Temperature Management and Health-Related Quality of Life in Children 3 Years After Cardiac Arrest

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OBJECTIVES: Therapeutic hypothermia minimizes neuronal injury in animal models of hypoxic-ischemic encephalopathy with greater effect when used sooner after the insult. Clinical trials generally showed limited benefit but are difficult to perform in a timely manner. In this clinical study, we evaluated the association between the use of hypothermia (or not) and health-related quality of life among survivors of pediatric cardiac arrest as well as overall mortality.

DESIGN: Single-center, retrospectively identified cohort with prospective assessment of health-related quality of life.

SETTING: PICU of a pediatric hospital.

PATIENTS: Children with either out-of-hospital or in-hospital cardiac arrest from January 2012 to December 2017.

INTERVENTIONS: Patients were assigned into two groups: those who received therapeutic hypothermia at less than or equal to 35°C and those who did not receive therapeutic hypothermia but who had normothermia targeted (36–36.5°C). The primary outcome was health-related quality of life assessment and the secondary outcome was PICU mortality.

MEASUREMENTS AND MAIN RESULTS: We studied 239 children, 112 (47%) in the therapeutic hypothermia group. The median (interquartile range) of lowest temperature reached in the 48 hours post cardiac arrest in the therapeutic hypothermia group was 33°C (32.6–33.6°C) compared with 35.4°C (34.7–36.2°C) in the no therapeutic hypothermia group ($p < 0.001$). At follow-up, 152 (64%) were alive and health-related quality of life assessments were completed in 128. Use of therapeutic hypothermia was associated with higher lactate and lower pH at baseline. After regression adjustment, therapeutic hypothermia (as opposed to no therapeutic hypothermia) was associated with higher physical (mean difference, 15.8; 95% CI, 3.5–27.9) and psychosocial scores (13.6 [5.8–21.5]). These observations remained even when patients with a temperature greater than 37.5°C were excluded. We failed to find an association between therapeutic hypothermia and lower mortality.

CONCLUSIONS: Out-of-hospital or in-hospital cardiac arrest treated with therapeutic hypothermia was associated with higher health-related quality of life scores despite having association with higher lactate and lower pH after resuscitation. We failed to identify an association between use of therapeutic hypothermia and lower mortality.

KEY WORDS: cardiac arrest; children; hypothermia; quality of life

Cardiac arrest is a major public health problem with substantial burden on children and their families. While survival following pediatric out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) is improving (1–3), it is also known that survivors experience considerable long-term neurologic impairment (4–7).

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RESEARCH IN CONTEXT

- Clinical trials of hypothermia in children after cardiac arrest have showed limited benefit due to the difficulties of optimal implementation of hypothermia as is done in “animal” studies that show benefit.
- In adult clinical studies after OHCA (TTM & TTM2 trials), targeted hypothermia at 33°C compared with targeted normothermia of either 36°C or 37.5°C or less respectively did not confer benefit.
- This observational study of children who suffered either an out-of-hospital or IHCA showed that very early use of TH was associated with higher HRQoL scores at long-term follow-up.

The effect of targeted temperature management (TTM) after cardiac arrest has been studied in both adult and pediatric populations. The TTM and TTM2 trials showed no benefit targeting a temperature of 33°C (hypothermia) compared with a targeted normothermia (temperature of 36°C in TTM and 37.5°C or less in TTM2) in adults after OHCA (8, 9). The Therapeutic Hypothermia After Pediatric Cardiac Arrest (THAPCA) trials (10, 11) similarly found no difference in survival with a favorable functional outcome between those cooled (32–34°C) and those maintained at normothermia (36–37.5°C). Despite this, there still remains uncertainty about the effect of hypothermia or specific temperature goals (12). Hypothermia, also, in order to be beneficial needs to be achieved very soon after return of spontaneous circulation (ROSC) following cardiac arrest (13, 14). However, none of the recent clinical trials have achieved this.

Health-related quality of life (HRQoL) (15) is an important outcome measure for pediatric patients affected by critical illness (16). HRQoL tools in the pediatric population such as Pediatric Quality of Life (PedsQL) have been validated and widely used (17, 18). However, there are limited studies assessing HRQoL post pediatric cardiac arrest (19). Our aim in this study was to determine, primarily, whether therapeutic hypothermia (TH) following pediatric cardiac arrest is associated with better long-term HRQoL and, secondarily, association with PICU mortality.

MATERIALS AND METHODS

Ethics approval was obtained from our institution's Human Research Ethics Committee (number 38055A). The study setting was a quaternary PICU with approximately 1,800 admissions per year in Victoria, Australia.

Study Population

We searched our database for all pediatric patients (up to 18 yr old) treated in the PICU after suffering a cardiac arrest between January 2012 and December 2017. This includes neonates, infants, and children who either experienced OHCA transferred directly to our PICU or IHCA. Inclusion criteria were requirement for chest compressions for at least 2 minutes, achievement of ROSC or established on extracorporeal membrane oxygenation (ECMO), and requirement for mechanical ventilation after the event. There were no exclusion criteria. At our institution, every patient is assumed to be eligible for ECMO after approximately 5 minutes of in-hospital cardiopulmonary resuscitation (CPR) with extracorporeal CPR (ECPR), unless there was a predetermined reason for not offering ECMO (e.g., limited or nonexistent surgical options, poor neurology, or overall very poor prognosis). Patients who sustain OHCA will occasionally receive ECPR at admission if they were deemed to have received early high-quality CPR from a witnessed arrest. For patients who died, decisions regarding withdrawal of life support are taken as a physician group and include a shared understanding of parent’s views and expectations of their child’s future quality of life.

Study Design

The study consisted of a retrospective collection of information with prospective assessment of HRQoL scores. We included data on comorbidities, preexisting neurologic condition, location of arrest, initial rhythm, CPR duration, initial lactate and pH after return of ROSC or ECPR, duration of mechanical ventilation, and temperature management. The temperature parameters recorded were target temperature, minimum and maximum temperature achieved in the first 48 hours, duration of TH, and duration of rewarming. TH is generally instituted in our PICU at a range of 33–34°C. The decision to initiate TH depends on the patient's clinical circumstances and often the treating team's preference, and in many instances, CPR duration was taken into consideration (e.g., > 5 min).

Measurement of HRQoL

For HRQoL assessments, we studied survivors residing in Australia. The PedsQL 4.0 generic core scales available through our institutions license were used to ascertain the HRQoL. This measurement tool takes into account the condition of the child over the last 30 days. The PedsQL 4.0 consists of 23 items: eight physical parameters and 15 psychosocial (emotional, social, and schooling parameters, each containing five items). The summary scores are transformed to a 0–100 scale with a higher score corresponding to a better HRQoL. Population norms for healthy Australian children have been reported (20). Measurements were obtained by a trained research assistant by inviting parents of children over telephone to participate. If the patient's parents could not be contacted after three phone calls, the patient was deemed lost to follow-up. HRQoL assessments were performed between January 12, 2019, and July 29, 2019. Only one experienced assessor was used and the assessor was blinded to the patient's post arrest temperature management.

Statistical Analysis

Our primary aim was to examine the relationship between use of TH and long-term HRQoL in children who survived cardiac arrest. The mean difference (MD) (95% CI) for TH versus No-TH for each of the three HRQoL measures were estimated by separate linear regression models with regression adjustment. "Regression adjustment estimators" used a two-step process to estimate the MD: 1) they fit linear regression models of the outcome on a predefined set of covariates for each of the treatment level (TH and No-TH) separately and 2) then compute the average of the predicted outcomes for each subject and each treatment level. The differences of these averages provide the MD for each of the three HRQoL outcome measures (physical, psychosocial, and total score). The MD can be interpreted as the change in mean HRQoL for children who did versus did not receive TH, conditional on included covariates. The regression model included the following covariates: IHCA versus OHCA, age in months (divided equally into four groups), CPR duration (min), lactate post ROSC (log-transformed), preexisting comorbidity, preexisting neurologic condition, duration of mechanical ventilation (log-transformed), requirement for ECPR, and time to HRQoL assessment (mo) from date of arrest. Finally, in order to assess whether TH versus No-TH varied in children who had ECPR, an interaction term was assessed. The interaction terms were used in a multivariable linear regression model for the outcome, which also adjusted for all the other study covariates.

The HRQoL scores for children in the TH and No-TH groups were also compared with published normative (20) HRQoL for Australian children.

Our secondary aim examined the association between TH and PICU mortality. This was evaluated using multivariable logistic regression analysis adjusted for the above-mentioned covariates except time to HRQoL assessment. The model utilized a backward elimination process removing variables with a p value of less than 0.15 while retaining the primary variable of interest (TH vs no-TH) and IHCA versus OHCA in the final model. Goodness of fit of the final model was assessed using the Hosmer-Lemeshow statistic and overall fit was assessed using the Brier score. Analysis was performed using STATA-IC (Version 16; Stata Corp, College Station, TX).

RESULTS

Patient Characteristics

During the 6-year period, 257 children were treated in the PICU following a cardiac arrest. Of these, 239 achieved ROSC and were included (**Appendix Table 1**, http://links.lww.com/PCC/B864, for characteristics of this cohort). After excluding those who died (76 in PICU and 11 post discharge), 152 were available for long-term HRQoL follow-up (**Appendix Fig. 1**, http://links.lww.com/PCC/B864).

The assessments were completed in 128 out of these 152 children at a median time of 3.8 years following arrest. The characteristics of the two study groups (TH and No-TH) who had HRQoL measurements are shown in **Table 1**. Children in the TH group were younger, had longer duration of CPR, had higher post resuscitation lactate, lower post resuscitation pH, and were more likely to be supported with ECMO (72% vs 22%).

Temperature Management

Median target temperature achieved in the TH group was 33°C. Median (interquartile range [IQR]) time to reach this temperature was 0 minutes (0–79 min). TH was continued for a median (IQR) duration of 51 hours (26–69 hr) and the duration of rewarming was a median of 12 hours (IQR, 7–17 hr). ECMO was used as a method of cooling in 72% of TH cases (36/50). When specified, a target temperature of 36°C was most common in the No-TH group, but our retrospective data did not allow us to determine with confidence the intended duration of temperature control in this group.

TABLE 1.
Clinical Characteristics of Children Who Survived ICU Discharge and on Whom the Primary Outcome (Health-Related Quality of Life) Assessments Were Made (*n* = 128)

Characteristic	Overall (*n* = 128)	Therapeutic Hypothermia (*n* = 50)	No Therapeutic Hypothermia (*n* = 78)	*p*
Age at arrest, mo	8.8 (0.9–65.4)	3.3 (0.7–61)	14 (1.5–93.4)	0.15
Female	62 (48)	23 (46)	39 (50)	0.66
Out-of-hospital arrest	35 (27)	12 (24)	23 (29)	0.50
In-hospital arrest	93 (73)	38 (76)	55 (71)	
Preexisting health condition				0.51
Cardiac	58 (45)	23 (46)	35 (45)	
Respiratory including airway	10 (8)	3 (6)	7 (9)	
Gastro intestinal/endocrine/metabolic	4 (3)	2 (4)	2 (3)	
CNS	9 (7)	1 (2)	8 (10)	
Genetic/syndrome	9 (7)	5 (10)	4 (5)	
Others	2 (2)	0	2 (2)	
None	36 (28)	16 (32)	20 (26)	
Preexisting comorbidity	92 (72)	34 (68)	58 (74)	0.43
Preexisting neurologic condition	14 (11)	3 (6)	11 (14)	0.15
Initial rhythm				0.01
Asystole	7 (6)	4 (8)	3 (4)	
Pulseless electrical activity	34 (27)	11 (22)	23 (30)	
Ventricular fibrillation or ventricular tachycardia	21 (17)	13 (26)	8 (11)	
Sinus bradycardia	43 (34)	19 (39)	24 (32)	
Sinus rhythm	20 (16)	2 (4)	18 (24)	
Duration of cardiopulmonary resuscitation, min	10 (3–20)	20 (12–38)	4 (3–10)	< 0.001
pH post ROSC	7.2 (7.01–7.32)	7.05 (6.8–7.2)	7.28 (7.12–7.37)	< 0.001
Lactate post ROSC, mmol/L	4.6 (2.1–8.6)	7.1 (4.3–11.5)	3.2 (1.6–6.1)	< 0.001
Duration of mechanical ventilation, hr	189 (84–351)	235 (156–500)	123 (44–270)	< 0.001
Use of extracorporeal membrane oxygenation	53 (41)	36 (72)	17 (22)	< 0.001
Time to health-related quality of life assessment, yr	3.8 (2.4–5.3)	3.8 (2.6–5.3)	3.8 (2.4–5.3)	0.78

ROSC = return of spontaneous circulation.
Values reported as either median (interquartile range) or as *n* (%).

Figure 1 shows individual patient level data for the minimum and maximum temperature reached in the 48-hour period after attaining return of circulation. The median (IQR) of the lowest temperature reached in the first 48 hours in TH versus No-TH group was 33.0°C (32.6–33.6°C) versus 35.4°C (34.7–36.2°C) ($p < 0.001$). The median (IQR) for the maximum temperature reached in the first 48 hours in the TH group versus No-TH group was 34°C (33.6–34.7°C) versus 37.5°C (37.1–38°C) ($p < 0.001$).

Primary Outcome

The time to assessment of HRQoL from the time of cardiac arrest was similar in both groups: median (IQR) of 3.8 years (2.6–5.3 yr) in the TH group versus 3.8 years (2.4–5.3 yr) in the No-TH group. The unadjusted HRQoL (95% CI) for physical, psychosocial, and total scores were higher in the TH group when compared with the No-TH group (**Table 2**). In the multivariable analysis, on average TH was associated with higher HRQoL scores for all three domains compared with those in the No-TH group (Table 2). The adjusted MD in physical score was 15.8 (95% CI, 3.5–27.9) points higher for the TH group compared with the No-TH group. Similar higher adjusted MD was observed for the TH group for psychosocial and total score. The individual regression coefficients for covariates used in regression adjustment for the TH and No-TH groups can be found in **Appendix Table 2** (http://links.lww.com/PCC/B864). There was no evidence of interaction, that is, differences in the association of primary exposure (TH or No-TH) by ECPR status for all three HRQoL outcomes ($p > 0.5$ for all three models).

A post hoc subgroup analysis performed after excluding children who had at least one temperature more than 37.5°C in the first 48 hours similarly showed

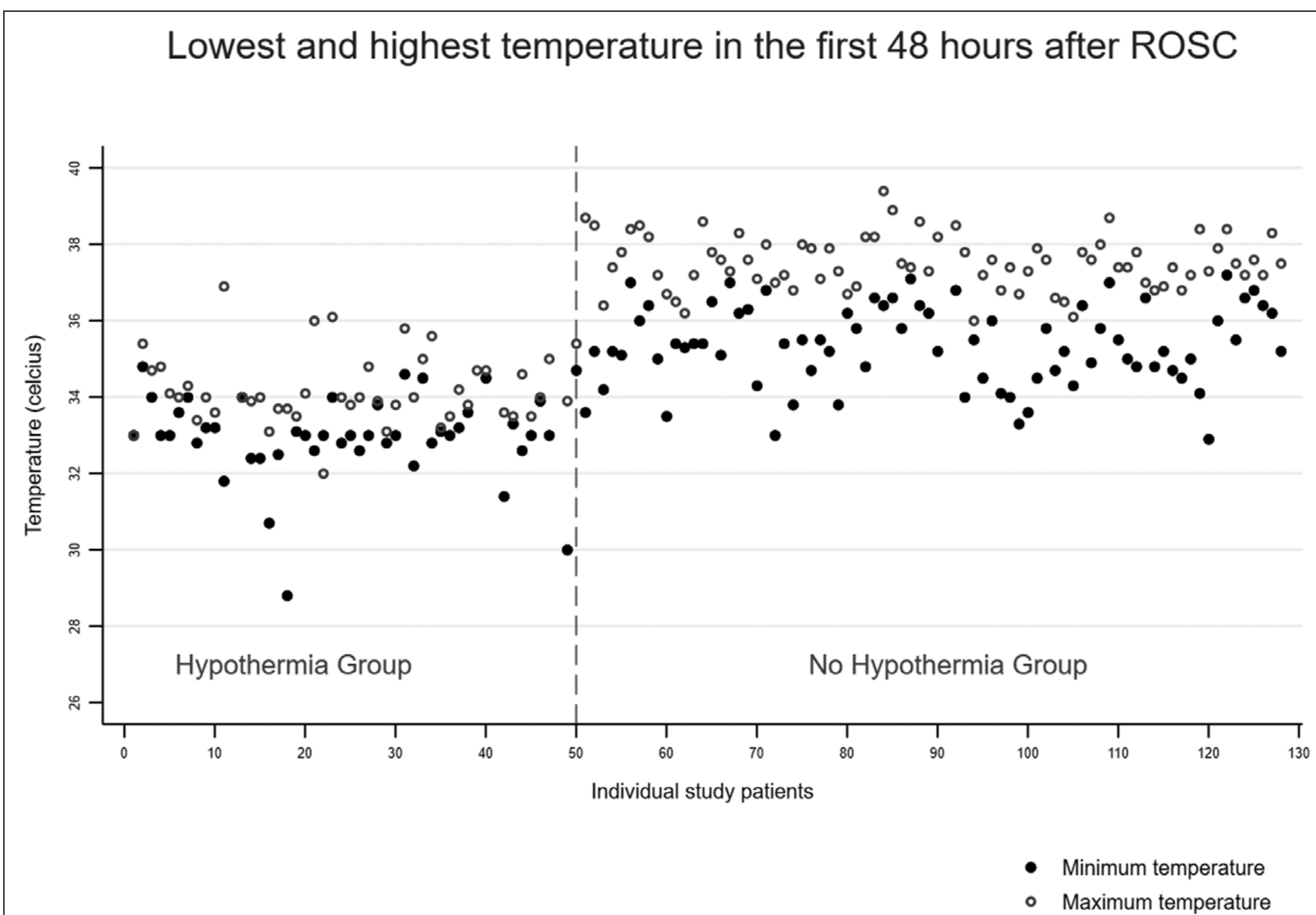

Figure 1. Individual patient level data for lowest and highest temperature in the first 48 hr after return of spontaneous circulation (ROSC) in participants for whom health-related quality of life assessments were completed ($n = 128$). *Solid* and *open dots* represent patient level data for minimum and maximum temperature achieved in the first 48 hr. *Vertical dash line* separates hypothermia from the "no hypothermia" group.

TABLE 2.
Mean difference (Hypothermia vs No Therapeutic Hypothermia) for All Three Health-Related Quality of Life Measures

Pediatric Quality of Life HRQoL Measure	Unadjusted Mean (95% CI) HRQoL Measure			Adjusted Mean (95% CI) HRQoL Measure			
	Therapeutic Hypothermia	No Therapeutic Hypothermia	Mean Difference	Therapeutic Hypothermia	No Therapeutic Hypothermia	Mean Difference[a]	*p*
Model 1: Physical summary score (*n* = 128)	78 (70.5–85.5)	65.9 (57.7–74)	12.1 (0.43–23.7)	79 (70.2–87.8)	63.2 (54.6–71.9)	15.8 (3.5–27.9)	0.01
Model 2: Psychosocial summary score (*n* = 126)	77.9 (73–82.8)	67.5 (61.6–73.5)	10.4 (2.1–18.7)	79.5 (74.6–84.4)	65.9 (59.9–71.9)	13.6 (5.8–21.5)	0.001
Model 3: Total summary score (*n* = 128)	76.9 (72–81.2)	67.4 (61.3–73.5)	9.5 (0.9–18)	77.6 (72.2–82.9)	66.4 (60.1–72.7)	11.2 (2.8–19.6)	0.009

HRQoL = health-related quality of life.
[a]Mean difference in HRQoL between “Therapeutic Hypothermia” vs “No Therapeutic Hypothermia” is obtained by regression adjustment after controlling for the following variables: time to HRQoL assessment (months) from date of arrest, extracorporeal membrane oxygenation, in-hospital cardiac arrest vs out-of-hospital cardiac arrest, lactate post return of spontaneous circulation (log-transformed), preexisting comorbidity, preexisting neurologic condition, and duration of mechanical ventilation (log-transformed).

TABLE 3.
Mean Health-Related Quality of Life Scores in Normative Data, Therapeutic Hypothermia, and Nontherapeutic Hypothermia Groups

Domain	Normative Data[a] (*n* = 1,455)	No Therapeutic Hypothermia (*n* = 78)	Mean Difference[b] (95% CI)	*p*	Therapeutic Hypothermia (*n* = 50)	Mean Difference[c] (95% CI)	*p*
Physical summary score	84.5 (12.3)	65.9 (35.9)	18.6 (15.3–21.9)	< 0.001	78 (26.4)	6.5 (2.8–10.1)	< 0.001
Psychosocial summary score	77.1 (14.1)	67.5 (26.1)	9.6 (6.2–13)	< 0.001	77.9 (16.9)	−0.8 (−4.8 to 3.2)	0.70

[a]Normative data obtained from adolescents in Australia. Data were taken from Wong et al (20).
[b]Mean difference represents comparison of normative data with no therapeutic hypothermia.
[c]Mean difference represents comparison of normative data with therapeutic hypothermia.
Data reported as mean (SD) and mean difference reported as mean (95% CI).

AT THE BEDSIDE

- Hypothermia treatment after cardiac arrest in children is associated with higher and clinically meaningful HRQoL scores in both the physical and psychosocial domains.
- Clinicians using hypothermia after cardiac arrest must consider striving to achieve target core temperature (33°C) very early after the cardiac arrest and maintain for 3 days.
- Patient- or parent-reported outcomes such as HRQoL scores are a valuable addition to the bedside clinician to understand the long-term impact of intensive care therapies.

higher mean HRQoL scores in association with TH (**Appendix Table 3**, http://links.lww.com/PCC/B864).

Finally, the HRQoL in children who had a cardiac arrest was compared with HRQoL scores for Australian children in the general population. Compared with normative data (20), No-TH was associated with lower scores in the physical and psychosocial domains (MD 18.6 and 9.6, respectively) (**Table 3**). We failed to identify such an association between use of TH and the psychosocial domain (MD –0.8). However, use of TH was associated with lower scores in the physical domain (MD of 6.5).

Secondary Outcome

Among children who achieved ROSC (n = 239), 112 (47%) received TH and 127 (53%) were in the No-TH group. The final multivariable logistic regression analysis for death in PICU was performed on 231 out of 239 (97%) patients achieving ROSC. After adjusting for covariates, we failed to identify an association between use of TH and PICU mortality (adjusted odds ratio, 1.30; 95% CI, 0.57–2.98). The goodness of fit of the final model (using Hosmer-Lemeshow chi-square goodness-of-fit test with 10 groups) showed a probability value of 0.88 and the Brier's score of overall fit was 0.13. The results of the final multivariable model are shown in **Appendix Table 4** (http://links.lww.com/PCC/B864).

DISCUSSION

This study of 128 children who survived a cardiac arrest shows an association between prior use of TH and higher mean HRQoL score. In regard to PICU mortality, we were not able to identify an association between the use of TH and reduced mortality.

In the experimental setting, hypothermia is able to prevent or mitigate early and late end-organ destructive processes triggered by an ischemic/ reperfusion injury (21). Physiologic mechanisms described are numerous (21) with some of these mechanisms occurring very early after the insult, and the speed of initiation of TH and shorter time to reach the desired target temperature (32–33°C) influences outcome (13).

In the PICU environment, even in well-resourced units, having a child with critical illness is extremely stressful for families. The complex clinical situation following a cardiac arrest often allows little time for a family to assimilate the burden on the child's potential outcome, let alone their ability to understand and provide informed consent for research. The situation becomes even more difficult with time critical interventions such as TH after cardiac arrest. It can be argued that it is unethical to require full prior written consent for time critical interventions in complex trials from extremely stressed and often uninformed parents (22). For future trials of cooling after cardiac arrest in children, alternate modes of obtaining consent such as deferred or delayed consent should be considered.

Few studies have looked at quality of life after pediatric cardiac arrest (7, 23). Of note, for parent proxy reports of HRQoL a minimum clinically important difference (MCID) for total, physical, and psychosocial scores have previously been calculated as 4.5, 6.9, and 5.5, respectively, by the developers of PedsQL (17). All of these MCIDs are well below the MDs identified in our study, confirming the significant associations in the TH and No-TH groups. Similarly, the observations in the HRQoL assessment in the No-TH group, for physical and psychosocial domains, in relation to normative data (20) with worsened findings were important and warrants further study. Finally, taken together these highlight not only the difference in HRQoL between the study groups (favoring hypothermia) but also how children treated with hypothermia were almost close to the normal population.

In the adult TTM and TTM2 trials (8, 9), the median time to reach target temperature (33°C) from ROSC was more than 10 and 5 hours, respectively, and in the pediatric THAPCA trials (10, 11), this time was greater than

6 hours. It is plausible that the higher HRQoL observed in the hypothermia arm of our study was secondary to both the effects of hypothermia and also the rapid initiation of TH. Experimental data suggest that TH, in order to be beneficial, must be initiated rapidly, maintained with tight temperature control for long enough (72 hr) and followed by a slow rewarming phase (21).

Our study has three main limitations, besides the obvious problems of retrospective identification of the TH and No-TH cohorts, and many unmeasured potential confounding factors. First, a baseline assessment of quality of life would have been helpful in reducing any potential bias associated with the treatment effect. We tried to minimize this problem by using premorbid neurologic status and comorbidity status in the regression adjustment. Second, we found an association between use of TH and HRQoL, but we failed to find an association between use of TH and mortality. This difference could be explained by a small sample size and insufficient control for confounding or it could represent a failure in any neuroprotective effect of TH in limiting mortality associated with devastating hypoxic brain injury, but having an effect on quality of life if the patient were to survive. Last, lack assessment of neurological outcome at the time of discharge and at the time of follow-up HRQoL assessment is also an omission that would be beneficial in future studies.

CONCLUSIONS

In survivors of pediatric cardiac arrest, the use of TH was associated with higher HRQoL scores. Potential factors influencing this observation in our single-center retrospective data are the rapid time to achieve TH and strict maintenance of TH. Our findings suggest that future studies on temperature management should endeavor to achieve hypothermia as early as possible and consider including quality of life scores as part of their outcome measures.

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