adult observational registry study with a cut off of less than 300 min to be associated with worse outcome.[6] In humans resuscitated after CA, the timing for onset and duration for targeted temperature management to attain optimal outcomes are unknown.

The Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital Trial (THAPCA-OH) was the first large multicenter trial that was completed in children who remained comatose after ROSC; the study examined 12 months outcomes with two different target temperatures to prevent fever, TH (32–34 °C) and TN (36.0–37.5 °C).[7] Analysis of THAPCA-OH data revealed no statistically significant differences in mortality or neurobehavioral outcomes between the two target temperature management interventions; median time interval from ROSC to goal temperature range was approximately 7.4 h, IQR 6.2–9.7 h.

The current study is an exploratory analysis to compare one year outcomes in patients enrolled in THAPCA-OH who achieved target temperature range earlier versus later in the initial intervention period. We examined one year outcomes for the following groups: (1) earlier versus later time to achieve goal temperature for all subjects; (2) earlier versus later times to achieve goal temperature separately for TH and TN cohorts; (3) earlier time to achieve goal temperature, comparing TH and TN groups, and later time to achieve goal temperatures comparing TH and TN groups. We hypothesized that (1) earlier times to goal temperature would be associated with better outcomes than later time to goal temperature and (2) temperature intervention group assignment (TH or TN) would not be associated with outcome.

Methods

Study design

The THAPCA-OH trial was supported by the National Heart Lung and Blood Institute (NHLBI) and results were published in 2015.[7] The rationale, study design, outcome selection process, protocol summary, and 12-month pilot vanguard phase were previously described.[8–10] Briefly, this was a randomized clinical trial conducted in pediatric intensive-care units at 38 children's hospitals in the United States and Canada.

Authors (VN, SS, FM) defined, by consensus, two levels of time to goal temperature from ROSC to investigate. **(1) *Group 1*** was defined as the earlier 33% (first tertile) of cases achieving the goal temperature range for each of the TH and TN interventions. **(2) *Group 2*** was defined as the remaining later 67% of cases achieving the goal temperature range for each intervention.

Patient population

The study population has been previously described in detail.[7] Briefly, children older than 48 h and less than 18 years who sustained CA, required chest compressions for at least two minutes, and remained dependent on mechanical ventilation after ROSC, met the inclusion criteria. Subjects who never reached the goal temperature range were excluded from this analysis. A full listing of exclusion criteria is provided in the Supplementary Appendix of the original trial report.[7]

Randomization and intervention

Eligible subjects were randomized to either TH or TN in a 1:1 ratio. Targeted temperature management was actively maintained for 120 h in both groups using the Blanketrol III. Children assigned to TH were maintained at 33 °C (range 32–34 °C) core temperature for 48 h. They were then rewarmed over 16 h or longer to a target temperature range of 36.8 °C (range 36–37.5 °C); this temperature was actively maintained throughout the remainder of the 120-h intervention period. Children randomized to TN received identical care except core temperature was actively maintained at 36.8 °C (range 36–37.5 °C) for 120 h. Additional details of targeted temperature management are described in the original trial publication.[7]

Outcomes

Two outcomes from the original trial and one modified outcome were examined. The primary outcome in the THAPCA-OH trial was survival with favorable neurobehavioral outcome at twelve-month follow-up, defined as an age-corrected standard score of $\geq$70 on the VABS-II composite score.[11] The VABS-II has an age-corrected mean of 100 and a standard deviation of 15; higher scores indicate better performance. The VABS-II data were collected centrally (Kennedy-Krieger Institute, Baltimore, MD) via telephone by a trained interviewer blinded to treatment assignment. As pre-specified in the trial protocol, enrolled children whose reported pre-arrest VABS-II scores were $<$70 (based on data from formal caregiver report at each site within 24 h of randomization) were not included in the primary efficacy analysis. Subjects with no baseline VABS-II available were considered eligible for the primary analysis if the baseline Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores were in the normal or mild disability category.[10,12,13] Scores for both scales range from 1 to 6, with lower scores representing less disability; patients with scores of either 1 or 2 on both scales were eligible for the primary analysis.

Secondary outcomes were survival twelve months after CA and VABS-II score at 12 months reduced no more than 15 points from baseline (measured as the difference from pre-arrest baseline to twelve-month measurement on the VABS-II). For the latter, deceased

patients and those with the lowest possible VABS-II score were assigned the worst possible outcomes, regardless of baseline function. We dichotomized the change in VABS-II score measured at one year as ≤15-point decline (good outcome) or >15-point decline from baseline (poor outcome).

Statistical analyses

The analysis for the primary outcome in this study was performed using a pre-specified modified intention-to-treat approach, excluding children with pre-arrest neurobehavioral impairment (VABS-II < 70) and other criteria described in the methods above. Secondary efficacy outcomes were analyzed among all children. The primary outcome, twelve-month survival and twelve-month change in VABS-II ≤ 15 points were compared between time-to-goal temperature range groups using Fisher's exact test. An alpha level of 0.05 was considered significant with two-sided tests used in all instances. No adjustment for multiple p-values was performed in this exploratory study. Logistic regression models were used to examine relationships between the three defined 12-month outcomes adjusting for other variables associated with outcome. Independent variables having a univariate p-value < 0.10 were considered in multivariable models. Stepwise selection was used to select the final models; assigned treatment group and time to goal temperature range group were controlled for and kept in the final models while only other characteristics with a p value less than 0.05 were retained. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

As originally reported, a total of 295 cases were randomized in the THAPCA-OH trial with 155 assigned to TH and 140 assigned to TN.[7] Fourteen patients (4.7%), four in the TH group and ten in the TN group, were excluded from the current study because they did not reach the goal temperature range. Two hundred and eighty-one (281) patients were included in this analysis. For the entire cohort, the medians and interquartile ranges of time for TH cases were 7.6 (6.2, 9.6) h; for TN cases were 7.4 (6.2, 9.8) h; and all cases were 7.4 (6.2, 9.7) h. Overall, Group 1 patients attained their target temperature at a median time of 5.8 h (IQR 5.2, 6.2) after ROSC; for the TH intervention and TN intervention subgroups the corresponding median with IQR values were 5.8 (5.2, 6.2) and 5.8 (5.0, 6.3) h respectively. In contrast, Group 2 patients achieved their target temperature range at a median of 8.8 h (IQR 7.4, 10.4) after ROSC; for the TH and TN intervention subgroups the corresponding median with IQR values were 8.8 (7.6, 10.0) and 8.6 (7.4, 11.4) h respectfully. See Fig. 1 for time from ROSC to the goal temperature range for all patients and the two intervention subgroups.

Overall, patients in the earlier compared to later time to goal temperature range (Group 1 versus Group 2) were similar by age, gender, etiology of arrest, first rhythm asystole, estimated duration of chest compressions, and number of adrenaline (epinephrine) doses. Patients in Group 1 (earlier time) had significantly lower body weight, were more likely to have a study hospital as first hospital, had higher first lactate reported, and had lower temperature at the time of onset of the study intervention (See Table 1). Among patients randomized to TH, the following characteristics differed between the earlier (Group 1) compared to later (Group 2) time to goal temperature groups: younger age, lower body weight, more likely to have apparent life threatening event/sudden infant death syndrome (ALTE/SIDS) and less likely to have drowning aetiology, longer estimated duration of chest compressions, more frequent requirement for chest compressions on first hospital arrival, receipt of more epinephrine doses, unwitnessed CA, higher first measured lactate level, and lower first temperature at onset of study intervention. In patients randomized to TN, the only differences between the earlier Group 1 compared to later Group 2 were lower first reported lactate and higher first reported temperature at time of the temperature intervention (See Table 1).

In Table 2, 12 month outcomes for Group 1 and Group 2 time to goal temperature are described overall and separately for the TH and TN groups. For the entire cohort, there were no differences in survival with a VABS-II ≥ 70 at 12 months, survival, or VABS-II decrease by no more than 15 points for early versus later time to goal temperature. For the subgroup receiving TH, survival was higher in those achieving a goal temperature later compared to earlier (p = 0.002). There were similar trends that did not achieve statistical significance for survival with VABS-II ≥ 70 at 12 months and VABS-II decrease by no more than 15 points from baseline (p value 0.07–0.08). For TN, there was no difference by earlier Group 1 versus later Group 2 time to goal temperature groups for any of these three outcomes, although there was a trend for higher survival at 12 months for TN cases achieving the goal range earlier (p = 0.065).

Table 3 examines outcomes separately for the TH and TN treated cases in Groups 1 and 2. For the earlier time to goal temperature (Group 1), survival was higher in the TN group (p = 0.02). For the later time to goal temperature (Group 2), survival was higher for those assigned to TH (p = 0.002).

Table 4 presents multivariate models for the three 12-month outcomes. For both survival with VABS-II ≥ 70 at one year and survival at one year, time to goal temperature and temperature intervention group were not associated with outcome, while primary etiology of CA and first measured lactate were significantly associated with outcome. For survival at 12 months with VABS-II decrease no more than 15 points from baseline, neither time to goal temperature or temperature intervention group were associated with outcome, while initial cardiac rhythm asystole and first measured lactate were significantly associated with outcome.

Discussion

This secondary cohort analysis of the THAPCA-OH trial found, in unadjusted analyses, that patients assigned to TH who achieved their goal temperature range earlier had worse outcomes, while patients who were assigned to TN who achieved their goal range earlier had better outcomes. These trends were likely primarily attributable to severity of illness and case-mix differences (i.e. confounding variables) in the cohorts for the earlier versus later time to goal temperature groups. In multivariate analyses, the associations of time to target temperature were no longer statistically significant after controlling for the primary etiology of CA, baseline lactate, and first rhythm asystole. Therefore, controlling for CA severity of illness was key in this investigation.

The THAPCA-OH trial was the first large pediatric CA trial which examined outcomes of TH and TN targeted temperature management in comatose children. The current report is the first pediatric study to examine whether time to the goal temperature range is associated with survival and good functional outcomes in a targeted temperature management intervention trial. In the adjusted multivariate analyses,

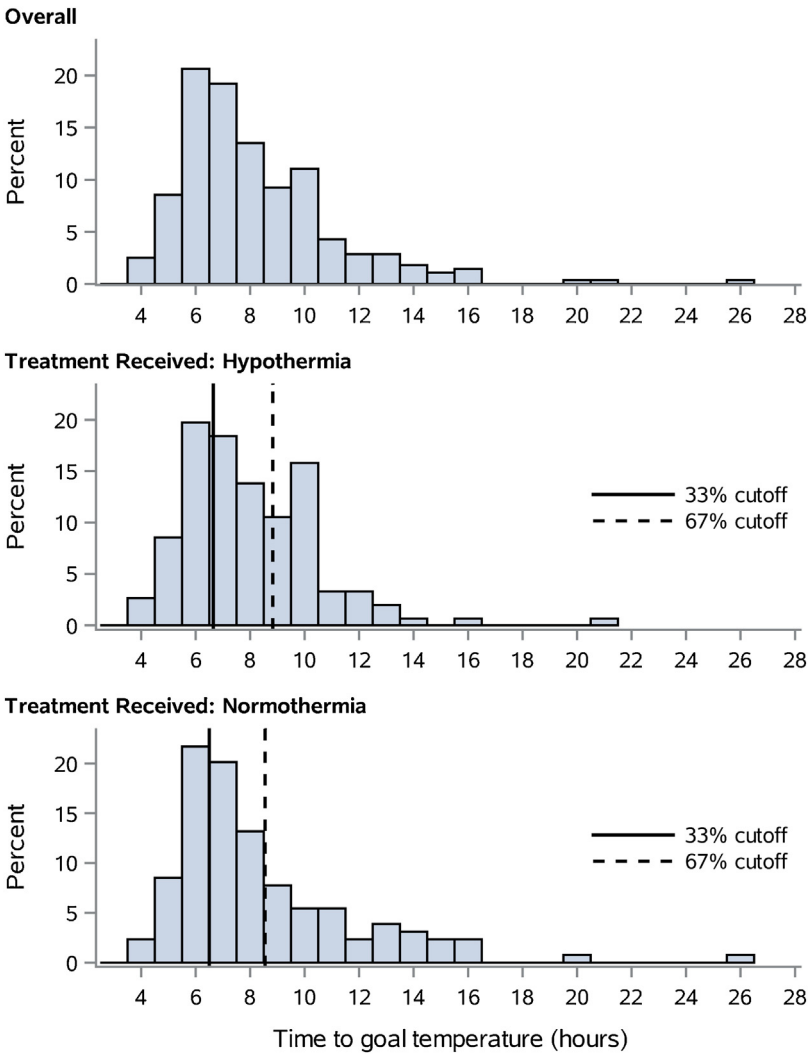

Fig. 1 – Time from ROSC to goal temperature range in THAPCA out of hospital trial. First and second tertiles of the time in hours from ROSC to goal temperature range, by treatment group, were Hypothermia 6.7, 8.8; Normothermia 6.5, 8.6; Overall 6.6, 8.8.

earlier versus later time to the goal temperature range (Group 1 versus Group 2) and target temperature group (TH versus TN) were not associated with any of the three outcomes assessed, while etiology of CA and baseline lactate measurement were associated with both survival and survival with VABS-II $\geq$ 70. For the outcome survival with VABS-II no more than 15 point less than baseline, initial CA rhythm asystole and higher baseline lactate were associated with worse outcome. Higher lactate has previously been associated with worse outcome after pediatric CA.[14] We previously reported from the THAPCA-OH trial database that etiology of CA was associated with survival and survival with 12 months VABS-II $\geq$ 70[15]; in the current study we demonstrated that the association persisted even after adjusting for time to the goal temperature range.

In adults, lower temperature on hospital arrival has been associated with worse outcome following CA.[16] In an adult observational registry study shorter time to target temperature for TH with a cut off of less than 300 min (5 h) was associated with worse outcome.[6] In TH-treated patients from the THAPCA-OH trial, etiology of CA, younger age, lower weight, longer estimated duration of chest compressions, higher number of epinephrine doses, higher first lactate measurement, and lower first reported temperature near time of intervention were associated with shorter time to goal temperature. Longer estimated duration of chest compressions, higher number of epinephrine doses and higher first lactate measurement have previously been reported to be associated with worse outcome for OH-CA.[14,15,17] Similarly, patients less than one year (younger, smaller) would more likely have the diagnosis of ALTE/SUID, which is known to have very poor outcomes.[17,18–20] It is likely that the first reported temperature at the start of the intervention for TH was lower in those with longer duration of chest compressions and in some etiologies of CA (e.g. ALTE/SUID). For TN, lower first lactate measurement and higher reported temperature at the start of the temperature intervention were associated with shorter time to the goal temperature range; these variables are associated with lower severity of illness and better outcomes.

Table 1 – THAPCA-OH characteristics by time to goal temperature and temperature intervention.

	Overall			Hypothermia			Normothermia		
	Group 1	Group 2	p-Value	Group 1	Group 2	p-Value	Group 1	Group 2	p-Value
	First 33% (N = 95)	First 33% (N = 95)		First 33% (N = 51)	Last 67% (N = 101)		First 33% (N = 44)	Last 67% (N = 85)	
Age at randomization (years): median (Q1, Q3)	1.5 (0.3, 7.4)	2.3 (0.6, 9.0)	0.105[a]	0.8 (0.3, 2.3)	3.5 (1.0, 12.0)	<.001[a]	3.2 (0.4, 10.8)	1.4 (0.3, 4.6)	0.069[a]
Age in years			0.367[b]			0.002[b]			0.222[b]
<1 year	43 (45%)	64 (34%)		28 (55%)	25 (25%)		15 (34%)	39 (46%)	
1–4 years	26 (27%)	60 (32%)		14 (27%)	33 (33%)		12 (27%)	27 (32%)	
5–12 years	12 (13%)	31 (17%)		4 (8%)	20 (20%)		8 (18%)	11 (13%)	
>13 years	14 (15%)	31 (17%)		5 (10%)	23 (23%)		9 (20%)	8 (9%)	
Male	65 (68%)	120 (65%)	0.595[b]	36 (71%)	64 (63%)	0.469[b]	29 (66%)	56 (66%)	1.000[b]
Weight (kg): median (Q1, Q3)	10.7 (5.9, 20.0)	13.2 (8.1, 32.0)	0.041[a]	10.0 (5.9, 15.0)	16.0 (10.0, 40.5)	<.001[a]	14.6 (5.9, 34.7)	11.0 (7.0, 18.8)	0.289[a]
Pre-existing condition	46 (48%)	91 (49%)	1.000[b]	20 (39%)	54 (53%)	0.122[b]	26 (59%)	37 (44%)	0.099[b]
Primary etiology of cardiac arrest			0.099[b]			0.004[b]			0.616[b]
Cardiac	9 (9%)	27 (15%)		2 (4%)	14 (14%)		7 (16%)	13 (15%)	
ALTE/SUID	21 (22%)	23 (12%)		14 (27%)	7 (7%)		7 (16%)	16 (19%)	
Drowning	18 (19%)	51 (27%)		11 (22%)	34 (34%)		7 (16%)	17 (20%)	
Other respiratory	35 (37%)	55 (30%)		16 (31%)	27 (27%)		19 (43%)	28 (33%)	
Other	3 (3%)	7 (4%)		2 (4%)	7 (7%)		1 (2%)	0 (0%)	
Unknown	9 (9%)	23 (12%)		6 (12%)	12 (12%)		3 (7%)	11 (13%)	
Initial rhythm asystole	51 (54%)	114 (61%)	0.250[b]	29 (57%)	56 (55%)	1.000[b]	22 (50%)	58 (68%)	0.056[b]
Estimated duration chest compressions: median (Q1, Q3)	25.0 (17.5, 41.0)	25.0 (15.0, 35.0)	0.477[a]	27.0 (18.5, 43.5)	21.0 (14.0, 33.0)	0.011[a]	25.0 (14.0, 35.0)	28.0 (17.5, 45.0)	0.126[a]
Chest compressions required on arrival at the first hospital	68 (72%)	115 (62%)	0.107[b]	38 (75%)	56 (55%)	0.012[b]	30 (68%)	59 (69%)	0.685[b]
Total doses of epinephrine (EMS and hospital): median (Q1, Q3)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	0.843[a]	4.0 (2.0, 6.0)	3.0 (1.0, 4.0)	0.041[a]	2.0 (1.0, 4.0)	3.0 (2.0, 6.0)	0.062[a]
Cardiac arrest witnessed	32 (34%)	73 (39%)	0.594[b]	12 (24%)	45 (45%)	0.028[b]	20 (45%)	28 (33%)	0.180[b]
First hospital was study hospital	38 (40%)	48 (26%)	0.020[b]	20 (39%)	25 (25%)	0.090[b]	18 (41%)	23 (27%)	0.116[b]
Baseline Lactate[c]: median (Q1, Q3)	7.5 (3.5, 11.1)	4.7 (2.9, 9.0)	0.026[a]	8.8 (6.0, 13.3)	3.8 (2.6, 6.9)	<.001[a]	4.4 (3.3, 8.7)	7.6 (4.0, 11.9)	0.034[a]
First reported temperature: Median (Q1, Q3)	35.6 (33.5, 36.6)	36.2 (34.4, 37.5)	0.002[a]	33.8 (32.8, 35.3)	36.9 (35.7, 37.7)	<.001[a]	36.6 (36.0, 37.5)	35.1 (33.6, 37.3)	<.001[a]

[a] Wilcoxon rank-sum test.

[b] Fisher's exact test.

[c] First lactate measurement up to 8 h after randomization (mmol/L).

Table 2 – THAPCA-OH outcomes by treatment received and time to goal temperature.

	Group 1 Earlier 33%	Group 2 Later 67%	p-Value
Overall			
Survival at 12 months with VABS-II ≥ 70	10/85 (12%)	32/164 (20%)	0.154[a]
Survival at 12 months	28/91 (31%)	68/182 (37%)	0.347[a]
VABS-II decreased no more than 15 points or improved	9/91 (10%)	29/180 (16%)	0.197[a]
Hypothermia			
Survival at 12 months with VABS-II ≥ 70	5/46 (11%)	22/89 (25%)	0.070[a]
Survival at 12 months	10/49 (20%)	47/99 (47%)	0.002[a]
VABS-II decreased no more than 15 points or improved	3/49 (6%)	18/99 (18%)	0.077[a]
Normothermia			
Survival at 12 months with VABS-II ≥ 70	5/39 (13%)	10/75 (13%)	1.000[a]
Survival at 12 months	18/42 (43%)	21/83 (25%)	0.065[a]
VABS-II decreased no more than 15 points or improved	6/42 (14%)	11/81 (14%)	1.000[a]

Denominators reflect the number of subjects with available outcomes at 12 months. Additionally, subjects with poor pre-arrest neurobehavioral function were excluded from analysis of the primary outcome, survival at 12 months with VABS-II ≥ 70.
[a] Fisher's exact test.

Table 3 – THAPCA-OH outcomes by time to goal temperature and treatment received.

	Hypothermia	Normothermia	p-Value
Group 1 (Earlier 33%)			
Survival at 12 months with VABS-II ≥ 70	5/46 (11%)	5/39 (13%)	1.000[a]
Survival at 12 months	10/49 (20%)	18/42 (43%)	0.025[a]
VABS-II decreased no more than 15 points or improved	3/49 (6%)	6/42 (14%)	0.293[a]
Group 2 (Later 67%)			
Survival at 12 months with VABS-II ≥ 70	22/89 (25%)	10/75 (13%)	0.077[a]
Survival at 12 months	47/99 (47%)	21/83 (25%)	0.002[a]
VABS-II decreased no more than 15 points or improved	18/99 (18%)	11/81 (14%)	0.424[a]

Denominators reflect the number of subjects with available outcomes at 12 months. Additionally, subjects with poor pre-arrest neurobehavioral function were excluded from analysis of the primary outcome, survival at 12 months with VABS-II ≥ 70.
[a] Fisher's exact test.

Limitations of the THAPCA-OH Trial have been previously described.[7] In addition, for the current investigation practical considerations in the implementation of the THAPCA-OH trial influenced time to attain goal temperature. A large proportion of study patients (70%) required transfer from a non-study hospital to a study site. In addition, the availability of guardians for obtaining informed consent and the study protocol, which required central venous and arterial lines to be placed in patients prior to the initiation of any intervention, were factors that delayed the onset of temperature management. Time to the goal range after ROSC for the entire cohort was a median of 7.4 h. This was longer than corresponding values in an adult trial that examined early initiation of cooling where time to goal temperature following ROSC was reported to be a mean of 4.2 h when started in the field and 5.5 h when initiated in the emergency room.[5] Nonetheless, in that trial outcomes were not improved with earlier initiation of cooling. It is also of note that the 2002 HACA trial had a time to the hypothermia goal temperature range (32–34 °C) of 8 h (4–16 IQR), and 19 of 132 (14%) never achieved the goal range.[4] However, improved outcome was reported in the group treated with TH with 24 h of cooling and rewarming of approximately 8 h compared to a usual care comparison group, which did not uniformly prevent fever. In the THAPCA-OH trial, the median and IQR times to goal temperature were Hypothermia 7.6 (6.2, 9.6); Normothermia 7.4 (6.2, 9.8); Overall 7.4 (6.2, 9.7); the 120-h duration of temperature control was much longer than previously studied in adult CA trials.[4,21,22]

It remains challenging to compare time intervals to achieve hypothermia in clinical trials with findings in pre-clinical models, and to replicate the scenarios of experimental studies in a clinical context. In a fetal sheep cerebral ischemia model, hypothermia onset up to 5.5 h after the initiating insult remains neuroprotective, and efficacy is lost when initiated 7.5 h after the event.[23] A recent report in a rat CA model further illustrated the potent role of timing of onset of hypothermia to attain benefit, and suggested a mechanism that contributed to the benefits of immediate post-resuscitation onset of hypothermia.[24] Specifically, they showed that early

Table 4 – Multivariable Logistic Regression Models of One Year Outcomes

Characteristic	Odds ratio (95% CI)	p-Value
Survival at 12 months with VABS-II ≥ 70		
Out-of-hospital tertile group		0.767
First 33%	0.87 (0.35, 2.19)	
Last 67%	Reference	
Treatment group		0.648
Normothermia	Reference	
Hypothermia	1.22 (0.53, 2.80)	
Primary etiology of cardiac arrest		0.003
Cardiac	Reference	
ALTE/SUID	0.23 (0.05, 1.06)	
Drowning	0.50 (0.17, 1.46)	
Other respiratory	0.10 (0.03, 0.35)	
Other/unknown	0.20 (0.05, 0.84)	
Baseline lactate (up to 8 h after randomization) (mmol/L)	0.67 (0.56, 0.80)	<.001
Survival at 12 months		
Out-of-hospital tertile group		0.805
First 33%	1.08 (0.57, 2.05)	
Last 67%	Reference	
Treatment group		0.652
Normothermia	Reference	
Hypothermia	1.15 (0.63. 2.08)	
Primary etiology of cardiac arrest		0.016
Cardiac	Reference	
ALTE/SUID	0.24 (0.07, 0.79)	
Drowning	1.00 (0.39, 2.57)	
Other respiratory	0.45 (0.18, 1.10)	
Other/unknown	0.34 (0.12, 1.01)	
Baseline lactate (up to 8 h after randomization) (mmol/L)	0.80 (0.74, 0.87)	<.001
VABS-II decreased no more than 15 points or improved		
Out-of-hospital tertile group		0.282
First 33%	0.62 (0.26, 1.49)	
Last 67%	Reference	
Treatment group		0.275
Normothermia	Reference	
Hypothermia	0.65 (0.30, 1.41)	
Initial cardiac arrest rhythm was asystole		0.007
No	Reference	
Yes	0.34 (0.15, 0.74)	
Baseline lactate (up to 8 h after randomization) (mmol/L)	0.81 (0.72, 0.92)	<.001

hypothermia resulted in rapid restoration of cerebral blood flow back to baseline levels, thereby limiting secondary injury, and contributing to improved neurological outcome. At this time for comatose adults and children following CA, optimal time to goal temperature has yet to be identified.

In conclusion, earlier time to attainment of the goal temperature range was not associated with better outcomes, for the whole population or for either the hypothermia or normothermia intervention subgroups, after adjusting for confounding factors related to cause of CA and severity of CA (lactate, asystole). In future clinical trials to evaluate temperature management, if more rapid attainment of goal temperature becomes feasible, it could be informative to re-evaluate whether earlier time to achieve goal temperature improves survival and functional outcomes.

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Conflict of interest

The authors declares that they have no conflict of interest.

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