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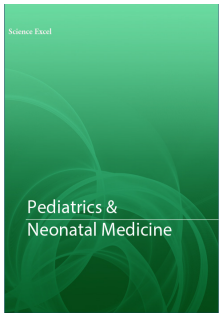
Original Article



A Pilot Randomized Control Trial of Safety and Feasibility of a Delayed Rewarming Intervention for Infants Following Cardiopulmonary Bypass Surgery

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Abstract

Objective: Investigate safety and feasibility of a 12-hour delayed rewarming intervention on infants following congenital heart disease (CHD) surgery.

Study Design: Pilot randomized control trial of infants <6 months old with CHD undergoing cardiopulmonary bypass surgery. Infants were randomized 1:1 to standard of care (SOC) or to delayed rewarming intervention, accomplished by using a commercially available temperature regulating blanket set to gradually rewarm from 35°C to 36.5°C in the 12-hours following surgery. Safety was assessed by comparing the frequency of severe adverse events (SAE) for 48 hours after surgery. Feasibility was assessed by analysis of temperature data.

Results: Twelve infants were randomized to SOC and 10 to the intervention group. Eight infants (36%) were female, 6 (27%) had Trisomy 21 and 7 (32%) had surgery in the first two weeks of life. Two SOC and one intervention infant had at least one SAE (p=0.57). Feasibility of the delayed rewarming intervention was demonstrated by a statistically significant difference in temperature over time between groups (p<0.001). Heart rates for infants in the intervention group were slower during and after the intervention, without significant changes in blood pressure. Infants in the intervention group had no evidence of coagulopathy with lower, but not statistically significantly lower, chest tube output at all-time points.

Conclusions: There were no differences in the number of SAEs for the delayed rewarming group and the temperature curve indicates that the intervention is feasible. The results of this small study, from a single, small volume center must be interpreted cautiously. (NCT03036072).

Introduction

Congenital heart disease (CHD) is the most frequently occurring birth defect in the United States affecting up to 40,000 infants each year. Despite significant advances in post-surgical survival, developmental outcomes remain suboptimal [1] with lower than expected intelligence quotients, hypotonia, microcephaly, language delay, and less independence in daily activities compared to age-matched peers [2-4]. In an effort to provide neuroprotection during cardiac surgery, intraoperative hypothermia has been in use since the 1950s [5]. Infants are typically cooled during cardiac surgery and then rapidly rewarmed upon completion of surgery at a rate of 1°C every 3-5 minutes to minimize risks associated with prolonged cardiopulmonary bypass (CPB). However, emerging evidence from animal models has shown that such rapid temperature changes following surgery may diminish or even negate the neuroprotective effect of intraoperative hypothermia [6,7]. Retrospective studies demonstrate that as many as 70% of infants experience fever after CHD surgery [8-10] yet few studies have investigated the effect of rapid rewarming or fever on the brain, which may be 0.5-1.0°C higher than the body [11].

One prospective study of children in India after Tetralogy of Fallot surgery demonstrated improved cognitive function on post-operative day five for those who rewarmed off bypass in a delayed manner as opposed to controls [12]. This study on children has not been replicated nor has a similar trial of safety or feasibility of "delayed rewarming" been performed in infants, who in Western countries are the age group typically undergoing CHD surgery. We therefore conducted a pilot clinical trial

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employing a delayed rewarming intervention, using an FDA-approved temperature regulating blanket, to slowly rewarm infants over 12-hours following CHD surgery. We aimed to assess safety of the intervention by comparing the frequency of severe adverse events (SAE) and feasibility by analyzing the temperature curve of the intervention group and comparing to the standard of care group.

Methods

Trial design

This was a pilot randomized control trial of infants with CHD randomly assigned 1:1 to either a delayed rewarming intervention or to standard of care.

Inclusion/Exclusion criteria

Infants under the age of 6 months with all types of CHD requiring CPB surgery and intraoperative hypothermia were recruited. Infants with known or suspected genetic syndromes were considered eligible. Exclusion criteria were suspicion of underlying coagulopathy (such as hemophilia) or metabolic disease such as an inborn error of metabolism. Infants who were recruited and randomized, but who died during surgery or remained on ECMO following surgery were excluded.

Setting

Maine Medical Center Pediatric Intensive Care Unit

Severe adverse events

A priori, SAEs were defined as occurring within 48 hours of completion of surgery and included death, need for cardiopulmonary resuscitation (CPR), need for extracorporeal membranous oxygenation (ECMO), return to the operating room (OR) for exploratory surgery, or adverse neurological outcome such as stroke or seizure. Stroke was defined as the sudden onset of a focal neurological disturbance such hemi-facial, arm or leg weakness or paralysis, or forced gaze deviation. Seizure activity was clinically defined by clinical features including rhythmic eye movements, facial twitching or jerking of one or more extremities that was not suppressible by external pressure and potentially associated with oxygen desaturation. All infants had electroencephalogram (EEG) following surgery to monitor for clinically silent seizure activity. SAE's were monitored for in real-time by the research team and reported to the data safety monitoring board (DSMB) within 24 hours of occurrence. The DSMB convened each time three infants were enrolled to assess safety of the intervention and monitor the overall conduct of the study.

Feasibility

Prior to the start of the project, we defined feasibility as the temperature regulating blanket performing according to the expectation of gradually rewarming infants from 35°C to 36.5°C during the 12-hours following CHD surgery. Temperature was monitored in real-time for individual patients, but evaluated by group for the feasibility outcome.

Treatment assignment

After informed consent was obtained, infants were randomly assigned 1:1 to the standard of care or the intervention group using a random number generator. The principal investigator assigned treatment at the time of randomization by opening sequentially numbered opaque envelopes in order that were generated by a statistician who was not part of the research team. Groups were not stratified by clinical or demographic factors.

Standard of care

For infants assigned to standard of care, cardiac surgery was performed according to usual practice with the degree of intra-operative hypothermia determined by the cardiothoracic surgeon and his team based on the anticipated complexity of the case. Following completion of the surgical procedure, the infant was rewarmed on CPB at a rate of 1°C every 3-5 minutes per institutional protocol. The infants achieved normothermia of 36-37°C and were transported from the OR to the Pediatric Intensive Care Unit (PICU) for routine post-operative care.

Intervention

For infants assigned to the intervention group, rewarming occurred on CPB, but stopped when the infant reached 35°C. The temperature was maintained at 35°C by carefully regulating the ambient temperature in the OR, by intermittent use of the Bair Hugger™ warming system at 38°C (not 43°C as is routine) and transfusing room temperature rather than warm packed red blood cells, fresh frozen plasma and/or cryoprecipitate. Upon completion of surgery, the infant was transported from the OR to the PICU at 35°C and placed on the Cincinnati Sub-Zero Kool-Kit® Neonate blanket (Cincinnati, OH, USA), which controlled the infant's temperature according to input from an esophageal temperature probe connected to the Cincinnati Sub-Zero Blanketrol® III system. The infants were incrementally rewarmed every two hours by 0.3°C for six hours and then by 0.2°C every two hours for six hours to the goal temperature of 36.5°C. Infants in the intervention group remained on the temperature regulating blanket set at 36.5°C for an additional 12 hours.

Data extraction

A research coordinator retrospectively collected clinical and demographic information from the electronic medical record. Vital signs including temperature, highest and lowest heart rate, highest and lowest systolic blood pressure and highest and lowest diastolic blood pressure were collected hourly for the first 12 hours after surgery and then within six hour intervals for the subsequent 36 hours. Chest tube output was recorded in cc/kg per eight hour interval for 48 hours after surgery. Type of vasopressor and number of hours of exposure was also recorded.

Statistical analysis

The goal was to recruit a sample size of 12 in each group which is considered acceptable for a trial in which there is no prior information on effect size upon which to base a power calculation [13]. Data was evaluated using an intention to treat analysis. Descriptive statistics were used to describe clinical and demographic characteristics for the intervention versus standard of care groups. The comparison of the number of infants with SAEs was performed using a Fisher's Exact test. The temperature data from the first 12 hours following surgery was graphed and then analyzed using a linear mixed effect model to test for between group differences over time. The other vital sign data for high and low heart rate, high and low systolic blood pressure and high and low diastolic pressure was graphically presented. All statistical analyses were performed using R statistical software (Version 3.5.1). This study was approved by the Maine Medical Center Institutional Review Board and full written informed consent was obtained from the parents of all participating subjects.

Results

From April 2016 to June 2017, parents of 30 eligible infants were approached for consent and 25 (83%) agreed to participate (Figure 1). One consented infant was randomized to the intervention group, but data was not collected as he was transferred prior to surgery to a different institution. Twelve of the remaining 24 infants were randomized to the standard of care group and twelve to the intervention group. Two infants in the intervention group were subsequently excluded due to one death in the OR and one remaining on ECMO following surgery. Nearly one third of the participants were female, the majority were Caucasian and about one-quarter had a diagnosis of Trisomy 21 (Table 1). The mean age of surgery for all infants was between 2-3 months with about one third having surgery in the first two weeks of life.

Severe adverse events

Two standard of care infants and one intervention infant had at least one SAE (p=0.57) (Table 2-supplemental). One infant in the standard of care group had a cardiac arrhythmia from hyperkalemia related to hemothorax and required CPR in the 48-hour period following surgery and returned to the OR for clot evacuation. Another standard of care infant also returned to the OR for clot evacuation as did an infant from the intervention group due to an unintentional internal mammary artery perforation by a sternal wire. The delayed rewarming intervention was terminated early for this infant at three hours after surgery due to concerns that the lower than normal temperature may have been contributing to the bleeding. No infants had clinical signs of stroke. On EEG, there was no seizure activity for any infant.

Temperature

Infants in the intervention group had a mean temperature on arrival to the PICU of 35.0°C (± 0.81°C) and gradually warmed to a mean of 36.4°C (± 0.77 °C) by 12 hours (Figure 2). Analysis of the first 12 hours using a linear mixed effects model revealed a highly significant time by group interaction with those infants in the intervention group (group 2) experiencing a 0.14°C increase in temperature per hour compared to the standard of care group (group 1) (p<0.001).

Cardiovascular system

Moderate hypothermia has a known association with bradycardia and infants were monitored for this as a potential adverse outcome related to the delayed rewarming intervention. Within each time interval, both a high and a low heart rate was recorded. With respect to the *high heart rates*, the means of infants in the intervention group were slower at all-time points compared to the standard of care group, even after they were normothermic (Figure 3A). The differences between groups for *low heart rate* were not as dramatic, but heart rates were slower in the intervention group for the first 5 hours after surgery (Figure 3B).

Both high and low systolic and high and low diastolic blood pressures were monitored to determine if the intervention group experienced hypo- or hypertension compared to the standard of care group. Infants in the intervention group had slightly higher systolic and diastolic pressures in the first 3 hours after arrival in the PICU, but seem to have lower systolic and diastolic pressures until 12-18 hours after surgery when they were again higher than the standard of care group (Figures 3C-3F). Infants in the intervention group had shorter duration of exposure to vasopressors including milrinone and dopamine compared to standard of care although this was also not statistically significant (Table 3-supplemental).

Coagulation function

Chest tube output was monitored as a proxy for excessive bleeding, considered a risk in patients with lower than normal temperatures. Across all time points, infants in the intervention group had lower (but not statistically significant), mean chest tube output compared to infants in the standard of care group (Figure 4-supplemental). There were no differences between groups for other markers of coagulation function including platelet level, PTT, INR or Fibrinogen (Table 3-supplemental).

Infection

White blood cell count (WBC) was monitored as a proxy for the ability to fight infection as this can be diminished in hypothermic patients. There was no statistically significant difference between groups in either the highest or lowest WBC (Table 3- supplemental).

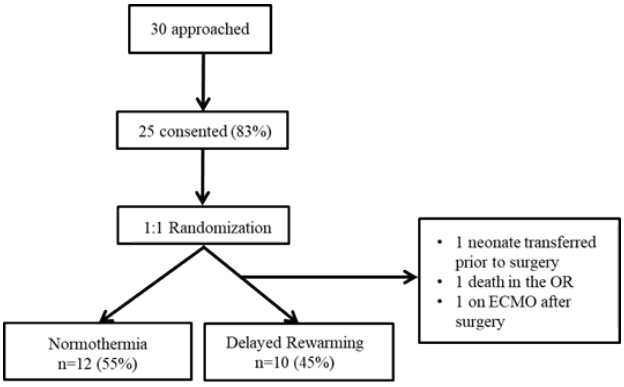
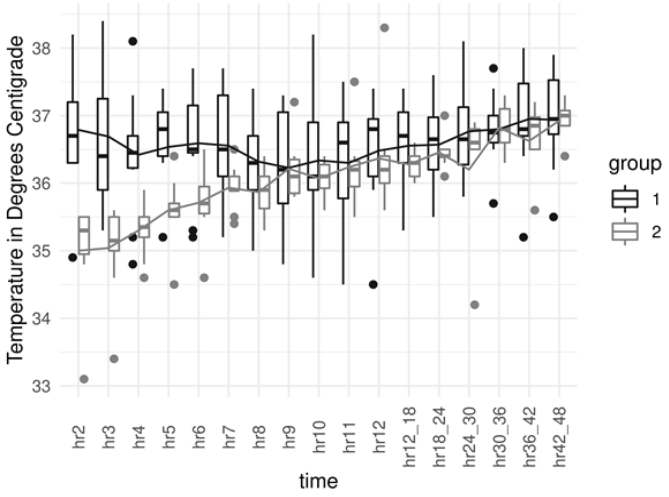


Figure 1. *Consort Diagram*



*Group 1 (black) is standard of care and Group 2 (grey) is delayed rewarming

Figure 2. *Mean Temperature over Time*

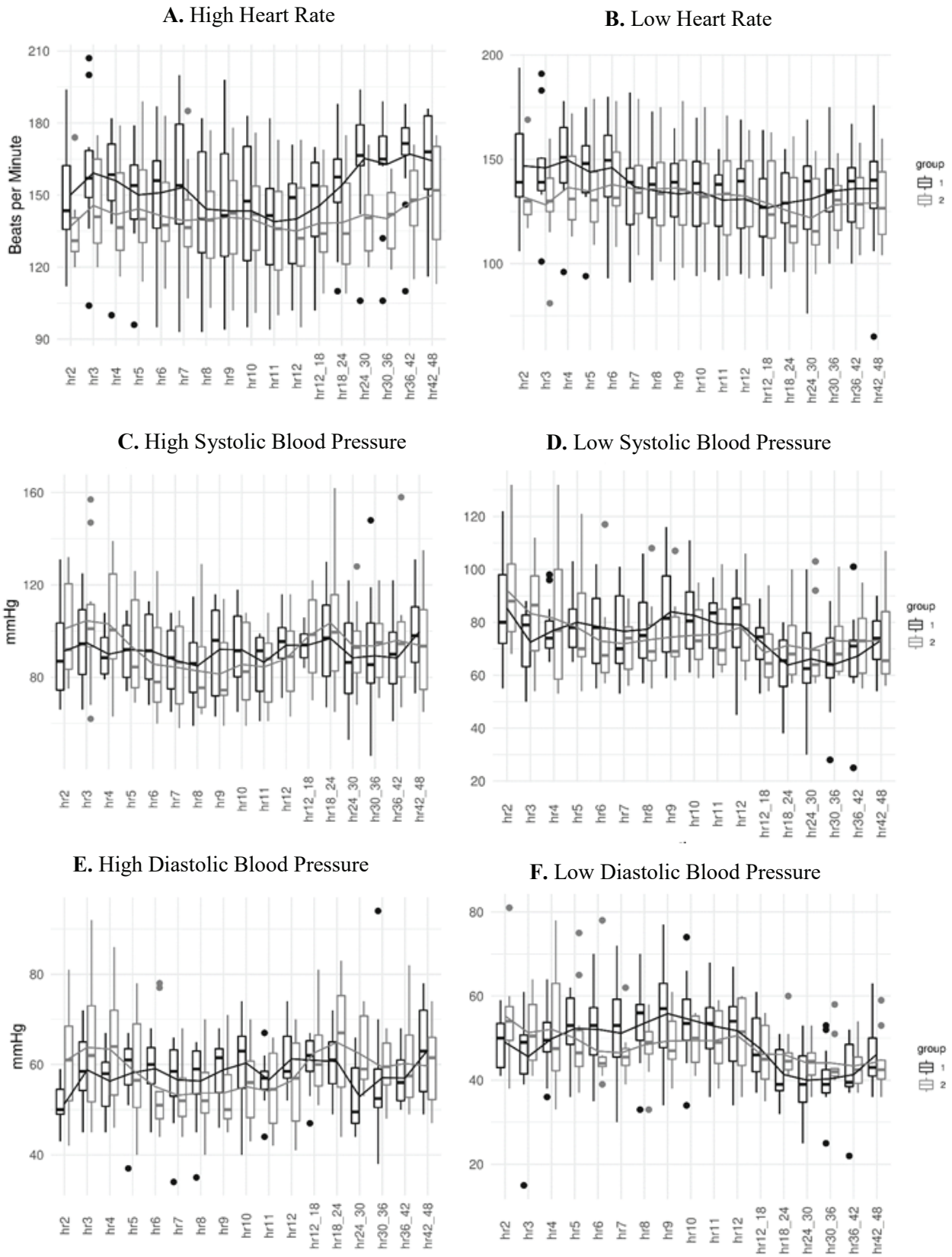


Figure 3. *High and low heart rate, high and low systolic and high and low diastolic blood pressure by group.*

Table 1. *Demographic and clinical characteristics of the cohort*

Characteristic		Standard of Care, n=12	Intervention, n=10	p-value
Cardiac Lesion	Tetralogy of Fallot	4 (33%)	3 (30%)	1.0
	AV Canal	2 (17%)	2 (20%)	1.0
	VSD	3 (25%)	2 (20%)	1.0
	Hypoplastic left	1 (8.3%)	1 (10%)	1.0
	Transposition	1 (8.3%)	2 (20%)	0.86
	Tricuspid atresia	1 (8.3%)	0	0.97
Female sex, n, (%)		4 (33%)	4 (40%)	1.0
White race, n, (%)		10 (83%)	8 (80%)	1.0
Trisomy 21, n, (%)		4 (33%)	2 (20%)	0.83
Age at surgery, in days		68	91	0.39
Age ≤ 14 days at time of surgery, n, (%)		4 (33%)	3 (30%)	1.0
Weight at surgery, kg		4.6 (1.4)	4.8 (1.3)	0.76
Bypass time, min		139 (48)	144 (50)	0.81
Cross clamp time, min		81 (42)	78 (51)	0.89
Lowest intraoperative temperature (°C)		28 (6.0)	28 (5.3)	0.98
Length of intubation, days		2.9 (2.0)	2.2 (1.0)	0.30

Abbreviations; Atrioventricular canal defect (AV canal); ventricular septal defect (VSD); Standard deviation (SD); kilogram (kg); Degrees Centigrade (°C)

EEG

Nineteen infants had EEG placed in the first 4-8 hours after arrival in the PICU. EEG continued for 48 hours unless they returned to the OR. There were no clinical or electrographic (visible only on EEG) seizures for infants in either group.

Discussion

This pilot study aimed to assess safety and feasibility of a delayed rewarming intervention following CHD surgery. To our knowledge, this is the first study to prospectively assess a device regulated temperature management intervention in infants with CHD in the immediate post-operative setting. We demonstrate that the temperature regulating device can achieve the goal of delaying the rewarming rate of infants without an increasing the frequency of severe adverse events. We acknowledge that our results must be interpreted carefully as we are a small volume center and this was a small pilot trial. We are hopeful that this data may be used to inform the design of a future more definitive and adequately powered clinical trial that would assess the impact of the delayed rewarming intervention on neurodevelopmental outcomes.

Several potential complications associated with mild hypothermia were carefully monitored and these included heart rate abnormalities, hypotension, coagulation dysfunction, and infection. As anticipated, infants in the intervention group had lower heart rates at each of the time intervals in the hours during which they were mildly hypothermic. Unexpectedly, the highest heart rates of these infants remained lower than the standard of care infants for the subsequent 36 hours after they were normothermic, a period of time when some mechanism other than temperature must have had this effect. This finding raises the possibility of a potential cardioprotective effect from this temperature management strategy, however this would need to be replicated in a substantially larger sample with other measures of cardiac function. It is of particular interest that while heart rates were slower in the intervention group, there was no evidence for a pattern that suggests a compensatory increase in either systolic or diastolic blood pressure. For infants in the intervention group, the vital sign differences may suggest that the delayed rewarming strategy is associated with overall improved hemodynamic stability. One additional argument for this is the fact that chest tube output, collected as a proxy for potential increased bleeding as a complication of the delayed rewarming intervention, demonstrated lower output at every time point for those infants who were in the intervention group. A larger study with less heterogeneity of CHD types and with more detailed evaluation of cardiac parameters including arrhythmias, pacing and echocardiography results would be required to assess this question more definitively.

While conducting this study at a single, low volume congenital heart surgery center allowed the research team to work closely with a small group of providers who were engaged with the project and who maintained a high-level of fidelity with the study intervention, there is the potential for the results not to be generalizable to medium and high-volume centers. Other study limitations include the fact that clinicians could not be blinded to the study intervention, which could introduce bias. The randomization scheme was implemented prior to surgery and unfortunately, there were three neonates, all from the delayed rewarming group who were excluded from analysis due to transfer, death or ECMO. This could also have introduced bias. A significant limitation of the study was the lack of neurodevelopmental endpoints. At the onset of the study, our goal was to measure s100b and neuron specific enolase, both serum biomarkers of brain injury, as proxies for a neurodevelopmental endpoint. We had hoped to compare levels over time; pre-operative, immediately post-operative and for up to the three days after surgery using blood samples that were scavenged from blood already drawn for other clinical testing (e.g. basic or comprehensive metabolic panel). This methodology was not effective for two reasons; first, no serum was available if a clinical test was not ordered and second, often there was insufficient residual serum left over for research testing. It remains unclear how well these results would have correlated with neurodevelopmental outcomes which would have been confounded not only by the presence of Trisomy 21, but also by the number of surgical procedures as some subjects required multiple surgical interventions and multiple anesthetic exposures, which has also been shown to impact neurodevelopmental outcome in this vulnerable population.

Conclusion

This small study is promising with regard to safety and feasibility of the delayed rewarming intervention in infants undergoing congenital heart surgery before age of 6 months. Additionally, heart rate and chest tube output in the intervention group was lower suggesting beneficial effects from the temperature management strategy. This study was not designed or powered to definitively assess the neurodevelopmental ramifications of the intervention. A larger study of the delayed rewarming intervention trialed on infants at multiple centers with a more homogeneous population would be required to determine if there is any neurodevelopmental impact of delayed rewarming and/or avoidance of fever in the post-operative period. Developmental testing performed 12-24 months following surgery should be considered as a possible primary outcome for this study with interim measures of pre and post-surgery magnetic resonance imaging of the brain and electroencephalogram recorded in the 48 hours following surgery.

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Conflicts of Interest Statement

The authors have no conflicts of interest relevant to this article to disclose.

Clinical trials registry

NCT03036072

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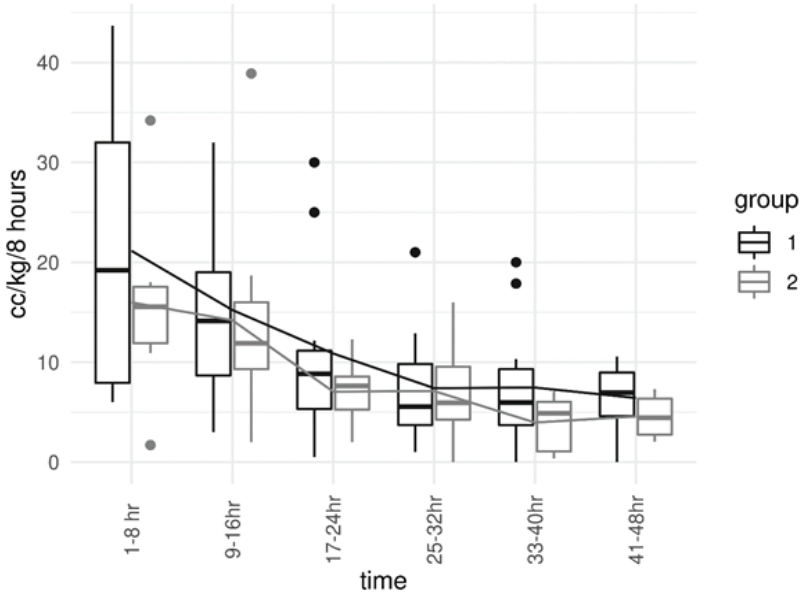
Supplementary Data



*Group 1 (black) is standard of care and Group 2 (grey) is delayed rewarming

Figure 4-Supplemental. *Chest tube output by group*

Table 2-Supplemental. *Severe adverse events by group*

	Standard of Care n=12	**Intervention n=10**	**p-value**
Number of infants with at least one severe adverse event, n, (%)	2 (16%)	1 (8%)	0.57
Death within 48 hours, n, (%)	0	0	n/a
ECMO after surgery, n, (%)	0	0	n/a
CPR after surgery, n, (%)	1 (8%)	0	1.0
Return to OR, n, (%)	2 (16%)	1 (8%)	0.57
Stroke or Seizure, n, (%)	0	0	n/a

Abbreviations; Extracorporeal membranous oxygenation (ECMO); cardiopulmonary resuscitation (CPR); operating room (OR), Not applicable (n/a)

Table 3-Supplemental. *Coagulation, infectious and metabolic variables by group*

Characteristic	**Standard of Care n=12**	**Intervention n=10**	**p-value**
Milrinone exposure, hours	63 (19)	56 (23)	0.47
Dopamine exposure, hours	53 (30)	34 (34)	0.18
Lowest platelet level	90 (29)	110 (63)	0.33
Highest PTT level	57 (46)	58 (37)	0.98
Highest INR	1.4 (0.3)	2.3 (2.6)	0.26
Highest fibrinogen	250 (36)	271 (58)	0.31
Lowest hematocrit	37 (11)	35 (7)	0.66
Highest hematocrit	44 (10)	44 (7)	0.89
Lowest WBC	9.1 (2.6)	8.9 (1.5)	0.86
Lowest glucose	105 (21)	109 (63)	0.61

* Excluded those who died in operating room and those who remained on extracorporeal membranous oxygenation (ECMO)
Standard deviation (SD); Prothrombin time (PTT); International normalized ratio (INR); white blood count (WBC)