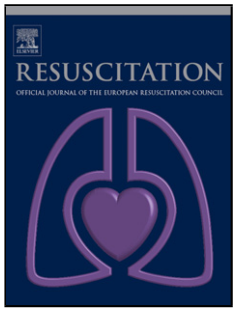
Evolution, safety and efficacy of targeted temperature management after pediatric cardiac arrest

Scholefield, Barney; Morris, Kevin P; Duncan, Heather P; Perkins, Gavin D; Gosney, Jessica; Skone, Richard; Sanders, Victoria; Gao, Fang

DOI:
10.1016/j.resuscitation.2015.04.007



Title: Evolution, safety and efficacy of targeted temperature management after paediatric cardiac arrest

Author: Barnaby R. Scholefield Kevin P. Morris Heather P. Duncan Gavin D. Perkins Jessica Gosney Richard Skone Victoria Sanders Fang Gao

PII: S0300-9572(15)00157-4
DOI: http://dx.doi.org/doi:10.1016/j.resuscitation.2015.04.007
Reference: RESUS 6369

To appear in: *Resuscitation*

Received date: 9-1-2015
Revised date: 18-3-2015
Accepted date: 15-4-2015

Please cite this article as: Scholefield BR, Morris KP, Duncan HP, Perkins GD, Gosney J, Skone R, Sanders V, Gao F, Evolution, safety and efficacy of targeted temperature management after paediatric cardiac arrest., *Resuscitation* (2015), http://dx.doi.org/10.1016/j.resuscitation.2015.04.007

Title: Evolution, safety and efficacy of targeted temperature management after paediatric cardiac arrest.

Authors: Barnaby R Scholefield[1,2] MRCPCH PhD, Kevin P Morris[1] FRCPCH MD, Heather P Duncan[1] MRCPCH MSc, Gavin D Perkins[3,4] FRCP, FFICM, MD, Jessica Gosney[1] MBChB, Richard Skone[1] FRCA, Victoria Sanders[1] MBChB, Fang Gao[2,4,5] FRCA, FFICM, MD

Affiliations:
[1] Paediatric Intensive Care Unit, Birmingham Children's Hospital, Birmingham, B4 6NH, UK
[2] School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, B15 2TT, UK
[3] Clinical Trials Unit, University of Warwick, Coventry, CV4 7AL, UK
[4] Academic Department of Anesthesia, Critical Care and Resuscitation, Heartland of England NHS Foundation Trust, B9 5SS UK
[5] Department of Anaesthesiology, The Second Affiliated Hospital & Yuying Children hospital of Wenzhou Medical University, Wenzhou, China

Address for correspondence to: Dr Barnaby R Scholefield, Consultant in Paediatric Intensive Care
Birmingham Children's Hospital, Paediatric Intensive Care Unit, Steelhouse Lane, Birmingham B4 6NH
[Barney.scholefield@bch.nhs.uk]

Short title: Targeted temperature management after cardiac arrest.

Key Words: paediatric critical care, therapeutic hypothermia, targeted temperature management, observational study, out-of-hospital cardiac arrest

Define all nonstandard abbreviations:
OHCA: Out-of-hospital cardiac arrest
PICU: Paediatric intensive care unit
ROSC: Return of spontaneous circulation
TTM: Targeted temperature management
STM: Standard temperature management

Funding Source: No funding was secured for this study.

Financial Disclosure: No financial relationships relevant to this article to disclose.

Conflict of Interest: No conflicts of interest to disclose.

Contributors statement
Dr Scholefield designed the current study protocol, data collection tool and database with substantial intellectual input from Prof Gao & Perkins, and Drs Morris and Duncan. Data collection was performed by Dr Scholefield, Dr Gosney, Dr Sanders and Dr Skone. Data cleaning, validation and queries were performed by Dr Scholefield. All statistical analysis was performed by Dr Scholefield with advice from Dr P Davies. Contributions to

interpretation of data were received from all authors. First draft of manuscript was written by Dr Scholefield with intellectual input from Drs Morris & Duncan and Prof Gao & Perkins. In addition, critical review and contributions of subsequent drafts were received from Drs Gosney, Sanders and Skone. All authors reviewed and approved the final draft of the manuscript prior to submission. All authors agree to be accountable for the accuracy and integrity of the piece of work.

Word count: 3118

ABSTRACT

Background

It is unknown whether targeted temperature management (TTM) improves survival after paediatric out-of-hospital cardiac arrest (OHCA). The aim of this study was to assess the evolution, safety and efficacy of TTM (32-34^{0}C) compared to standard temperature management (STM) (<38^{0}C).

Methods

Retrospective, single centre cohort study. Patients aged >one day up to 16 years, admitted to a UK Paediatric Intensive Care Unit (PICU) after OHCA (January 2004 to December 2010). Primary outcome was survival to hospital discharge; efficacy and safety outcomes included: application of TTM, physiological, haematological and biochemical side effects.

Results

Seventy three patients were included. Thirty eight patients (52%) received TTM (32-34^{0}C). Prior to ILCOR guidance adoption in January 2007, TTM was used infrequently (4/25; 16%). Following adoption, TTM (32-34^{0}C) use increased significantly (34/48; 71% Chi^2 p<0.0001).

TTM (32-34^{0}C) and STM (<38^{0}C) groups were similar at baseline. TTM (32-34^{0}C) was associated with bradycardia and hypotension compared to STM (<38^{0}C). TTM (32-34^{0}C)

reduced episodes of hyperthermia (>38^{0}C) in the 1st 24 hours; however, excessive hypothermia (<32^{0}C) and hyperthermia (>38^{0}C) occurred in both groups upto 72 hours, and all patients (n=11) experiencing temperature <32^{0}C died. The study was underpowered to determine a difference in hospital survival (34% (TTM (32-34^{0}C)) vs. 23% (STM (<38^{0}C)); p=0.284). However, the TTM (32-34^{0}C) group had a significantly longer PICU length of stay.

Conclusions

TTM (32-34^{0}C) was feasible but associated with bradycardia, hypotension, and increased length of stay in PICU. Temperature <32^{0}C had a universally grave prognosis. Larger studies are required to assess effect on survival.

INTRODUCTION

It is unknown whether targeted temperature management (TTM) (32-34°C) improves survival and reduces brain injury for infants and children after out-of-hospital cardiac arrest (OHCA) (1). TTM is the active treatment of inducing and maintaining a specific body temperature for a specific duration of time attempting to improve health outcomes (2). Randomized controlled trials in the 2000s renewed interest in 12-24 hours of TTM (32-34°C) as a therapeutic intervention in adult survivors of OHCA (3, 4) and for 72 hours in neonates after birth asphyxia (5). The International Liaison Committee on Resuscitation (ILCOR) introduced guidance in April 2006 that TTM (32-34°C) may be: 1) *beneficial* for adolescents who remain comatose following resuscitation from sudden, witnessed, ventricular fibrillation OHCA and 2) *considered* for infants and children who remain comatose following resuscitation from cardiac arrest (6). More recent adult studies confirm a role for 24 hours of TTM but show that a higher temperature target (TTM 36°C) produces similar results to a lower target (TTM 33°C) (7). The randomized control trials of Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA studies) of OHCA (NCT00878644) and in-hospital cardiac arrest (NCT00880087) investigating TTM at 33°C for 48 hours versus TTM at 36.7°C are on-going (8, 9).

Paediatric retrospective studies of TTM have been limited (10-12). Two studies showed no difference in survival outcome with TTM (33-34°C) versus the institutions usual standard temperature management (STM). The usual STM practice was to maintain normothermia by avoiding hyperthermia (<38°C), but frequently did not involve using active temperature control devices (4, 10).These studies included small numbers of OHCA patients and contained very unbalanced groups with regards illness severity, with greater use of TTM (32-34) in the more severe group. One recent study from Taiwan did show a statistically significant increase in survival after 72 hours of TTM (33-34°C) (12). However, the OHCA

population was small and differences between healthcare systems may limit generalizability. These studies identified that inadvertent overcooling (<32°C) and hyperthermia (>38°C) increased the risk of worse outcome.

The ILCOR TTM (32-34°C) guidance was adopted in our paediatric intensive care unit (PICU) in 2007. TTM (32-34°C) use has developed iteratively and culminated in the use of servo-controlled temperature management devices and a standardized protocol. The aim of this study was to assess evolution, safety and efficacy of TTM (32-34°C) in a tertiary PICU and compare to usual institutional standard temperature management (STM) (aiming to avoid hyperthermia; $>38^0$C).

PATIENTS AND METHODS

The hospital research committee (Institutional Review Board) approved the study and waived the need for consent given the observational nature of the study.

Settings and participants

This retrospective, single-centre, cohort study included infants and children admitted to the PICU after OHCA between January 2004 and December 2010. Patients were included if aged between at least one day and 16 years, admitted to PICU after an OHCA with return of spontaneous circulation (ROSC). OHCA was defined as no cardiac output and pulseless for greater than one minute as confirmed by a trained medical practitioner/paramedic prior to

arrival at an emergency department. Patients were identified via the Paediatric Intensive Care Audit Network (PICANet) (13) and local admission databases.

Data collection and assessment

Case records were reviewed with data-verification at inputting and analysis stage. Patients were divided into two groups, targeted temperature management (TTM 32-34°C) and standard temperature management (STM). The use of TTM was defined *a priori* as documented active TTM to maintain a core temperature between 32-34°C. STM group included patients whose temperature was maintained at normothermia using rescue temperature controlling measures to avoid hyperthermia (>38°C).

Data were collected on patient demographics, cardiac arrest resuscitation events, aetiology of arrest, presence of chronic conditions and TTM dosing factors (start time, depth and duration of hypothermia, and length of rewarming) using Utstein defined criteria where available (14).

Physiological variables were collected including; core temperature, heart rate, systolic blood pressure, partial pressure of carbon dioxide ($PaCO_2$ measured at 37^0C; alpha-stat method(15)) in the blood, haematological and biochemical parameters. First, we compared values up to four hours post PICU admission for TTM and STM groups to ascertain any differences in risk of mortality. Secondly, the proportions with abnormal values or adverse events within 72 hours of PICU admission were compared. Core temperatures were measured as either rectal, oesophageal or bladder. Episodes of excessive hypothermia were defined as

temperature less than 32°C and hyperthermia greater than 38°C. Adverse events included: seizures, bradycardia (<10th centile for age and sex)(16), hypotension (<5th centile for age and sex)(17), use of critical care organ support and monitoring. The primary outcome was survival at hospital discharge.

Targeted temperature management

In January 2007, following ILCOR guidance in April 2006, the PICU clinical team considered TTM(32-34°C) for OHCA patients on a case by case basis. TTM (32-34°C) was initiated in the PICU with the use of servo-controlled water blanket cooling mattresses (Blanketroll II, Cincinnati Sub Zero, Ohio, USA) to reduce temperature between 32 to 34^{0}C for 24 hours followed by controlled rewarming, by 0.5^{0}C every 2 hours, to 37^{0}C.

Neuromuscular blocking drugs were used to prevent or treat shivering in conjunction with intravenous sedation and analgesia (morphine and midazolam). Patients were invasively ventilated with arterial blood gases monitoring. Standard 'neuroprotective' $PaCO_2$ target range was 4.5 to 5.0kPa. Inotropes were used to maintain age appropriate blood pressure. Intracranial pressure monitoring was not used in this population. Clinical neurological assessment and additional neurological monitoring or imaging was performed if required;

however, appropriate, active withdrawal of intensive care occurred following established UK guidelines which do not always require formal ancillary neurological assessment (18). Prior to January 2007, and in patients after 2007 not receiving TTM (32-34°C), STM practice followed recommendations to avoid hyperthermia (>38°C). Initial treatment included paracetamol and surface cooling with ice packs, followed by servo-controlled water blanket cooling mattresses (Blanketroll II) if unsuccessful.

Statistical Analysis

Descriptive data were reported as median and interquartile range (IQR) or mean ± 95% confidence interval of the mean for continuous variables and as frequencies and percentages for categorical variables. Parametric continuous data were analysed using the unpaired Student t-test and non-parametric continuous data with the Mann Whitney U test or Kruskal-Wallis, as appropriate. Categorical data were analysed using the Fisher's exact tests. Chi squared trend test was used for change over time. Two sided p values of <0.05 are reported here. Data analyses were performed using either IBM-SPSS Statistics version 19.0 software (SPSS Inc, Chicago, USA) or Minitab 16 (USA).

RESULTS

Evolution

Seventy three patients were included, 38 (52%) received TTM (32-34°C) and 35 (48%) STM (<38°C). Prior to ILCOR guidance adoption in January 2007, TTM (32-34°C) was used infrequently (4/25; 16%). Following adoption, TTM (32-34°C) use increased significantly and was initiated in 34/48; 71% of patients (p <0.0001, Fig. 1).

There were no differences in age, sex or weight in patients receiving either treatment (table 1). TTM (32-34°C) was used more frequently in patients whose cause of arrest was unknown and less in patients presenting with cardiac arrest associated with trauma (including traumatic brain injury). Prevalence of OHCA occurring in the home or being witnessed was similar for patients receiving TTM (32-34°C) and STM (<38°C) (table 2). However, patients receiving TTM (32-34°C) had significantly more reported episodes of bystander CPR. Only six patients presented in a shockable rhythm (ventricular fibrillation or ventricular tachycardia) and 5 out of 6 received TTM (32-34°C). Total duration of CPR was not significantly different (40 minutes (TTM 32-34°C) versus 29 minutes (STM); p=0.23) as was median duration of CPR in the emergency department (12 versus 13 minutes; p=0.98). A small proportion of cases (3% (TTM) vs. 9% (STM); p=0.24) had ROSC prior to arrival at the emergency department.

Safety

Hyperthermia (>38°C) in the first 24 hours after PICU admission was significantly less frequent in patients receiving TTM (32-34°C) (1/35; 3%) versus STM (12/32; 38%, p<0.001) (Supplementary APPENDIX tables A1). However, hyperthermia episodes at any point in the first 72 hours post admission were not significantly different (TTM (15/28; 39%) versus STM (14/35; 50%)) (p = 0.46). Five (7%) patients in the study presented to the ED with a temperature below 30°C, of these patients one received TTM (32-34°C) and four STM (<38°C). Four patients who received TTM (32-34°C) and two who received STM (<38°C) experienced severe hypothermia (temperature <32°C) *after* arrival to PICU. All eleven patients, with a recorded temperature <32°C from ED admission to 24 hours post PICU admission died prior to PICU discharge.

More patients receiving TTM (32-34°C) experienced bradycardia (<10th centile for age) (42% versus 19%; p=0.04) and systolic blood pressure (BP) hypotension (<5th centile for age) (63% versus 28%; p=0.004) within 72 hours of admission. No patients required treatment for bradycardia. There was also no statistically significant difference in the proportion of patients receiving inotropic support. (74% vs. 54%; p=0.08). Only one patient in the TTM (32-34°C) group received extra corporeal life support (ECLS) for refractory cardiac arrest and rewarming due to profound hypothermia on admission (admission core temperature 14°C).

Lactate, pH, glucose, insulin use, base deficit and the Paediatric Index of Mortality 2 (PIM2) score results were similar between the two treatment groups at PICU admission (Supplementary APPENDIX tables A2). Sixty four percent (41/64) had bilateral unresponsive pupils on PICU admission with no differences noted between treatment groups. Similar proportion of patients experienced episodes of seizures (8% versus 14%), thrombocytopenia (36% versus 36%), hypernatremia (24% versus 25%), hypokalaemia (66% versus 46%) and hypomagnesaemia (57% versus 38%) in TTM (32-34°C) and STM (<38°C) groups. Nearly 50% of patients in both groups experienced hypocarbia (<4.0kPa).

No patients received renal replacement therapy. MRI and EEG investigations were more common in the TTM (32-34°C) group, although a greater number of MRIs (71%; 17/24) and EEGs (89%; 17/19) were performed after 2007.

Efficacy

Patients receiving TTM (32-34°C) were significantly colder during the 24 hours of TTM therapy (Fig. 2). Median temperature at the start of TTM (32-34°C) was 35.0 (IQR [33.8 to 36.2])°C. Induction of temperature to target temperature took a median of 02:00

hours:minutes (IQR [0:00 to 03:15]). In those patients with a temperature >35°C at the start of TTM (32-34°C), induction of temperature to target temperature occurred at a median rate of 0.91 (IQR [0.5 to 1.5]) °C/hr. Four patients (11%) had overshoot hypothermia (<32°C) following induction. Median target temperature was 33.4°C and was maintained for a median of 22:30 hours:minutes (IQR [16:37 to 24:44]). Rewarming occurred over a median of 10:30 hours:minutes (IQR [07:00 to 14:45]) at a rate of 0.3 (IQR [0.23 to 0.44])°C/hr. Three patients receiving TTM (32-34°C) died prior to rewarming.

Overall survival to hospital discharge of patients admitted to PICU after OHCA was 29% (21/73) (Table 3). Survival was not significantly different between TTM (32-34°C) and STM (<38°C) treatment groups (34% vs. 23%; p=0.28).

TTM (32-34°C) patients stayed in PICU longer compared to STM (<38°C) (Median 4.1 (IQR [3.0 to 6.8] days vs. 1.3 (IQR [0.5 to 6.7]) days; p <0.001). This difference was accounted for by patients dying sooner in the STM (<38°C) group compared with the TTM (32-34°C) group (Table 3). There were a similar proportion of patients in both groups who had withdrawal of life sustaining intensive care support prior to death.

DISCUSSION

The aim of this study was to assess the evolution, efficacy and safety of TTM (32-34°C) in paediatric patients. TTM (32-34°C) use was used frequently in post OHCA patients after the 2007 ILCOR guidance. Hospital survival rates were 11% higher in the TTM (32-34°C) group

(34% v 23%; p=0.284) but did not reach statistical significance. The study included patients over a seven year period; however, was underpowered to confirm this difference with certainty. Overall the two groups were comparable across a range of known risk factors for post cardiac arrest survival except bystander CPR and lower core temperature on PICU admission (19). These results are similar to previous reported comparisons of TTM (32-34°C) and usual institutional STM (<38°C) in the paediatric population (10, 11). However, in these studies in contrast to the current study, TTM (32-34°C) was used predominately in patients with a higher predicted risk of mortality and included patients after in-hospital cardiac arrest.

This study confirms that TTM (32-34°C) is feasible in paediatric patients. TTM (32-34°C) was successfully administered in 38 patients. Evidence suggests time to target temperature should be as short as possible, whilst avoiding unintentional overshoot to temperature <32°C (20); however, rapid reduction in temperature has also been associated with worse neurological injury (21). Unintentional overshoot in temperature to <32°C occurred in 11% of patients, similar to the 15-17% rate in other retrospective studies (4, 10) but significantly less than the 75% reported by Topjian et al (22). Increased mortality has been reported in subgroups who are overcooled (6) although the causal association has not been established. The use of servo-controlled cooling units, rather than manual temperature control (e.g. ice-packs), may account for the reduction in unintentional overshoot.

Controlled rewarming and the avoidance of overshoot hyperthermia (>38°C) are required to prevent hemodynamic instability, rapid electrolyte changes and worsening of neurological injury (23, 24). Patients were rewarmed at a median rate of 0.3°C/hour, but only 32% re-warmed less than or equal to 0.25°C/hour and of concern, 39% experienced hyperthermia. The optimal rewarming rate after TTM (32-34°C) in humans has not been established with a

tendency to decrease rates over the last 10 years (25). Improvements to rewarming strategies and prolonged active control of normothermia may be required to avoid rebound hyperthermia as exposure to hyperthermia in the post-hypothermia phase has also been associated with increased mortality and poor neurological outcome (26).

Reduction in core temperature in humans is known to be associated with a concomitant reduction in heart rate in sedated patients (27). Bradycardia and hypotension is therefore a consistent finding in studies of TTM (32-34°C), irrespective of underlying disease process (10, 11, 27). Although bradycardia is believed to not require treatment, the management of hypotension is more controversial. An increase in the proportion of patients with bradycardia and hypotension in the TTM (32-34°C) group was observed. This was associated with increased inotropic support though this did not reach significance. Recently, hypotension in the 1st 6 hours after ROSC in children has been shown to be associated with higher in-hospital mortality and worse neurological outcome (28). In the current study hypotension episodes up to 72 hours after ROSC were included. It remains unclear whether the timing of hypotension or the concomitant treatment is important in determining outcome. Certainly, invasive, continuous monitoring of arterial blood pressure is recommended with TTM (32-34°C).

A number of findings differed to previously published studies. Seizure frequency was low (11%) with no difference between TTM (32-34°C) or STM (<38°C) groups. Abend et al identified a higher rate of seizures (47%; 9/19) in a prospective study of therapeutic hypothermia in paediatric cardiac arrest patients (29). Formal electroencephalography (EEG) monitoring was performed in only 26% of our patients and may account for the lower rate. Continuous EEG monitoring may allow improved identification and treatment in this

311 population (30, 31). Hypocarbia ($PaCO_2$ <4kPa) occurred in nearly half of both TTM (32-
312 34°C) and STM (<38°C) patients in the first 24 hours of the study potentially exposing
313 patients to cerebral vasoconstriction and cerebral ischemia. Episodes of hypocarbia and/or
314 hypercarbia compared to normocarbia are associated with worse neurological outcome in
315 adult cardiac arrest survivors and should be avoided (32). Continuous end tidal CO_2
316 monitoring may therefore be beneficial.
317
318 TTM (32-34°C) has changed the traditional timing of clinical, electrophysiological and
319 neuro-imaging investigation to predict outcome after hypoxic ischemic brain injury (33-36).
320 Delayed clearance of sedative drugs alters timing for neurological and brain death testing,
321 prolonging PICU length of stay (37). This effect was observed with a four-fold increase in
322 PICU length of stay for TTM (32-34°C) patients who eventually died compared to STM non-
323 survivors. The inclusion of only OHCA patients may explain the comparative shorter length
324 of stay for STM patients (1.3 days) compared to Doherty et al (11) (9.0 days (IQR [5.0 to
325 22.3])) and Fink et al (10) (5 days (IQR [1 to 14])). A temporal trend of increasing time to
326 withdrawal of intensive care support and death along with an increased use of MRI and EEG
327 investigations was also noted. This may reflect a change in clinical practice when predicting
328 outcome with a delayed assessment and increased use of multi-modal methods of outcome
329 prediction occurring over time.
330
331 The prolonged duration of treatment associated with the TTM (32-34°C) group may reflect
332 an optimistic view of paediatric intensivists for a good outcome following OHCA, influenced
333 in part by the positive findings of neonatal and adult TTM (32-34°C) trials (3-5, 7). Twenty
334 four hours of TTM (32-34°C) followed by 12-16 hours rewarming enables a period of active
335 PICU treatment, correction and titration of physiology variables and a delay to neurological

prognosis. This positive approach after OHCA contrasts the historic views of poor outcome despite PICU management and may have postively effected patient outcome.

Neonatal studies after birth asphyxia have supported the recommendations of TTM (33°C) for 72 hours (5). These study populations were carefully selected with a homogenous pathology and severity assessed by predefined stratification criteria. However, the paediatric OHCA population is heterogenous; variable aetiologies, co-morbidities and resuscitation factors limit the ability to extrapolate the neonatal findings to paediatric OHCA.

This study has the following limitations. 1) This is a single centre study and is still relatively small despite a seven year data collection period. 2) Data from a single centre may limit the general applicability of the overall findings to other centres. 3) Owing to the retrospective nature of this study we were unable to separate patients in the STM (<38°C) group who had reactive hyperthermia (>38°C) treatment only and those initiated on an active normothermia targeted temperature management. 4) Changes in clinical management of OHCA may have changed over the study period. It was identified that the use of TTM (32-34°C), neuro-imaging and neuro-electrophysiological monitoring increased in the second half of the study and there may have been other confounding factors (e.g. new resuscitation guidelines in 2005) not identified. 5) The use of TTM (32-34°C) was not randomized with the potential for case selection bias. 6) The primary outcome was hospital survival as neurological outcome data was not available, but should be collected in future studies.

CONCLUSION

This study assessed the evolution, safety and efficacy of TTM (32-34°C) compared with STM (<38°C) after OHCA. TTM (32-34°C) use increased significantly after ILCOR 2007

guidance. TTM (32-34°C) was effectively administered in the paediatric population but resulted in bradycardia and hypotension. It did not significantly increase survival to hospital discharge but increased PICU length of stay. Avoidance of excess hypothermia (<32°C) is recommended. Further studies are required to demonstrate whether TTM (32-34°C) is cost-effective, and improves the proportion of patients with good neurological survival after OHCA.

ACKNOWLEDGEMENT

We acknowledge the statistical advice from Dr P Davies and administrative support from Mr K Ali and Ms H Osmani at Birmingham Children's Hospital.

TABLES & FIGURES

Table 1 Demographics and relationship to treatment groups

Table 2 Cardiac arrest resuscitation factors, PICU interventions and relationship to treatment groups

Table 3 Survival outcomes in relationship to treatment groups

FIGURES

Figure 1 Percentage of patients receiving targeted temperature management (TTM) and standard temperature therapy (STM)

Dashed red line indicates first publication date of ILCOR guidelines for paediatric TTM use: Published on-line April 17th 2006 - "Induction of hypothermia (32 to 34°C) for 12 to 24 hours should be considered in children who remain comatose after resuscitation from cardiac arrest." (38)

Figure 2 Temperature profiles of patients receiving targeted temperature management and standard temperature therapy.

Mean temperature (with 95% confidence intervals for the mean). TTM: targeted temperature management. STM: Standard temperature management.

SUPPLEMENTARY APPENDIX

Table A1 Adverse events within 72 hours of admission

Table A2 Physiological variables available between ROSC to four hours after PICU admission and relationship to treatment groups

REFERENCES

1. Scholefield B, Duncan H, Davies P, Gao Smith F, Khan K, Perkins GD, Morris K. Hypothermia for neuroprotection in children after cardiopulmonary arrest. Cochrane Database Syst Rev. 2013;2:CD009442.
2. Nunnally ME, Jaeschke R, Bellingan GJ, et al. Targeted temperature management in critical care: A report and recommendations from five professional societies. Crit Care Med. 2011;39(5):1113-25.
3. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346(8):557-63.
4. HACA. Hypothermia After Cardiac Arrest Study Group, Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549-56.
5. Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;1:CD003311.
6. Kleinman ME, de Caen AR, Chameides L, et al. Part 10: pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122(16 Suppl 2):S466-515.
7. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33 degrees C versus 36 degrees C after Cardiac Arrest. N Engl J Med. 2013.
8. Moler FW, Silverstein FS, Meert KL, et al. Rationale, timeline, study design, and protocol overview of the therapeutic hypothermia after pediatric cardiac arrest trials. Pediatr Crit Care Med. 2013;14(7):e304-15.
9. Pemberton VL, Browning B, Webster A, Dean JM, Moler FW. Therapeutic hypothermia after pediatric cardiac arrest trials: the vanguard phase experience and implications for other trials. Pediatr Crit Care Med. 2013;14(1):19-26.
10. Fink EL, Clark RS, Kochanek PM, Bell MJ, Watson RS. A tertiary care center's experience with therapeutic hypothermia after pediatric cardiac arrest. Pediatr Crit Care Med. 2010;11(1):66-76.
11. Doherty DR, Parshuram CS, Gaboury I, et al. Hypothermia therapy after pediatric cardiac arrest. Circulation. 2009;119(11):1492-500.
12. Lin J-J, Hsia S-H, Wang H-S, Chiang M-C, Lin K-L. Therapeutic Hypothermia Associated With Increased Survival After Resuscitation in Children. Pediatric Neurology. 2013;48(4):285-90.
13. PICANet. Paediatric Intensive Care Audit Network National Report 2008 - 20102011 18th July 2012. Available from: http://www.picanet.org.uk/Documents/General/Annual%20report%20published%202011/Annual_report_02_12_11.pdf.
14. Zaritsky A, Nadkarni V, Hazinski MF, et al. Recommended guidelines for uniform reporting of pediatric advanced life support: the Pediatric Utstein Style. A statement for healthcare professionals from a task force of the American Academy of Pediatrics, the American Heart Association, and the European Resuscitation Council. Resuscitation. 1995;30(2):95-115.
15. Murkin JM. Cerebral autoregulation: the role of CO2 in metabolic homeostasis. Semin Cardiothorac Vasc Anesth. 2007;11(4):269-73.
16. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011;377(9770):1011-8.
17. Samuels M, Wieteska S. Advanced Paediatric Life Support: The Practical Approach / Advanced Life Support Group 5th ed. Manchester: Wiley-Blackwell: BMJ books; 2010.
18. RCPCH. Withholding or Withdrawing Life Sustaining Treatment in Children: A Framework for Practice 2004 20th May 2012 Available from: http://www.rcpch.ac.uk/sites/default/files/Witholding.pdf.
19. Nagata T, Abe T, Noda E, Hasegawa M, Hashizume M, Hagihara A. Factors associated with the clinical outcomes of paediatric out-of-hospital cardiac arrest in Japan. BMJ open. 2014;4(2):e003481.
20. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med. 2009;37(7 Suppl):S186-202.
21. Haugk M, Testori C, Sterz F, Uranitsch M, Holzer M, Behringer W, Herkner H. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. Crit Care. 2011;15(2):R101.
22. Topjian A, Hutchins L, DiLiberto MA, et al. Induction and maintenance of therapeutic hypothermia after pediatric cardiac arrest: efficacy of a surface cooling protocol. Pediatr Crit Care Med. 2011;12(3):e127-35.
23. Hildebrand F, van Griensven M, Giannoudis P, et al. Effects of hypothermia and re-warming on the inflammatory response in a murine multiple hit model of trauma. Cytokine. 2005;31(5):382-93.

24. Maxwell WL, Watson A, Queen R, Conway B, Russell D, Neilson M, Graham DI. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. J Neurotrauma. 2005;22(8):873-84.
25. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009;37(3):1101-20.
26. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. Resuscitation. 2013;84(12):1734-40.
27. Thoresen M, Whitelaw A. Cardiovascular changes during mild therapeutic hypothermia and rewarming in infants with hypoxic-ischemic encephalopathy. Pediatrics. 2000;106(1 Pt 1):92-9.
28. Topjian AA, French B, Sutton RM, et al. Early postresuscitation hypotension is associated with increased mortality following pediatric cardiac arrest. Crit Care Med. 2014;42(6):1518-23.
29. Abend NS, Topjian A, Ichord R, et al. Electroencephalographic monitoring during hypothermia after pediatric cardiac arrest. Neurology. 2009;72(22):1931-40.
30. Friedman D, Claassen J, Hirsch LJ. Continuous electroencephalogram monitoring in the intensive care unit. Anesth Analg. 2009;109(2):506-23.
31. Hosain SA, Solomon GE, Kobylarz EJ. Electroencephalographic patterns in unresponsive pediatric patients. Pediatr Neurol. 2005;32(3):162-5.
32. Roberts BWMD, Kilgannon JHMD, Chansky MEMD, Mittal NMD, Wooden JMD, Trzeciak SMDMPH. Association Between Postresuscitation Partial Pressure of Arterial Carbon Dioxide and Neurological Outcome in Patients With Post-Cardiac Arrest Syndrome. Circulation. 2013;127(21):2107-13.
33. Abend NS, Topjian AA, Kessler SK, et al. Outcome prediction by motor and pupillary responses in children treated with therapeutic hypothermia after cardiac arrest. Pediatr Crit Care Med. 2012;13(1):32-8.
34. Young GB. Clinical practice. Neurologic prognosis after cardiac arrest. N Engl J Med. 2009;361(6):605-11.
35. Nakagawa TA, Ashwal S, Mathur M, Mysore M. Clinical report-Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics. 2011;128(3):e720-40.
36. Fugate JE, Wijdicks EF, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol. 2010;68(6):907-14.
37. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. Crit Care Med. 2011;39(6):1538-42.
38. ILCOR. The International Liaison Committee on Resuscitation (ILCOR) consensus on science with treatment recommendations for pediatric and neonatal patients: pediatric basic and advanced life support. Pediatrics. 2006;117(5):e955-77.

491 Table 1 Demographics and relationship to treatment groups

	Total Group n =73	TTM n=38	STM n = 35	*p*
Age (years)	1.0 (0-5.0)	1.5 (0-5.8)	1.0 (0-4.0)	0.74
Weight (kg)	8 (4-15)	10 (6-20)	6 (4-12)	0.06
Age category (Utstein[a])				0.57
1-30 days	7 (10%)	5 (13%)	2 (6%)	
31 days to < 1 yr	23 (32%)	10 (26%)	13 (38%)	
1yr to < 4yrs	21 (29%)	11 (29%)	10 (29%)	
4yrs to < 12yrs	9 (13)	4 (11%)	5 (15%)	
12yrs to < 16yrs	12 (17%)	8 (21%)	4 (12%)	
Male	25 (34%)	17 (45%)	8 (23%)	0.08
Any Chronic Condition	33 (45%)	15 (39%)	18 (51%)	0.30
Neurological	17 (23%)	9 (24%)	8 (23%)	0.93
Respiratory	13 (18%)	7 (18%)	6 (17%)	0.89
Cardiac	4 (5%)	1 (3%)	3 (9%)	0.27
Prematurity	3 (4%)	1(3%)	2 (6%)	0.60
Metabolic	4 (5%)	2 (4%)	2 (3%)	0.71
Gastrointestinal	1 (1%)	1 (3%)	0	1.00
Renal	1 (1%)	0	1 (3%)	1.00
Transported from different admitting hospital	37 (51%)	21 (55%)	16 (47%)	0.49
Etiology of arrest				
Not Known	12 (16%)	9 (23%)	3 (9%)	0.12
Pulmonary	16 (22%)	9 (24%)	7 (20%)	0.78
Cardiac	5 (7%)	4 (11%)	1 (3%)	0.19
Trauma (including traumatic brain injury)	11 (14%)	3 (8%)	8 (23%)	0.10
Drowning/Submersion	6 (8%)	3 (7%)	3 (9%)	1.00
Neurological (non-trauma)	7 (10%)	2 (5%)	5 (14%)	0.25
Sepsis	5 (7%)	2 (5%)	3 (9%)	0.67
Strangulation	3 (4%)	2 (5%)	1 (3%)	1.00
Sudden infant death syndrome	2 (3%)	0	2 (5%)	0.23
Other	6 (8%)	4 (11%)	2 (6%)	0.68

492 [a] Utstein pre-defined age groups with modified upper age limit to less than 16 years (13)(14). Results expressed
493 as Median (Inter-quartile range) or number (percent). Allocation to multiple chronic conditions was permitted.
494 Fisher's exact test was used for categorical variable and Mann Whitney U test for continuous variables.
495

495

496 Table 2 Cardiac arrest resuscitation factors, PICU interventions and relationship to treatment groups

Cardiac arrest resuscitation events	Total Group n =73	TTM n=38	STM n = 35	*p*
Location own home (versus public place or other)	45 (68%)	23 (70%)	22 (67%)	0.79
Witnessed arrest	45 (65%)	23 (62%)	22 (69%)	0.57
Bystander CPR	45 (65%)	30 (81%)	15 (47%)	0.003
VF/VT[a] (vs. PEA/ bradycardia/asystole)	6 (9%)	5 (14%)	1 (3%)	0.20
Pulseless electrical activity (PEA)	10 (15%)	6 (17%)	4 (13%)	
Bradycardia	7 (6%)	2 (16%)	5 (11%)	
Asystole	43 (65%)	22 (63%)	21 (67%)	
Ventricular fibrillation (VF)	5 (8%)	5 (14%)	0 (0)	
Pulseless Ventricular tachycardia (VT)	1 (2%)	0 (0)	1 (3%)	
Defibrillation attempted	10 (14%)	7 (18%)	3 (10%)	0.28
Epinephrine doses during resuscitation[b]	3 (1-4)	3 (1-4)	3 (1-4)	0.83
No epinephrine given during resuscitation	6 (9%)	2 (5%)	4 (13%)	0.40
Time duration from cardiac arrest onset to ROSC (mins)	38 (24-49)	40 (26-56)	29 (21-46)	0.23
ROSC prior to ED admission	8 (6%)	2 (3%)	6 (9%)	0.24
Time from ED admission to ROSC (mins)[c]	12 (5-19)	12 (4-20)	13 (8-18)	0.98
Time duration from ROSC to PICU admission (hrs:mins)	02:57 (01:13-04:34)	02:50 (01:24-04:51)	03:20 (00:50-04:29)	0.67
PICU interventions				
Mechanical ventilation	73 (100%)	38 (100%)	35 (100%)	1.00
Inotropes after resuscitation	47 (64%)	28 (74%)	19 (54%)	0.08
Two or more inotropes	11 (15%)	8 (21%)	3 (9%)	0.19
HFOV	2 (3%)	2 (3%)	2 (3%)	1.00
ECMO	1 (1%)	1 (3%)	0	1.00
Renal replacement therapy	0	0	0	
Insulin therapy	19 (26%)	13 (34%)	6 (17%)	0.10
Neuromuscular blockade after PICU admission	31 (42%)	16 (42%)	15 (43%)	0.95
Anti-seizure therapy	10 (14%)	6 (16%)	4 (11%)	0.74

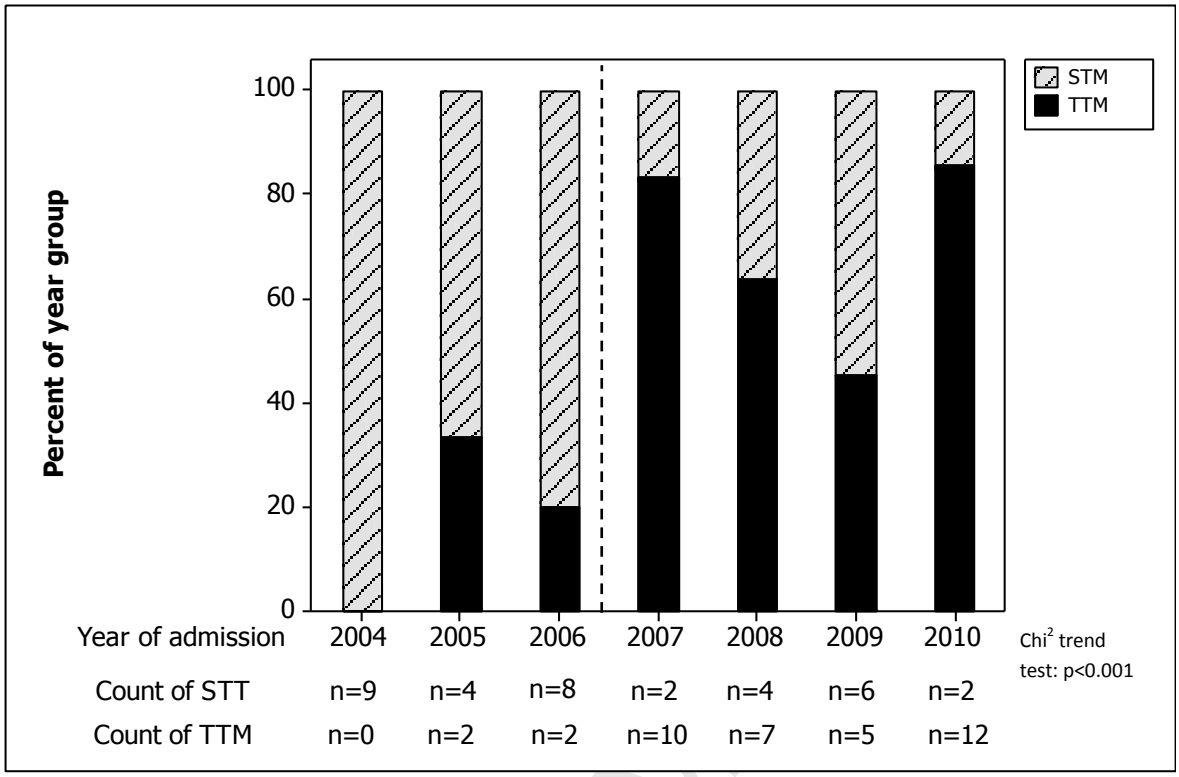
CPR denotes cardiopulmonary resuscitation. ROSC denotes return of spontaneous circulation. ED: emergency department, PICU Paediatric intensive care unit. [a]First recorded rhythm after cardiac arrest. VF: ventricular fibrillation, VT: ventricular tachycardia, PEA: pulseless electrical activity. Unavailable (missing) values were excluded from calculations of summary statistics. Data was missing for location (7), witnessed status (4), Bystander (4), presenting electrical rhythm (7), Defibrillation attempt (6), Epinephrine dose (4), duration from cardiac arrest (5), ROSC prior to Ed admission (4), Time from ED admission (4), time duration ROSC to PICU (5). Results expressed as Median (Inter-quartile range) or number (percent). Chi^2 test or Fishers exact test was used for categorical variable. [b] median value rounded up to nearest whole value. [c] Only patients receiving CPR at ED admission were included in calculation, Fishers exact test was used for categorical variable and Mann Whitney U test for continuous variables. ** p value < 0.05 comparing treatment groups

508 Table 3 Survival outcomes in relationship to treatment groups

	Total Group n =73	TTM n=38	STM n = 35	*p*
Outcome				
Survival to PICU discharge	22 (30%)	14 (37%)	8 (23%)	0.19
Survival to Hospital discharge	21 (29%)	13 (34%)	8 (23%)	0.28
PICU Length of stay (LOS) (days)	3.1 (1.3-6.6)	4.1 (3.0-6.8)	1.3 (0.5-6.7)	<0.001
PICU LOS for survivors (days)	6.5 (2.9-7.6)	6.2 (3.0-7.8)	6.7 (0.9-8.1)	0.81
PICU LOS for non-survivors (days)	2.4 (0.8-4.7)	4.1 (2.6-5.2)	1.2 (0.4-2.4)	<0.001
Withdrawal of intensive care support (proportion of patients who died in PICU [n=51])	46 (90%)	24 (100%)	22 (81%)	0.31
Fulfilled brain death criteria (proportion of patients who died in PICU [n=51])	9 (18)	5 (21%)	4 (15%)	0.73

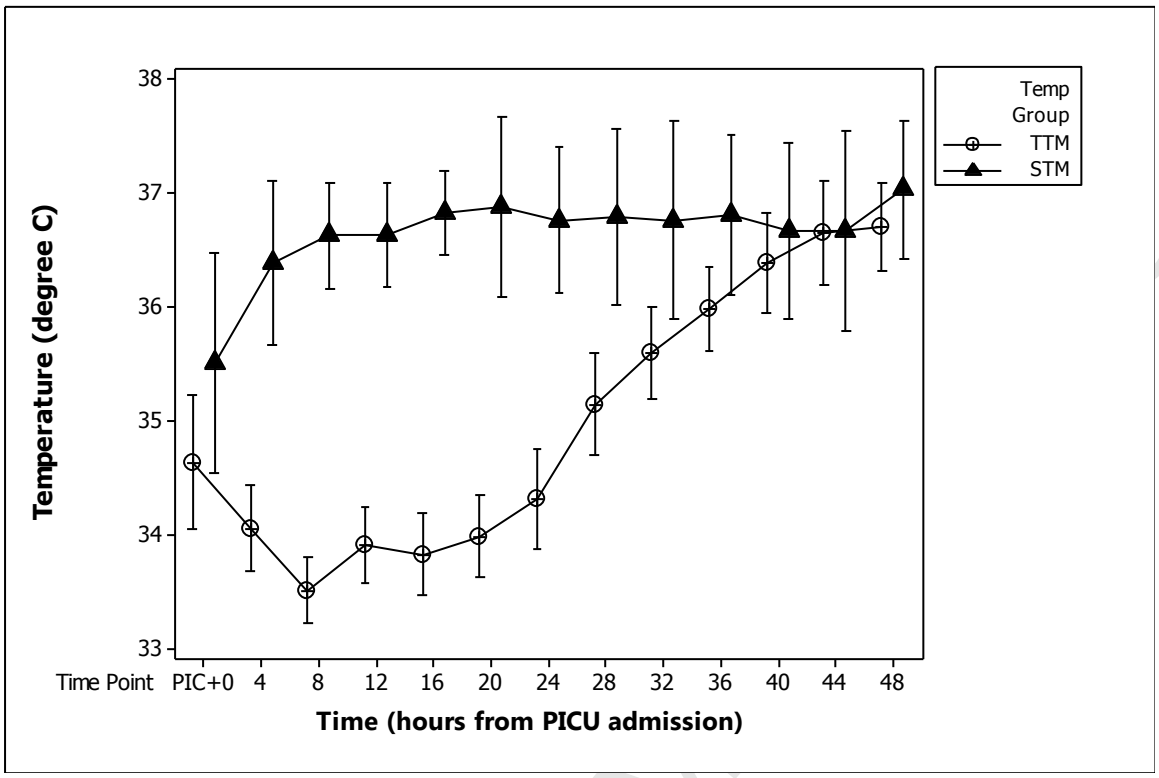
509 Results expressed as Median (Inter-quartile range) or number (percent). LOS: length of stay. Fisher's exact test
510 was used for categorical variable and Mann Whitney U test for continuous variables.
511
512
513

Figure 1 Percentage of patients receiving targeted temperature management (TTM) and standard temperature management (STM)



Dashed line indicates first publication date of ILCOR guidelines for paediatric TTM use: Published on-line April 17th 2006 - "Induction of hypothermia (32 to 34°C) for 12 to 24 hours should be considered in children who remain comatose after resuscitation from cardiac arrest." (37)

Figure 2 Temperature profiles of patients receiving targeted temperature management and standard temperature management.



Mean temperature (with 95% confidence intervals for the mean). TTM: targeted temperature management (32-34°C). STM: Standard temperature management (<38°C).