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Clinical paper

Comparative before-after study of fever prevention versus targeted temperature management following out-of-hospital cardiac arrest

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Abstract

Background: International guidelines for neuroprotection following out-of-hospital cardiac arrest (OHCA) recommend fever prevention ahead of routine temperature management. This study aimed to identify any effect of changing from targeted temperature management to fever prevention on neurological outcome following OHCA.

Methods: A retrospective observational cohort study was conducted of consecutive admissions to an ICU at a tertiary OHCA centre. Comparison was made between a period of protocolised targeted temperature management (TTM) to 36 °C and a period of fever prevention.

Results: Data were available for 183 patients. Active temperature management was administered in 86/118 (72%) of the TTM cohort and 20/65 (31%) of the fever prevention group. The median highest temperature prior to the start of temperature management was significantly lower in the TTM group at 35.6 (IQR 34.9–36.2) compared to 37.9 °C (IQR 37.7–38.2) in the fever prevention group (adjusted $p < 0.001$).

There was no difference in the proportion of patients discharged with Cerebral Performance Category 1 or 2 between the groups (42% vs. 40%, $p = 0.88$). Patients in the fever prevention group required a reduced duration of noradrenaline (36 vs. 46 h, $p = 0.03$) and a trend towards a reduced duration of propofol (37 vs. 56 h, $p = 0.06$).

In unadjusted analysis, use of active temperature management (irrespective of group) appeared to be associated with decreased risk of poor outcome (OR = 0.43, 95% CI 0.23–0.78) but after adjustment for patient age, presenting rhythm, witnessed arrest and duration of CPR, this was no longer significant (OR = 0.93, 95% CI 0.37–2.31, $p = 0.88$).

Conclusion: Switching from TTM to fever prevention following OHCA was associated with similar rates of neurological outcomes, with a possible decrease in sedation and vasopressor requirements.

Keywords: Out-of-Hospital Cardiac Arrest, Targeted temperature management, Therapeutic Hypothermia, Neuroprognostication

Introduction

Temperature manipulation in early survivors of out of hospital cardiac arrest (OHCA) has been widely studied over the last two decades, supported by the clinical observation that fever is associated with worse neurological outcomes after cardiac arrest.[1] Randomised controlled trials (RCTs) have evaluated the effect of varying degrees of induced hypothermia on either survival[2,3] or survival with good neurological function.[4–8] The most recently published of these, the multicentre Targeted Temperature Management 2 trial (TTM2) compared targeted hypothermia at 33 °C to maintenance of normothermia in the first 72 h post cardiac arrest but did not demonstrate a survival benefit or improvement in neurological function after a period of targeted hypothermia.[3]

In response to successive trial data, international guidelines and clinical practice have evolved through an era of targeted hypothermia and stringent temperature control[9] to the current more permissive strategy of fever prevention – tolerating temperatures up to 37.7C in the first 72 h after cardiac arrest.[10] The current European Resuscitation Council guidelines are supported by a meta-analysis of the various trials evaluating TTM strategies, which concluded that

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targeted hypothermia does not reduce mortality or improve favourable neurological outcome when compared to normothermia.[11]

Following the publication of the TTM2 trial the Intensive Care Units (ICU) at our centre switched from a protocol of routine targeted temperature management after OHCA to a fever prevention strategy, focused on maintaining core temperature at or below 37.7C.

The aim of this study was to compare neurological outcome, duration of sedation and vasopressors, and prevalence of hypo- and hyperthermia in OHCA patients before and after transition to fever prevention at our centre.

Methods

A retrospective cohort study was conducted of all consecutive admissions to the ICUs at Barts Heart Centre, a large urban teaching hospital, following out of hospital cardiac arrest during the study periods 1st January to 31st December 2019 (TTM period) and 1st November to 31st July 2022 (fever prevention period).

The study was registered as a local service evaluation as defined by the National Institutes of Health Research and as such ethical approval was not required.

Clinical and temperature management

In our system, emergency medical services (EMS) directly transport all resuscitated patients with OHCA and suspected cardiac cause (ST segment elevation on ECG after return of spontaneous circulation, initial rhythm of ventricular fibrillation or ventricular tachycardia, or clinical suspicion) to the Heart Attack Centre. In keeping with international guidelines, patients are acutely transferred to the catheterisation laboratory if there are electrocardiographic criteria of occlusive myocardial infarction, cardiogenic shock or refractory arrhythmia. Standard post-OHCA care included neuroprotective ventilation and mean arterial pressure targets. Sedation to a Richmond agitation sedation scale of −4 or less was administered during the period of protocolised temperature management, with choice of sedative at the discretion of the treating clinician.

During the study periods, where indicated, targeted temperature management was delivered with the Arctic Sun ® 5000 (Franklin, NJ, USA) cooling device. Prior to 2021 ('TTM period'), the protocol used routine temperature management to 36 °C for the first 24h post admission, with temperature maintained <37.5 °C for a further 48 h. After 2021 ('fever prevention period'), unit protocols permitted cooling only for prevention of fever – defined as temp > 37.8 °C – within the first 72 h of admission. Device based cooling was only instituted if and when core temperature reached the protocolised thresholds for initiation. The cohort of patients who remained hypo- or normo-thermic during the protocolised periods did not receive device-based cooling. Paracetamol 1 g every 6 h was prescribed routinely unless there was a contra-indication and initial passive cooling was permitted in the fever prevention cohort.

Data collection and statistical analysis

Patients were included if the admission diagnosis was "out of hospital cardiac arrest" as per the Intensive Care National Audit and Research Consortium (ICNARC) case mix programme dataset. Patient characteristics, circumstances of cardiac arrest and pre-hospital management were collected according to the Utstein template.[12] ICU data were extracted from the electronic patient record, ICU paper charts and EMS documentation within the patient's paper notes. Results are reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[13]

Outcome

The primary outcome was the Glasgow-Pittsburgh Cerebral Performance Category (CPC) at discharge from hospital. A good outcome was considered CPC 1 or 2 at hospital discharge. Secondary outcomes included ICU length of stay, duration of mechanical ventilation, prevalence of fever (time spent >37.7 °C), prevalence of hypothermia (time spent <35.0 °C), hours of sedation and hours of vasopressor use.

Statistical analysis

All statistical analysis was undertaken using R version 4.2.2. (R Foundation for Statistical Computing, Vienna, Austria). There was no imputation of missing data. Dichotomous outcomes were assessed using chi-squared test and continuous outcomes assessed with Kruskal-Wallis test or Wilcoxon rank-sum test as appropriate. In the primary analysis, p values were adjusted for multiple comparisons using the Holm-Bonferroni correction. Adjustment for confounding was performed with multivariable logistic regression using an a priori parsimonious model consisting of known predictors of neurological outcome following out-of-hospital cardiac arrest (age, presenting rhythm, presence of witnessed cardiac arrest, and duration of CPR).

All code used for analysis can be made available upon request to the corresponding author.

Results

A total of 183 patients were included: 118 during the targeted temperature management (TTM) period and 65 during the fever prevention (FP) period. In the cohort as a whole, the median age was 60 years (IQR 48–71) and the median pre-morbid Rockwood frailty score was 3 (IQR 2–4).

The majority of patients (n = 140, 76%) received bystander CPR; 17% (n = 31) had a public access defibrillator applied and 14% (n = 26) received bystander defibrillation prior to EMS arrival. The median duration of CPR was 20 minutes (IQR 13–33). At arrival to hospital, median lactate was 4.3 $\mu mol.L^{-1}$ (IQR 2.3–7.3) and median pH was 7.21 (IQR 7.10–7.29). Three-quarters of patients (n = 136, 74%) had no motor response to stimulation on arrival.

There were no significant differences in baseline characteristics between the two cohorts (Table 1); there was a non-statistically significant decrease in the proportion of patients presenting with an initial shockable rhythm in the fever prevention period (73% vs. 81%) and a corresponding decrease in the proportion of patients with an initial rhythm of asystole (5% vs 8%, unadjusted p value for initial rhythm = 0.053). Characteristics of patients with and without fever in the FP period are outlined in Table S1.

Use of targeted temperature management

Temperature measurements were available for 148 patients (n = 99 from TTM period, n = 49 from fever prevention period), Fig. 1. The median patient temperature in the first 24 h was lower in the TTM period at 36.0 (35.7–36.0) °C compared with the fever prevention period (36.4 (35.5–36.9) °C, adjusted p = 0.009), but not across the first 72 h of admission (TTM period = 36.4 °C (36.1–36.7) vs.

Table 1 – Characteristics of 183 patients admitted to intensive care with out-of-hospital cardiac arrest during study period.

	TTM period n = 118	Fever prevention period n = 65	p
Age	59.5 (49.3–71.0)	61.0 (45.0–69.0)	0.38
Sex			
Male	92 (78%)	52 (79%)	1.00
Female	26 (22%)	13 (21%)	
Ethnicity			0.36
White	58 (49%)	36 (55%)	
Black	6 (5%)	4 (6%)	
Asian	22 (19%)	14 (22%)	
Other/Unknown	34 (29%)	11 (17%)	
Pre-arrest Rockwood frailty score	3 (2–4)	3 (2–3)	0.95
Initial rhythm			0.073
VF/VT	95 (81%)	47 (72%)	
PEA	13 (11%)	15 (23%)	
Asystole	10 (8%)	3 (5%)	
Bystander CPR	86 (73%)	54 (83%)	0.28
Bystander defibrillation	13 (11%)	13 (20%)	0.30
Total down time (minutes)	20.0 (13.5–33.0)	20.0 (12.8–31.5)	0.78
Total intra-arrest adrenaline dose (mg)	1 (0–2)	1 (0–3)	0.97
Initial lactate	4.4 (2.7–7.7)	3.8 (1.9–7.2)	0.12
Initial pH	7.21 (7.12–7.29)	7.22 (7.09–7.29)	0.96
Initial motor response			0.72
1	87 (76%)	48 (74%)	
2	2 (2%)	3 (5%)	
3	6 (5%)	6 (9%)	
4	6 (5%)	2 (3%)	
5	8 (7%)	4 (6%)	
6	5 (4%)	2 (3%)	

TTM = targeted temperature management; VF = ventricular fibrillation; VT = ventricular tachycardia; PEA = pulseless electrical activity; CPR = cardiopulmonary resuscitation

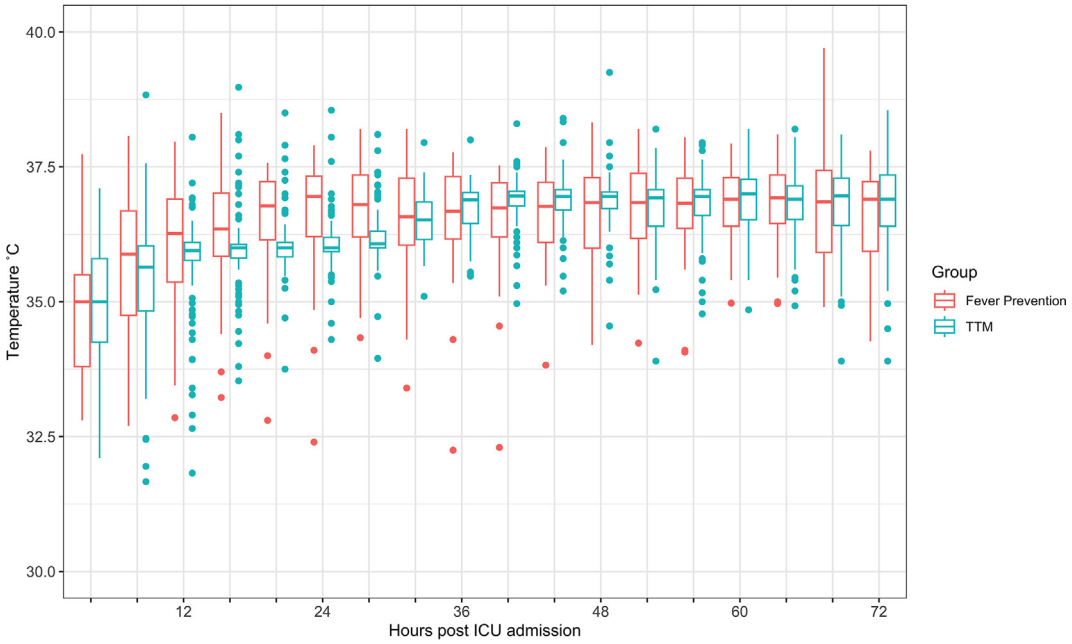

Fig. 1 – Distribution of post-admission temperature in the first 72 h post ICU admission from 148 patients admitted to ICU after out-of-hospital cardiac arrest. Summary of mean temperature over 4 hour periods post-ICU admission. FP = Fever Prevention; TTM = Targeted Temperature Management.

fever prevention period = 36.6 °C (35.7–37.1), p = 0.12). Fever (defined as temperature >37.7 °C) occurred in 45% of patients in the TTM group (45/99) and 49% of patients in the fever prevention group (24/49), p = 0.73. Hypothermia (defined as temperature <35.0 °C) occurred in the majority of patients: 66% of the TTM group (64/99) and 80% (39/49) of the fever prevention group, p = 0.09.

Table 2 reports temperature management utilisation, sedation and vasopressor use and neurological outcomes between groups. Active temperature management was used in 86/118 patients (72%) in the TTM group for a median of 49 h and 20/65 (31%) of the fever prevention group for a median of 43 h. Characteristics of the patients in the TTM period who did and did not receive a temperature control intervention are outlined in Table S2 and reasons for non-adherence to the TTM protocol are described in Supplementary Table S3. Median highest temperature recorded prior to active temperature management in the TTM group was significantly lower at 35.6 °C (IQR 34.8–36.2) compared to 37.9 °C (IQR 37.7–38.2) in the fever prevention group (adjusted p <0.001). Fig. 2 displays rolling median temperature at 4-hour intervals in patients with and without an active temperature management device in both periods; reduced temperature variability was seen in patients who received a temperature management device.

Outcomes

There was no difference in the primary outcome of neurologically intact survival to hospital discharge between the TTM and fever prevention groups. Survival to hospital discharge with Cerebral Performance Category 1 or 2 occurred in 42% (50/118) of patients in the TTM group and 40% (26/65) in the fever prevention group (p = 0.88). There was no difference between the TTM and fever prevention groups in either duration of mechanical ventilation (median 4.0 (2.0–8.0) days vs. 5.0 (2.0–10.0) days, p = 0.44) or ICU length of stay (median 4.5 (1.6–9.5) days vs. 5.8 (2.1–11.6) days, p = 0.32). These results were unchanged in sensitivity analysis including only patients who survived > 72 h (Supplemental Appendix).

Sedation and vasopressor usage

Table 3 displays total hours of vasopressor and sedation used in each group. Numerically, there were reductions in the duration of all included vasopressor and sedative agents except dexmedetomidine during the fever prevention group. However, the only one of these to reach statistical significance was reduced duration of noradrenaline in the fever prevention group (median 36 (18–57 h) vs. 46 (26–66) h in the TTM group, p = 0.03). Dexmedetomidine had increased use (12% vs 3%, p = 0.03) in the fever prevention group but no significant difference in duration.

Association between fever, TTM use and outcome

While there was no change in neurologically intact survival between patients in the TTM and fever prevention cohorts, in unadjusted analysis patients who actually received active temperature management had lower odds of poor neurological outcome (OR 0.43, 95% confidence interval (CI) 0.23–0.78, p < 0.001). A statistically higher median temperature in the first 24 h was also observed in patients with good neurological outcome (36.0 °C (IQR 36.0–36.7) than those with poor outcome (35.9 °C (IQR 35.3–36.0), OR for 1 degree rise in temperature 0.40 (95% CI 0.23–0.64, p < 0.001). Fever was present in 51% of patients with good outcome and 44% of patients with poor outcome (p = 0.50).

A multivariable logistic regression module was created to adjust the observed association between TTM use, median temperature and outcome for known predictors of neurological outcome in OHCA and is presented in Table 4. These factors include patient age, presenting rhythm of VF or VT, witnessed cardiac arrest, and duration of cardiac arrest ('downtime'). After adjustment for these confounding variables, the association between TTM use and outcome was no longer significant (adjusted OR for poor outcome = 0.93, 95% CI 0.37–2.31, p = 0.88), but the association with median temperature in the first 24 h remained (adjusted OR for poor outcome with 1 degree rise in median T° = 0.49, 95%CI 0.26–0.85, p = 0.02). Presenting rhythm of VF/VT was associated with better outcome (OR = 0.33, 95% CI 0.11–0.92, p = 0.04), and increased duration of cardiac arrest worsened outcome (OR for 1 minute increase = 1.06, 95% CI 1.03–1.09, p < 0.001).

Discussion

Our data have demonstrated the impact of abandoning strict targeted temperature management strategies in favour of fever prevention within our Intensive Care Units. Median temperatures in the first

Table 2 – Management and outcomes of 182 patients admitted to intensive care with out-of-hospital cardiac arrest during study period.

	TTM period n = 118	Fever prevention period n = 65	p
Temperature on arrival	35.0 (34.1–35.8)	34.7 (34.1–35.9)	0.92
TTM used	86 (72%)	20 (31%)	<0.001
Max T° prior to TTM	35.6 (34.9–36.2)	37.9 (37.6–38.1)	<0.001*
TTM duration (h)	49 (30–65)	43 (21–57)	0.18
Median T° first 24 h	36.0 (35.7–36.0)	36.4 (35.5–36.9)	0.009*
Median T° first 72 h	36.4 (36.0–36.7)	36.6 (35.7–37.1)	0.11
Fever (T° > 37.7)	45/99 (45%)	24/49 (49%)	0.73
Hypothermia	64/99 (65%)	39/49 (80%)	0.09
CPC at Hospital Discharge			0.88
1–2	50 (42%)	26 (40%)	
3–5	68 (58%)	39 (60%)	
Duration of mechanical ventilation (days)	4.0 (2.0–8.0)	5.0 (2.0–10.0)	0.44
ICU length of stay (days)	4.5 (1.6–9.5)	5.8 (2.1–11.6)	0.32

CPC = Glasgow-Pittsburgh Cerebral Performance Category. * = p < 0.05.

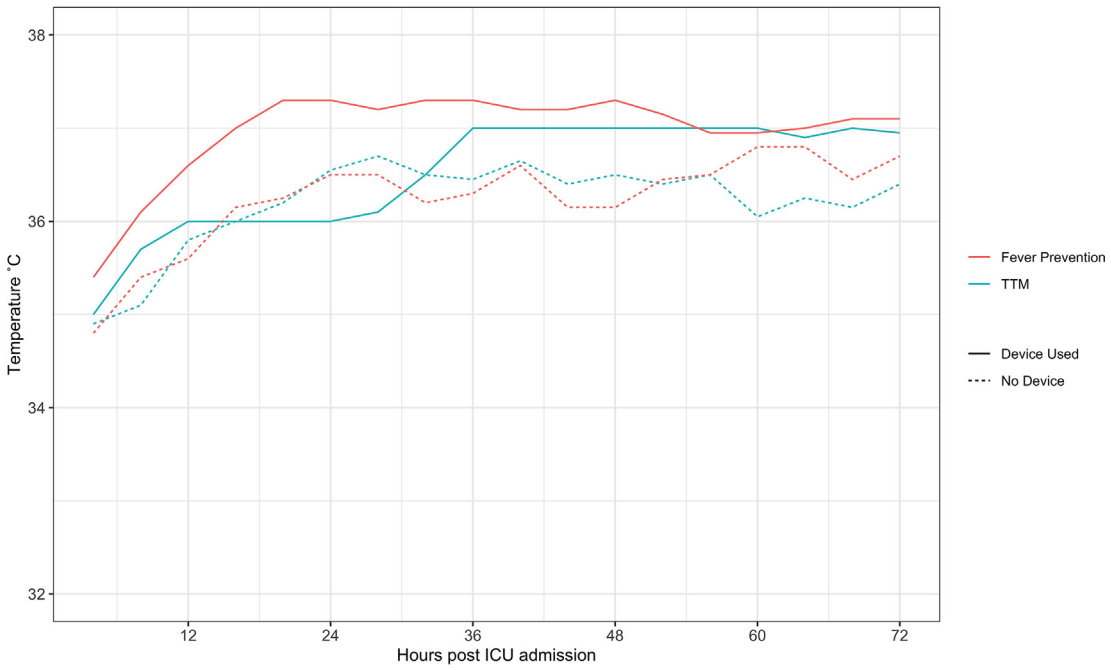

Fig. 2 – Rolling median temperature across 4-hour intervals for patients admitted to ICU post cardiac arrest stratified by temperature management protocol and actual device use.

Table 3 – Use of vasopressor and sedation by temperature management strategy in 183 patients admitted to intensive care following out-of-hospital cardiac arrest.

	TTM period n = 118	Fever prevention periodn = 65	p
Total vasopressor (h)	49 (14–82)	37 (14–69)	0.28
Adrenaline	29 (25%)	12 (18%)	0.62
Median (h)	34 (19–52)	23 (13–36)	0.18
Noradrenaline	84 (71%)	47 (72%)	1.00
Median (h)	46 (26–66)	36 (18–57)	0.03*
Vasopressin	33 (28%)	15 (23%)	0.82
Median (h)	35 (17–49)	22 (11–37)	0.17
Total sedation (h)	106 (36–138)	91 (35–132)	0.31
Propofol	96 (81%)	49 (75%)	0.45
Median (h)	52 (24–71)	37 (18–67)	0.06
Midazolam	16 (14%)	7 (10%)	0.89
Median (h)	18 (8–39)	19 (16–36)	0.59
Fentanyl	88 (75%)	45 (69%)	0.99
Median (h)	54 (32–69)	45 (23–66)	0.30
Dexmedetomidine	4 (3%)	8 (12%)	0.03*
Median (h)	7 (6–13)	17 (6–34)	0.54

* = $p < 0.05$.

24 h after ICU admission were higher during the period of fever prevention compared to the TTM era (36.4 °C vs 36.0 °C, p = 0.009), with a higher maximum temperature prior to initiating active temperature management. This reflects a real change in practice after the publication of the TTM2 trial. Nolan et al.[14] similarly observed an increase in average temperature within the first 24 h in UK Intensive Care Units when evaluating the implementation of findings from the original TTM trial, which showed that temperature control at 36 °C was equivalent to targeting 33 °C.[2] The more modest difference in our study reflects a smaller magnitude of change from controlled normothermia (TTM group) to fever prevention.

An absence of difference in our primary outcome of recovery with good neurological function, as determined by the Cerebral Performance Category score at hospital discharge, is in keeping with the body of major studies that have not shown harm from targeted temperature strategies compared to fever prevention. Importantly, premorbid function in our study assessed by the Rockwood Clinical Frailty Scale suggested that in each group most patients had good function before their cardiac arrest and, therefore, the potential to achieve a meaningful functional outcome. Multivariable analysis confirmed that the known positive prognostic factors of VF/VT cardiac arrest[15] and shorter duration of cardiac arrest[16] remained true within

Table 4 – Univariable and muultivariable logistic regression analysis for neurological outcome (CPC 1–2) at hospital discharge in 183 patients admitted to intensive care after out of hospital cardiac arrest.

	Good outcome n = 76	Poor outcome n = 107	OR for poor outcome	p
Univariable analysis				
TTM used	53 (70%)	53 (50%)	0.43 (0.23–0.78)	<0.001*
Median T° 24	36.0 (36.0–36.7)	35.9 (35.3–36.0)	0.40 (0.23–0.64)	<0.001*
Fever	33/65 (51%)	36/82 (44%)	0.76 (0.39–1.48)	0.50
Multivariable analysis				
TTM used	53 (70%)	53 (50%)	0.93 (0.37–2.31)	0.88
Median T° 24	36.0 (36.0–36.7)	35.9 (35.3–36.0)	0.49 (0.26–0.85)	0.02*
Age (years)	58 (47–65)	62 (49–72)	1.02 (0.99–1.05)	0.13
Rhythm = VF/VT	68 (89%)	74 (69%)	0.33 (0.11–0.92)	0.04*
Downtime (mins)	15 (9–23)	28 (16–41)	1.06 (1.03–1.09)	<0.001*
Witnessed arrest	65 (86%)	83 (76%)	0.45 (0.15–1.26)	0.13

CPC = Glasgow-Pittsburgh Cerebral Performance Category. VF = ventricular fibrillation. VT = ventricular tachycardia. * = $p < 0.05$.

our study population. We find it reassuring that in the absence of any other major changes in post-resuscitation care that our outcomes have remained comparable between the two study periods and take this to demonstrate consistent practice within our centre.

Despite the reduction in the use of active temperature management from 70% to 30% between the two periods in our study, the proportion of patients with fever in each group remained the same. This may suggest that any beneficial effect of temperature management to 36 °C is also seen with effective fever prevention. That said, we did not observe any association between fever and outcome in this study, even after sensitivity analysis which excluded patients who died within 72 h of admission (and therefore had less time to experience fever).

Whilst in the earlier TTM group there was a clear protocol for temperature control within the first 72 h of Intensive Care admission the fever prevention strategy is less prescriptive. Although temperature control is commenced at a threshold of 37.8 °C, the decision to discontinue the therapy within the first 72 h is at clinician discretion and influenced by timing of clinical assessments and decision-making practices, often confined to a twice daily ward round. Furthermore, current guidelines advocate avoidance of fever for *at least 72* h and do not stipulate a precise end point.[10] However, more recent evidence from a sub study of the BOX trial – published after the most recent European guidelines – suggests no difference in neurological outcome whether fever prevention is continued to 36 or 72 h post cardiac arrest, albeit after an initial 24 h of targeted temperature management at 36 °C.[17]

Targeted temperature management has traditionally been used with deep sedation as part of a 'neuroprotective' strategy and in part to allow neuromuscular blockade for shivering control.[18] The TTM2 trial maintained a similar depth and duration of sedation for both intervention arms[3]; one potential benefit of a switch to fever prevention outside a controlled clinical trial could be a reduction in the duration of sedation and therefore sedation-associated vasopressor requirement. Whilst we found that the duration of sedative use between TTM and fever prevention groups did not meet statistical difference for any of propofol, fentanyl or midazolam, in this retrospective study the total cumulative doses of sedative agents are unknown and it is possible that these may have differed.

Our finding that noradrenaline use was reduced in the fever prevention group may be explained by a shorter duration of propofol sedation (though this did not reach statistical significance), but other explanations include a difference in the post-cardiac arrest syndrome between the two groups[19] and greater vasodilation in patients receiving targeted temperature management. Data on mean arterial pressure were not collected in this study, but there was no change in clinical procedures regarding blood pressure targets during the time periods included in this study. Further, it is conceivable that differences in the actual temperature management delivered with accompanying differences in sedation dosing may have contributed to a difference in vasopressor use between these two groups.

In summary, these data suggest that in a real-world setting, a move to a fever prevention strategy was not associated with a significant change in neurological outcomes or length of ICU stay. Similar results have been observed from a single centre before-after study in Finland,[20] and a large Australian OHCA cohort, in which patients ineligible for the TTM2 trial demonstrated similar or better neurological outcomes when treated with fever prevention compared to therapeutic hypothermia.[21] More broadly, a recent systematic review of fever therapy in febrile adults found insufficient evidence to confirm or refute any benefit in quality of life.[22] These results do not, however, exclude the potential benefit of hypothermia in subgroups such as patients with non-shockable rhythms and those with cardiogenic shock.[8,23]

Limitations

The study had several limitations. As with any before-after analysis, any effect of other changes in practice during the studied time period may have confounded the results. Although we controlled for known predictive factors of neurological outcome in the multivariable analysis, there may have been other differences in the patient populations which affected the results. Fever may have acted as a competing risk in this study, given the number of patients who died prior to 72 h (and therefore had less time to experience fever); however, the sensitivity analysis excluding these patients demonstrated virtually identical results.

We also were unable to collect data on the exact set point of temperature management applied, or the doses of sedation and vasopressor administered. Temperature data were absent in 35/183 patients (19%); owing to the hybrid nature of documentation in our unit (paper and electronic notes), there were also missing data relating to sedation and vasopressor use. 10% of patients did not receive

TTM when indicated due to a protocol violation reflecting the challenges of rigorous protocol institution outside of a clinical trial.

Conclusion

In a single-centre before-after comparison, a switch from targeted temperature management at 36 °C to fever prevention in patients admitted to intensive care after OHCA had no effect on neurological outcomes. A reduction in vasopressor requirement and possible reduction in sedation duration was seen in the fever prevention group. The impact of device-based fever prevention on neurological outcomes in OHCA is being formally assessed in the STEPCARE trial (NCT05564754).

CRediT authorship contribution statement

P. Leadbeater: Writing – original draft, Data curation. **A. Warren:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **E. Adekunle:** Writing – review & editing, Investigation, Data curation. **H. Fielden:** Writing – review & editing, Investigation, Data curation. **J. Barry:** Writing – review & editing, Resources, Project administration, Data curation, Conceptualization. **A.G. Proudfoot:** Conceptualization, Project administration, Data curation, Writing – review and editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [AP is funded by a Medical Research Council Clinical Academic Research Partnership Award (Ref:MR/W03011X/1) and the Barts Charity. All other authors declare no conflict of interest.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resplu.2023.100538.

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REFERENCES

1. Zeiner A, Holzer M, Sterz F, et al. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Arch Intern Med. 2001;161:2007.
2. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013;369:2197–206.
3. Dankiewicz J, Cronberg T, Lilja G, et al. Hypothermia versus normothermia after out-of-hospital cardiac arrest. N Engl J Med. 2021;384:2283–94.
4. Hypothermia after Cardiac Arrest Study Group. Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest. N Engl J Med. 2002;346:549–56.
5. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.
6. Lilja G, Nielsen N, Friberg H, et al. Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C. Circulation 2015;131:1340–9.
7. Kirkegaard H, Søreide E, de Haas I, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA 2017;318:341–50.
8. Lascarrou JB, Merdji H, Le Gouge A, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019;381:2327–37.
9. Donnino MW, Andersen LW, Berg KM, et al. Temperature management after cardiac arrest. Resuscitation 2016;98:97–104.
10. Sandroni C, Nolan JP, Andersen LW, et al. ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med 2022;48:261–9.
11. Granfeldt A, Holmberg MJ, Nolan JP, Soar J, Andersen LW. Targeted temperature management in adult cardiac arrest: Systematic review and meta-analysis. Resuscitation 2021;167:160–72.
12. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: A Statement for Healthcare Professionals From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 2015;132:1286–300.
13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9.
14. Nolan JP, Orzechowska I, Harrison DA, Soar J, Perkins GD, Shankar-Hari M. Changes in temperature management and outcome after out-of-hospital cardiac arrest in United Kingdom intensive care units following publication of the targeted temperature management trial. Resuscitation. 2021;162:304–11.
15. Nichol G, Thomas E, Callaway CW, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31.
16. Goto Y, Funada A, Goto Y. Relationship between the duration of cardiopulmonary resuscitation and favorable neurological outcomes

after out-of-hospital cardiac arrest: a prospective, nationwide, population-based cohort study. J Am Heart Assoc. 2016;5 e002819.
17. Hassager C, Schmidt H, Møller JE, et al. Duration of device-based fever prevention after cardiac arrest. N Engl J Med. 2023;388:888–97.
18. Paul M, Bougouin W, Dumas F, et al. Comparison of two sedation regimens during targeted temperature management after cardiac arrest. Resuscitation 2018;128:204–10.
19. Neumar RW, Nolan JP, Adrie C, et al. Post-Cardiac Arrest Syndrome: Epidemiology, Pathophysiology, Treatment, and Prognostication A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118:2452–83.
20. Tirkkonen J, Skrifvars MB. Change of target temperature from 36 °C to strict fever avoidance only in comatose cardiac arrest survivors – A before and after study. Resuscitation 2023;188 109796.
21. Bray J, Smith K, Stub D, Cameron P, Finn J, Bernard S. OR22 Temperature control in clinical trials versus the real world: application of the TTM2 trial criteria. Resuscitation 2022;175:S22–3.
22. Holgersson J, Ceric A, Sethi N, Nielsen N, Jakobsen JC. Fever therapy in febrile adults: systematic review with meta-analyses and trial sequential analyses. BMJ 2022;12 e069620.
23. Levy B, Girerd N, Amour J, Besnier E, Nesseler N, Helms J, et al. Effect of Moderate Hypothermia vs Normothermia on 30-Day mortality in patients with cardiogenic shock receiving venoarterial extracorporeal membrane oxygenation: a randomized clinical trial. JAMA. 2022;327:442–53.