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Clinical paper

Exploring the safety and efficacy of targeted temperature management amongst infants with out-of-hospital cardiac arrest due to apparent life threatening events☆

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ABSTRACT

Objective: To explore the safety and efficacy of targeted temperature management amongst infants with out-of-hospital cardiac arrest due to an apparent life threatening event (ALTE) recruited to the Therapeutic Hypothermia after Paediatric Cardiac Arrest Out-of-Hospital trial.
Methods: Fifty-four infants (48 h to <1 year of age) with ALTE who received chest compressions for ≥2 min, were comatose, and required mechanical ventilation after return of circulation were included. Infants were randomised to therapeutic hypothermia (33 °C) (n = 26) or therapeutic normothermia (36.8 °C) (n = 28) within six hours of return of circulation. Outcomes included 12-month survival with Vineland Adaptive Behaviour Scales, Second Edition (VABS-II) score ≥70, 12-month survival, change in VABS-II score from pre-arrest to 12 months post-arrest, and select safety measures.
Results: Amongst infants with pre-arrest VABS-II ≥70 (n = 52), there was no difference in 12-month survival with VABS-II ≥70 between therapeutic hypothermia and therapeutic normothermia groups (2/25 (8.0%) vs. 1/27 (3.7%); relative risk 2.16; 95% confidence interval 0.21–22.38, p = 0.60). Amongst all evaluable infants (n = 53), the change in VABS-II score from pre-arrest to 12 months post-arrest did not differ (p = 0.078) between therapeutic hypothermia and therapeutic normothermia groups, nor did 12-month survival (5/26 (19.2%) vs. 1/27 (3.7%); relative risk 5.19; 95% confidence interval 0.65–41.50, p = 0.10).
Conclusions: Mortality was high amongst infants that were comatose after out-of-hospital cardiac arrest due to ALTE in both therapeutic hypothermia and therapeutic normothermia treated groups. Functional status was markedly reduced among survivors. (ClinicalTrials.gov, NCT00878644)

Introduction

Sudden infant death syndrome (SIDS) is the leading cause of post-neonatal infant death in industrialised countries.[1–3] SIDS is defined as the sudden death of an infant less than one year of age which is unexplained after a thorough case investigation, complete autopsy, examination of the death scene and review of the clinical history.[3] Near-miss cases in which a SIDS event is believed to have been in process but is interrupted or resolved prior to death is referred to as an apparent life threatening event (ALTE).[4] ALTE is defined as an episode that is frightening to the observer and that is characterised by some combination of apnoea, colour change, marked change in muscle tone, choking or gagging, and in some cases the observer fears that the infant has died.[4] Severe ALTE events that lead to cardiac arrest often result in hypoxic-ischaemic encephalopathy (HIE), the treatment of which is primarily supportive.

Therapeutic hypothermia (TH) has become standard treatment for neonates with moderate and severe HIE based on randomised controlled trials demonstrating reduced risk of death and developmental disability.[5–7]TH is recommended for neonates with HIE

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who meet the inclusion criteria of these trials which include gestational age ≥36 weeks and chronological age ≤6 h; pH ≤ 7.0 or base deficit ≥16 mmol/L in umbilical cord blood or blood obtained in the first hour after birth; and moderate to severe encephalopathy on physical examination.[8–13] However, reports describing the use of TH for neonates not meeting these criteria have recently been published.[14–16] For example, TH has been used to treat sudden unexplained post-natal collapse (SUPC) in apparently healthy neonates in the first 24 h of life; yet, no randomised controlled trials of TH for this condition exist. Whether TH could benefit even older infants with cardiac arrest due to ALTE is also unknown.

The Therapeutic Hypothermia after Paediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) Trial was a randomised controlled trial comparing the efficacy of TH with that of therapeutic normothermia (TN) on survival with good functional outcome in children one year after out-of-hospital cardiac arrest.[17] All children recruited to the trial were comatose and required mechanical ventilation after return of circulation, and were at high risk for neurologic disability. Results of the trial showed that TH did not confer a significant benefit on survival with good functional outcome compared to TN. The objective of this study is to explore the safety and efficacy of TH versus TN among infants with ALTE who were recruited to the THAPCA-OH Trial. This exploratory subgroup analysis is the first to compare TH and TN for treatment of out-of-hospital cardiac arrest due to ALTE.

Methods

Design and setting

The THAPCA-OH trial was conducted in 36 paediatric intensive care units (PICUs) in the United States (U.S.) and Canada from September 1, 2009 through December 31, 2012. Twenty-five of these PICUs contributed infants to the ALTE cohort. Details of the THAPCA-OH trial were previously published.[17–20] The trial was approved by the Institutional Review Boards at all sites and the Data Coordinating Centre. Parental permission was obtained for all participants.

Participants

Children >48 h and <18 years of age who had an out-of-hospital cardiac arrest with chest compressions for ≥2 min, and who required mechanical ventilation after return of circulation met the original inclusion criteria for the THAPCA-OH Trial.[17,18] Major exclusion criteria for the THAPCA-OH Trial included the inability to be randomised within six hours of return of circulation, a Glasgow Coma Scale motor score of 5 or 6,[21] a decision by the clinicians to withhold aggressive treatment, and out-of-hospital cardiac arrest due to trauma. Additional inclusion criteria for this subgroup analysis include age <1 year at the time of out-of-hospital cardiac arrest, and ALTE as the aetiology of arrest. Investigators at the local sites determined the aetiology of arrest at the time of study entry based on the admitting history and physical examination; aetiologies were selected from a predefined list which included the term ALTE/SIDS-like event. A CONSORT flow chart for the THAPCA-OH Trial was previously published.[17]

Interventions

Children recruited to the THAPCA-OH Trial were randomised 1:1 to TH or TN, using permuted blocks stratified by clinical centre and age.[17,18] Children assigned to TH were pharmacologically sedated and paralysed, and cooled (or warmed, if indicated) by surface cooling using a Blanketrol III cooling unit (Cincinnati SubZero, Cincinnati) in servo-control mode. Core body temperature was monitored with two probes (oesophageal, bladder, or rectal), one of which was connected to the Blanketrol III and the other to the bedside monitor. Blankets were applied anteriorly and posteriorly to achieve and maintain a core body temperature of 33 °C (32–34 °C) for 48 h. Children were then rewarmed over 16 h or longer to 36.8 °C (36–37.5 °C) and maintained at this temperature for the duration of the 120 h intervention period. Children assigned to TN received the same care except that core temperature was actively maintained at 36.8 °C (36–37.5 °C) for 120 h with the Blanketrol III. Clinicians determined all other aspects of care.

Outcomes

The primary outcome for the THAPCA-OH Trial was survival with good functional outcome at 12 months post-arrest.[17–19] Functional outcome was assessed using the Vineland Adaptive Behaviour Scales, Second Edition (VABS-II).[22] The VABS-II is a caregiver report measure of adaptive behaviour from birth to adulthood. Adaptive behaviour is defined as an individual's performance on daily life activities necessary for personal and social independence. The VABS-II domains include communication, daily living, socialisation, and motor skills. The number of tasks that can be performed in each domain is standardised for the child's age. In U.S. norms, the mean VABS-II score is 100 and the standard deviation (SD) is 15. Higher scores indicate better functioning. Survival with good functional outcome at 12 months post-arrest was defined as survival with VABS-II score ≥70.

VABS-II assessments were completed with parents 12 months post-arrest via telephone by trained interviewers from the Kennedy Krieger Institute. As pre-specified in the THAPCA-OH Trial protocol,[17,18] recruited children with pre-arrest VABS-II scores <70 (based on VABS-II data obtained by formal parental interview at the local site within 24 h of randomisation) were not included in the primary efficacy analysis. Children without a pre-arrest VABS-II score were included in the primary efficacy analysis if both pre-arrest Paediatric Overall Performance Category (POPC) and Paediatric Cerebral Performance Category (PCPC) scores[23] were in the normal or mild disability range. POPC rates function related to overall health and PCPC rates function related to neurologic status. Both scales range from 1 to 6 with lower scores representing less disability; children with scores of 1 or 2 on both scales were eligible for the primary efficacy analysis.

Secondary efficacy outcomes were 12-month survival and change in VABS-II from pre-arrest to 12 months post-arrest. Deceased children and those with the lowest possible VABS-II score at 12 months were assigned the worst possible outcomes. Additional outcomes were 12-month POPC and PCPC scores[23] and Mullen Scales of Early Learning (Mullen).[24] The Mullen is a measure of cognitive function designed for infants and young children. Safety outcomes included blood product use, serious arrhythmias, and culture-proven infections during the first 7 hospital days, and 28-day mortality. Adverse events were any untoward medical occurrence deemed to be clinically significant by the site investigator and were recorded through the first 14 hospital days.

Statistical analysis

Baseline characteristics of infants were summarised using frequencies and percentages for categorical variables and either the median and quartiles (Q_1, Q_3) or mean and SD for quantitative variables. The primary efficacy outcome was analysed using a pre-specified modified intention-to-treat approach, excluding children with poor pre-arrest neurobehavioural function. Secondary efficacy outcomes were analysed amongst all children. Safety outcomes were analysed amongst treated patients only. Significance of associations between treatment groups and the primary and sec-

Table 1
Baseline characteristics.

Characteristic	Hypothermia group (N = 26)	Normothermia group (N = 28)	P-Value[a]
Age at randomisation (months): median [Q1, Q3]	3.5 [2.0, 6.0]	3.0 [1.0, 4.0]	0.168
Male	18/26 (69.2%)	14/28 (50.0%)	0.176
Race			0.925
Black or African American	7/26 (26.9%)	6/28 (21.4%)	
White	16/26 (61.5%)	18/28 (64.3%)	
Other/unknown	3/26 (11.5%)	4/28 (14.3%)	
Hispanic or Latino	3/26 (11.5%)	3/28 (10.7%)	0.868
Known history of prematurity[b]	17/26 (65.4%)	16/28 (57.1%)	0.586
Patient had no pre-existing condition	18/26 (69.2%)	19/28 (67.9%)	1.000
Pre-existing prenatal condition	6/26 (23.1%)	3/28 (10.7%)	0.286
Pre-existing lung or airway disease	3/26 (11.5%)	3/28 (10.7%)	1.000
Pre-existing congenital heart disease	1/26 (3.8%)	0/28 (0.0%)	0.481
Pre-existing gastrointestinal disorder	3/26 (11.5%)	4/28 (14.3%)	1.000
Pre-existing neurologic condition	2/26 (7.7%)	0/28 (0.0%)	0.227
Any other significant pre-existing medical condition	3/26 (11.5%)	4/28 (14.3%)	1.000
Pre-cardiac arrest VABS-II[c] Score: Mean ± SD	93.9 ± 17.76	103.0 ± 13.51	0.093
Pre-cardiac arrest PCPC[d]			0.736
Normal = 1	24/26 (92.3%)	27/28 (96.4%)	
Mild disability = 2	1/26 (3.8%)	1/28 (3.6%)	
Moderate disability = 3	1/26 (3.8%)	0/28 (0.0%)	
Cardiac arrest witnessed	2/25 (8.0%)	4/27 (14.8%)	0.670
Chest compressions administered by bystander	19/26 (73.1%)	22/27 (81.5%)	0.526
Initial cardiac arrest rhythm noted by EMS or hospital			0.551
Asystole	14/26 (53.8%)	19/28 (67.9%)	
Bradycardia	1/26 (3.8%)	0/28 (0.0%)	
Pulseless electrical activity (PEA)	5/26 (19.2%)	5/28 (17.9%)	
Ventricular fibrillation or tachycardia	2/26 (7.7%)	0/28 (0.0%)	
Unknown	4/26 (15.4%)	4/28 (14.3%)	
Continuous estimated duration of chest compressions: median [Q1, Q3]	31.0 [21.0, 49.0]	32.5 [25.0, 36.0]	1.000
Chest compressions still required at hospital arrival	23/26 (88.5%)	24/27 (88.9%)	1.000
Total number of doses of adrenaline administered by EMS and at hospital: median [Q1, Q3]	4.0 [3.0, 5.0]	4.0 [2.0, 5.0]	0.938
Time from return of circulation to treatment initiation (h): median [Q1, Q3]	5.8 [5.3, 6.3]	6.1 [5.3, 7.0]	0.489

[a] Two-sided Wilcoxon rank-sum or Fisher's exact test.
[b] Prematurity is ≤38 weeks gestational age at birth.
[c] Vineland Adaptive Behaviour Scales, Second Edition.
[d] Paediatric Cerebral Performance Category.

ondary outcomes were examined using Fisher's exact test and the Wilcoxon Rank Sum test, and the magnitudes of these associations were assessed with risk differences and relative risks. Differences in cause of death and safety outcomes between treatment groups were also examined using Fisher's exact test. Rates of culture-proven infection were examined using exact confidence intervals (CI) and treatment groups were compared using exact score tests from Poisson regression. Kaplan–Meier curves with an associated log-rank test were generated to compare time to death between treatment groups. All analyses were completed using SAS software v9.4 (Cary, NC). For these exploratory analyses, an alpha level of 0.05 was used with two-sided tests conducted. There was no adjustment for multiple statistical testing and no predetermined power calculation for the ALTE cohort.

Results

Of 295 children recruited to the THAPCA-OH Trial, 54 (18.3%) had ALTE as the aetiology of cardiac arrest. Twenty-six were randomised to TH and 28 to TN. One infant assigned to TH had baseline VABS-II <70 and was ineligible for the primary efficacy analysis. Another infant assigned to TN had unknown vital status at 12 months post-arrest. Overall, the primary outcome was evaluable for 52 infants with ALTE.

Baseline characteristics were similar for infants in the TH and TN groups (Table 1). Overall, 32 (59.3%) were male, 34 (62.9%) were White, and median age was 3.0 months (Q_1, Q_3 2.0, 5.0 months). Thirty-three (61.1%) were prematurely born (≤38 weeks gestational age at birth), and 17 (31.5%) had at least one pre-existing condition. Pre-arrest VABS-II score was 98.6 ± 16.2 (mean ± SD). Cardiac arrest was witnessed for 6 (11.1%) and bystander compressions performed for 41 (75.9%). Initial arrest rhythm was asystole for 33 (61.1%). Estimated duration of chest compressions was a median 32.0 min (Q_1, Q_3 25.0, 43.5 min). Compressions were required at the time of hospital arrival for 47 (87.0%) and the median number of adrenaline (epinephrine) doses administered by emergency medical services and hospital personnel was 4 (Q_1, Q_3 2, 5). Body temperature reported prior to the initiation of the intervention was lower for the TH than TN group (34.0 °C vs. 35.3 °C, p = 0.046). Laboratory values reported prior to the initiation of the intervention were similar between treatment groups (Supplemental material 1).

The proportion of infants who survived with VABS-II ≥70 at 12 months post-arrest did not differ between the TH and TN groups (2/25 (8.0%) vs. 1/27 (3.7%); relative risk 2.16; 95% CI 0.21–22.38, p = 0.60) (Table 2). Twelve-month survival also did not differ between TH and TN groups (5/26 (19.2%) vs. 1/27 (3.7%); relative risk 5.19; 95% CI 0.65–41.50, p = 0.10); nor did survival time (log rank test p = 0.45) (Fig. 1). Cause of death was similar between groups (p = 0.39) with brain death or withdrawal of life support due to poor neurologic prognosis reported for 39 (82.9%) infants (Table 3). Change in VABS-II score from pre-arrest to 12 months post-arrest did not differ between TH and TN groups (p = 0.078) (Table 2). All 12-month survivors (n = 6) had a decline in VABS-II

Table 2
Primary and secondary outcomes.

Outcome	Treatment		Risk difference	Relative risk	P-Value
	Hypothermia group	Normothermia group			
Primary outcome[a]					
Survival at 12 months with VABS-II[b] ≥70	2/25 (8.0%)	1/27 (3.7%)	4.3 (−8.5, 17.1)	2.16 (0.21, 22.38)	0.603[d]
Secondary outcomes[c]					
Survival at 12 months	5/26 (19.2%)	1/27 (3.7%)	15.5 (−1.2, 32.3)	5.19 (0.65, 41.50)	0.100[d]
Change in VABS-II from baseline to 12 months					0.078[e]
Death	21/26 (80.8%)	26/27 (96.3%)			
Lowest possible VABS-II score	1/26 (3.8%)	0/27 (0.0%)			
VABS-II decreased >30 points	2/26 (7.7%)	1/27 (3.7%)			
VABS-II decreased 16–30 points	2/26 (7.7%)	0/27 (0.0%)			
VABS-II decreased no more than 15 points or improved	0/26 (0%)	0/27 (0%)			

[a] Two patients were excluded from the analysis (1 hypothermia patient had baseline VABS <70 and 1 normothermia patient had unknown vital status at month 12).
[b] Vineland Adaptive Behaviour Scales, Second Edition.
[c] One normothermia patient exluced from analysis because of unknown vital status at month 12.
[d] Fisher's exact test.
[e] Wilcoxon Rank Sum test.

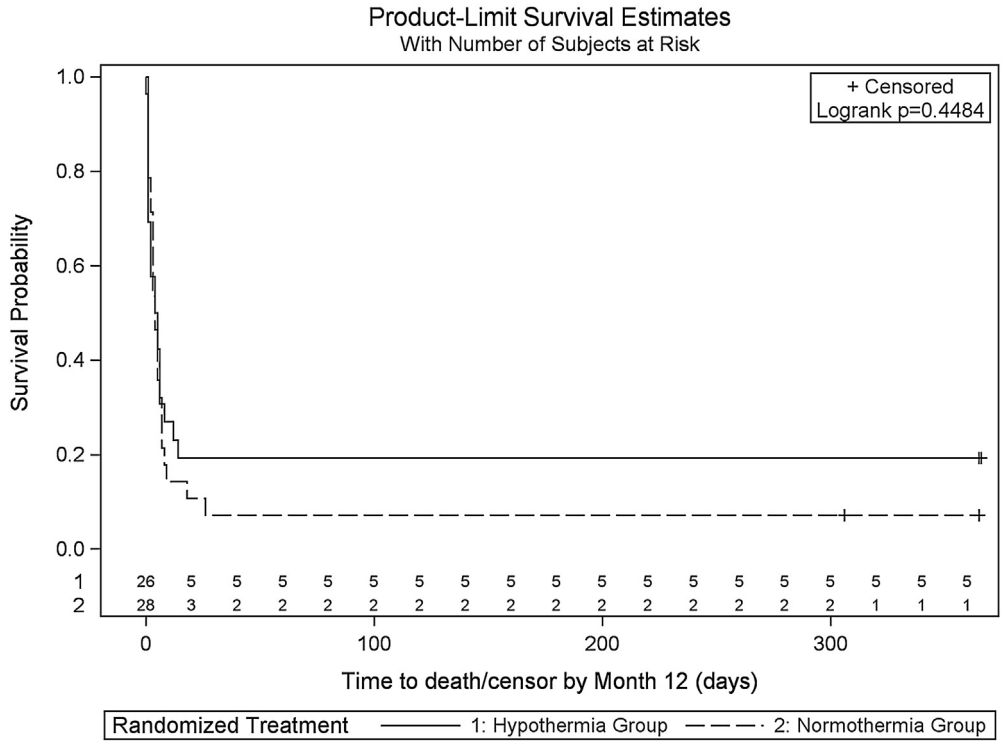

Fig. 1. Survival curve though 365 days for therapeutic hypothermia and therapeutic normothermia groups.

Table 3
Cause of death.

Cause of death	Treatment assigned		P-Value
	Hypothermia group (N = 21)	Normothermia group (N = 26)	
Neurologic brain death declared	9 (42.9%)	5 (19.2%)	0.388[a]
Withdrawal for poor neurologic prognosis	9 (42.9%)	16 (61.5%)	
Cardiovascular failure/futility	2 (9.5%)	3 (11.5%)	
Respiratory failure/futility	0 (0.0%)	1 (3.8%)	
Withdrawal for other system failure	1 (4.8%)	1 (3.8%)	

[a] Fisher's exact test.

score >15 points (1 SD). Twelve month POPC and PCPC scores and Mullen composite scores are shown in Supplemental material 2. All 12-month survivors had POPC and PCPC scores ≥3 (i.e., moderate or greater disability) and Mullen composite scores ≤69 (i.e., well below average).

The proportion of infants receiving blood products during the first 7 hospital days was lower in the TH than TN group (17/24 (70.8%) vs. 27/28 (96.4%), p = 0.018) (Table 4). The proportion of infants with serious arrhythmias (p = 1.0), culture-proven infection (p = 1.0), or 28 day mortality (p = 0.227) did not differ between

Table 4
Safety outcomes within 7 days of hospitalisation and 28-day mortality.

Safety outcome	Treatment received		P-Value
	Hypothermia group (N = 24)	Normothermia group (N = 28)	
Any blood product	17 (70.8%)	27 (96.4%)	0.018[a]
Cryoprecipitate	4 (16.7%)	5 (17.9%)	1.000[a]
Fresh frozen plasma	10 (41.7%)	14 (50.0%)	0.588[a]
Packed red blood cells/whole blood	16 (66.7%)	23 (82.1%)	0.186[a]
Platelets	5 (20.8%)	5 (17.9%)	1.000[a]
Any serious arrhythmias	1 (4.2%)	2 (7.1%)	1.000[a]
Asystole	1 (4.2%)	1 (3.6%)	1.000[a]
Ventricular (sustained VT greater than 30 s, VF, Torsades)	0 (0.0%)	1 (3.6%)	1.000[a]
Other type of arrhythmia	1 (4.2%)	0 (0.0%)	0.715[a]
Any culture-proven infection (no. of subjects, %)	7 (29.2%)	8 (28.6%)	1.000[a]
Blood	3 (12.5%)	2 (7.1%)	0.815[a]
Respiratory	5 (20.8%)	3 (10.7%)	0.447[a]
Urine	0 (0.0%)	4 (14.3%)	0.115[a]
Any culture-proven infection (no. of infections)	8	9	
Blood	3	2	
Respiratory	5	3	
Urine	0	4	
Days of expected daily data collection	126	142	
Any culture-proven infection (Rate/100 days 95% CI)[b]	6.4 (2.7, 12.5)	6.3 (2.9, 12.1)	1.000
Blood	2.4 (0.5, 7.0)	1.4 (0.2, 5.1)	0.671
Respiratory	4.0 (1.3, 9.3)	2.1 (0.4, 6.2)	0.487
Urine	0.6 (0.0, 2.4)	2.8 (0.8, 7.2)	0.128
All cause 28-day mortality	19 (79.2%)	26 (92.9%)	0.227[a]

[a] Fisher's exact test.
[b] Confidence intervals and p-values from exact Poisson regression.

groups. Rates of culture-prove infection per 100 days also did not differ between groups (p = 1.000). Amongst infants with culture-proven infection, the respiratory tract was the most common site of infection and *Staphylococcus aureus* was the most common organism (Supplemental material 3). The proportion of infants with hypoglycaemia documented as an adverse event during the intervention period was greater in the TH than TN group (4/24 (16.7%) vs. 0/28 (0%), p = 0.039). The proportion of infants with other adverse events was similar between groups (Supplemental material 4).

Discussion

Prior studies in term and preterm neonatal animal models have shown that cooling immediately after hypoxic-ischaemic injury is associated with reduced brain energy expenditure and improved neuropathological and functional outcomes.[25] These animal studies served as a basis for clinical trials of TH in human newborns with HIE due to birth asphyxia; these trials led to current guidelines recommending use of TH in this population.[7] We conducted this exploratory cohort analysis of infants <1 year of age with ALTE recruited to the THAPCA-OH trial because ALTE is a common cause of out-of-hospital cardiac arrest in infants. We considered that ALTE leading to cardiac arrest is most often due to respiratory causes resulting in a period of hypoxia prior to arrest, similar to infants with birth asphyxia. We also considered that infants <1 year of age might be closer to newborns in terms of brain plasticity and responsiveness to TH than older children might be. SIDS is also the most common cause of death in infants 1 to 12 month of age in developed countries thus making evaluation of potential therapies for near-miss cases important.

Findings from our study show no difference in survival with good functional outcome 12 months post-arrest between TH- and TN-treated infants with cardiac arrest due to ALTE. We also found no difference in the change in neurobehavioural function from pre-arrest to 12 months post-arrest or 12-month survival between the TH and TN groups. Although the estimated difference in 12-month survival may appear clinically important (i.e., 5/26 (19.2%) vs. 1/27 (3.7%); relative risk 5.19), clinicians must be aware that the 95% CI for the relative risk crosses 1 suggesting the possibility of harm from TH (i.e., lower limit of 95% CI 0.65) as well as benefit (upper limit of 95% CI 41.50). Mortality among infants with cardiac arrest due to ALTE was high in both treatment groups with most deaths occurring after withdrawal of life support due to poor neurologic prognosis or determination of brain death. All survivors had moderate or greater disability based on the degree of decline in VABS-II scores between baseline and 12 months post-arrest and 12-month POPC, PCPC and Mullen scores.

Many risk factors for SIDS have been described including genetic (e.g., male gender), developmental (e.g., peak age range 2–4 months) and environmental (e.g., prone positioning).[1,2] Some have suggested that risk factors for SIDS parallel those associated with susceptibility to infection and that SIDS may result from dysregulation of inflammatory responses.[26] Various toxigenic bacteria or their toxins have been identified amongst infants with SIDS.[27,28] For example, toxin producing *S. aureus* has been frequently isolated from the nasopharynx of infants with SIDS. Prone positioning can increase the temperature in the nasopharynx providing a permissive environment for the induction of staphylococcal toxins. Young infants would be most susceptible to these toxins during the period when their maternal IgG concentrations are low and before their own immune systems mature. Massive cytokine release and exaggeration of inflammation in response to bacterial toxin could contribute to poor arousal, apnoea, hypoxia and shock in young infants.[26,28] In our study, culture-proven infection occurred in almost a third of infants with ALTE in both treatment groups. Respiratory infections typically diagnosed by endotracheal tube aspirate cultures were the most common type of infection. For some infants, the identified organism was likely present in the respiratory tract prior to the cardiac arrest event, and for others, acquired during the resuscitation or later.

Blood product use was common amongst infants with cardiac arrest due to ALTE. The high proportion of infants receiving blood products may be related to the small blood volume of infants and

tendency for infants to develop anaemia with frequent laboratory blood sampling. Blood product use was less in the TH group than the TN group. This is contrary to what might be expected since TH may theoretically contribute to coagulopathy and increased bleeding.[29] Serious arrhythmias were an infrequent complication amongst infants with ALTE and did not differ between treatment groups. Hypoglycaemia occurred in a greater proportion of infants in the TH group than the TN group. Hypoglycaemia was also reported as an adverse event in trials of TH for neonates ≤6 h of age with moderate and severe hypoxic-ischaemic encephalopathy although no differences between TH and control groups were observed.[8,9,11,12] TH can decrease insulin sensitivity and insulin secretion by the pancreas resulting in hyperglycaemia[29]; hypoglycaemia can develop during rewarming as insulin sensitivity is restored. Both hypo- and hyperglycaemia have been associated with unfavourable outcome in neonates ≤6 h of age with hypoxic-ischaemic encephalopathy.[30]

Strengths of the THAPCA-OH trial include the multicentre randomised controlled trial design and 12-month neurobehavioural follow-up of surviving children. Limitations of this subgroup analysis include the small number of infants with cardiac arrest due to ALTE and thus, insufficient statistical power to detect all but very large differences between treatment groups. For example, over 900 infants would have been required for an adequately powered trial to detect a treatment difference for the primary outcome survival with VABS-II ≥70, assuming the true rates were exactly as observed in our smaller sample. Findings from this study are not generalisable to all infants with ALTE; infants recruited to the THAPCA-OH trial met specific inclusion and exclusion criteria, and were at high risk for neurologic injury. Additionally, infants for whom a decision was made to withhold aggressive intensive care during the first six hours after return of circulation were excluded. Whether a different duration of cooling, depth of cooling, or therapeutic window would affect outcomes of infants with cardiac arrest due to ALTE is also unknown.

Conclusions

Infants who are comatose after out-of-hospital cardiac arrest due to ALTE have high mortality regardless of TH or TN treatment. Functional outcome is severely reduced amongst survivors. This is the first randomised study of TH versus TN in infants with cardiac arrest due to ALTE and may inform the planning of future interventional trials for infants with this condition.

Conflict of interest statement

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Appendix A. Supplementary data

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