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Clinical paper

24 vs. 72 hours of hypothermia for pediatric cardiac arrest: A pilot, randomized controlled trial☆

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ABSTRACT

Aim: Children surviving cardiac arrest (CA) lack proven neuroprotective therapies. The role of biomarkers in assessing response to interventions is unknown. We hypothesized that 72 versus 24 h of hypothermia (HT) would produce more favorable biomarker profiles after pediatric CA.

Methods: This single center pilot randomized trial tested HT (33 ± 1 °C) for 24 vs. 72 h in 34 children with CA. Children comatose after return of circulation aged 1 week to 17 years and treated with HT by their physician were eligible. Serum was collected twice daily on days 1–4 and once on day 7. Mortality was assessed at 6 months.

Results: Patient characteristics, baseline biomarker concentrations, and adverse events were similar between groups. Eight (47%) and 4 (24%) children died in the 24 h and 72 h groups, p = .3. Serum neuron specific enolase (NSE) concentration was increased in the 24 vs. 72 h group at 84 h–96 h (median [interquartile range] 47.7 [3.9, 79.9] vs. 1.4 [0.0, 11.1] ng/ml, p = .02) and on day 7 (18.2 [3.2, 74.0] vs. 2.6 [0.0, 12.8] ng/ml, p = .047). Serum S100b was increased in the 24 h vs. 72 h group at 12 h–24 h, 36 h–84 h, and on day 7, all p < 0.05. HT duration was associated with S100b (but not NSE or MBP) concentration on day 7 in multivariate analyses.

Conclusion: Serum biomarkers show promise as theragnostic tools in pediatric CA. Our biomarker and safety data also suggest that 72 h duration after pediatric CA warrants additional exploration.

Introduction

Children with cardiac arrest (CA) have mortality rates approaching 50% for in-hospital and 80–90% for out-of-hospital events, with many survivors having neurological disability and patients lacking neuroprotective therapies [1–8]. Blood-based biomarkers including neuron specific enolase (NSE), S100b, and myelin basic protein (MBP), originating from neurons, astrocytes, and myelin, respectively, may be helpful to assist in selecting patients for therapies and as theragnostic and prognostic tools in patient care and research [9–11].

Clinical trials initially showed that hypothermia (HT) at 32–34 °C improved outcomes in adults with out-of-hospital CA (12 and 24 h

Abbreviations: HT, hypothermia; PICU, pediatric intensive care unit; RCT, randomized controlled trial; PCPCscore, Pediatric Cerebral Performance Category

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duration) and in neonates with birth asphyxia 72 h (h) of HT is standard of care [12–16]. Since the initiation of this study, the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trials in children with CA detected no superiority of 48 h of HT versus controlled normothermia [17,18] and a controlled temperature of 36 °C are not superior to 33 °C for targeted temperature management (TTM) in adults [19].

Our unit practice at the time of study initiation (prior to participating in THAPCA) was in favor of the use of HT but was unprotocolized [20]. The objective of this single center randomized pilot trial was to evaluate two HT durations for feasibility and safety. We selected durations with evidence of efficacy in other populations: adults (24 h) and neonates (72 h). We hypothesized that patients in the 72 h HT group would have more favorable brain injury blood biomarker levels compared to patients in the 24 h HT group.

Methods

Study period

This trial was conducted between November 2009 and December 2013. The University of Pittsburgh Institutional Review Board approved the RCT (NCT00797680) at the Children's Hospital of Pittsburgh.

Enrollment of patients

We enrolled 34 children between the ages 1 week and 17 years who were admitted to the ICU with return of spontaneous circulation (ROSC) after in- or out-of-hospital CA. CA was defined as receipt of chest compressions for pulselessness by a healthcare worker. Subjects were included if they had an indwelling arterial or venous catheter for blood draws, had a Glasgow Coma Scale score ≤ 8 after ROSC, and had HT initiated by their ICU attending. Subjects were excluded if they had a do not resuscitate status, were pregnant, had any contraindication for MRI, had another simultaneous acute brain disease (including traumatic brain injury), were undergoing brain death evaluation, had a metabolic disease affecting the brain, or had active hemorrhage or a pre-existing coagulation defect. Children enrolled in this study who had a clinical brain MRI also had brain MR Spectroscopy performed; imaging results will be reported separately. Enrollment in this study began one year prior to THAPCA. Once THAPCA was approved at our center, we prioritized enrollment in THAPCA. Children that did not qualify for THAPCA were then evaluated for inclusion in this study.

Consent, randomization, and intervention

Informed consent was obtained from the subject's parent or guardian by the primary investigator or qualified co-author. Subjects were assigned a group through stratified block randomization, with CA location (in vs. out of hospital) as strata given differences in outcomes for pediatric CA, using computer assignment. Randomization schedule was generated by a statistician's software program and stored in sealed envelopes. Since HT was initiated for clinical reasons the intervention was already started prior to the consent process.

Temperature control

All subjects had continuous temperature monitoring in two anatomical locations (esophageal, rectal, bladder catheter, and/or extracorporeal circuit probes). All patients were treated using a cooling blanket. Other measures of temperature control were applied as needed including cold saline infusion, cold packs, room temperature regulation, and tepid bath. HT was maintained at 33 ± 1 °C for either 24 or 72 h based on assignment. Once the goal treatment duration was achieved, patients were rewarmed by 0.5 °C every 4 h to normothermia (37 °C) [21].

Patient care

We previously described post-resuscitation care in our PICU including prevention of secondary neurologic insults, treatment of organ dysfunction, and investigation of cause of CA if unknown [22,23]. Subjects in both groups received similar care except for the study intervention.

Data collection

We collected data collected from medical charts using the Utstein template for CA, including subject demographics, details about the CA and resuscitation, post-resuscitation care and treatment, and adverse events [24].

Serum biomarkers

Three milliliters of blood were collected twice daily (days 1–4) and once on day 7 after ROSC. Samples were centrifuged, aliquoted, frozen at −70 °C, and analyzed in batches. Serum NSE, S100b, and MBP were measured in duplicate using commercially available ELISAs (International Point of Care, Toronto, Ontario, Canada). NSE concentration was corrected for hemolysis [25]. The sensitivity of the assays was 0.1 ng/mL for NSE and MBP and 0.01 ng/mL for S100b. The coefficient of variation for each assay was < 10%. An experienced technician blinded to subject treatment and outcomes performed all biomarker measurements. Clinical team members were unaware of the biomarker results. Samples were assessed in 12 h blocks from ROSC due to time-dependent changes in biomarkers and one time at 7 days for all analyses. No sample time points were missed from living subjects but not all survived to day 7. Higher serum concentrations of the biomarkers studied here are associated with injury and potential for worse outcome{Berger, 2005 #4703}{Fink, 2014 #8299}.

Follow-up evaluations

The PI assigned the pre-arrest, hospital discharge, and 6 month Pediatric Cerebral Performance Category (PCPC) scores, and was blinded to biomarker results but not to clinical course. Six month outcomes were performed in surviving children either over the telephone (almost always) or during in-person interview with the parent or guardian during a scheduled outpatient visit.

Outcome measures

The primary outcome was serum biomarker concentrations on day 7 (post-rewarming) by randomized group. Secondary outcomes included unfavorable outcome and mortality at 6 months post-CA. Unfavorable outcome was defined as PCPC score 4, 5, or 6 or increase > 1. Adverse events were assessed through the PICU stay or 28 days, whichever was shortest.

Sample size

Our sample size was derived to detect significant differences between our two treatment groups and was driven by the variable serum NSE. We choose to have an equal number of subjects in each group. Based on Tiainen, et al, we assume that the range of standard deviation is 2.0-4.0 μg/mL{Tiainen, 2003 #4254}. We assumed that the concentration of serum NSE in 72 h HT group would have the same standard deviation as that in 24 h HT group. In the following sample size calculations, the type I error rate is set as 0.05 and power = 80%.

Twenty subjects were targeted for recruitment for each treatment group. Power calculations were based on 18 subjects per treatment group after accounting for an anticipated 10–15% attrition rate. Type I error rate is 0.05. The study was designed to have 80% power to detect