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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-