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Clinical paper

Changing target temperature from 33 °C to 36 °C in the ICU management of out-of-hospital cardiac arrest: A before and after study☆

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ABSTRACT

Introduction: In December 2013, our institution changed the target temperature management (TTM) for the first 24 h in ventricular fibrillation out-of-hospital cardiac arrest (VF-OHCA) patients from 33 °C to 36 °C. This study aimed to examine the impact this change had on measured temperatures and patient outcomes.
Methods: We conducted a retrospective cohort study of consecutive VF-OHCA patients admitted to a tertiary referral hospital in Melbourne (Australia) between January 2013 and August 2015. Outcomes were adjusted for age and duration of cardiac arrest.
Results: Over the 30-month period, 76 VF-OHCA cases were admitted (24 before and 52 after the TTM change). Patient demographics, cardiac arrest features and hospital interventions were similar between the two periods. After the TTM change, less patients received active cooling (100% vs. 70%, $p < 0.001$), patients spent less time at target temperature (87% vs. 50%, $p < 0.001$), and fever rates increased (0% vs. 19%, $p = 0.03$). During the 36 °C period, there was a decrease in the proportion of patients who were discharged: alive (71% vs. 58%, $p = 0.31$), home (58% vs. 40%, $p = 0.08$); and, with a favourable neurological outcome (cerebral performance category score 1-2: 71% vs. 56%, $p = 0.22$).
Conclusion: After the change from a TTM target of 33 °C to 36 °C, we report low compliance with target temperature, higher rates of fever, and a trend towards clinical worsening in patient outcomes. Hospitals adopting a 36 °C target temperature to need to be aware that this target may not be easy to achieve, and requires adequate sedation and muscle-relaxant to avoid fever.

Introduction

Since the publication of two seminal studies[1,2] over a decade ago, therapeutic hypothermia (32 °C–34 °C) for at least 24 h has been recommended in the post-resuscitation care for comatose survivors of cardiac arrest.[3,4] More recently, the recommended targeted temperature for this treatment was expanded from a range of 32–34 °C to 32–36 °C[5,6] following results from the targeted temperature management (TTM) trial.[7] The TTM trial allocated patients to either 32–34 °C or 36 °C, and found no difference in outcomes.

Following publication of the TTM trial, many centres have adopted a target temperature of 36 °C.[8–10] However, achieving a target temperature of 36 °C may be problematic, with a recent study reporting a significant risk of fever in the first 24 h of ICU admission.[11]

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In December 2013, the intensive care unit (ICU) at The Alfred Hospital changed the post-resuscitation target temperature for ventricular fibrillation out-of-hospital cardiac arrest (VF-OHCA) patients from 33 °C to 36 °C. This paper presents the findings of a retrospective cohort study of patients admitted before and after this change which examined compliance with the targeted temperature and patient outcomes.

Methods

Setting

This study was performed on consecutive, non-traumatic, VF-OHCA patients admitted to The Alfred Hospital ICU (Melbourne, Australia) between January 2013 and August 2015. The Alfred Hospital is a quaternary referral hospital in Melbourne, Australia, with cardiac services including interventional cardiology, extra-corporeal membrane oxygenation (ECMO) and cardiac transplantation.[12] This study was approved by The Alfred Hospital Human Research and Ethics Committee.

Ambulance response to OHCA patients in our region is delivered by a single emergency medical service, Ambulance Victoria. Treatment protocols follow the Australian and New Zealand Council on Resuscitation Guidelines (Available from: www.resusc.org.au). At the time of this study two prehospital OHCA trials were enrolling patients. The RINSE trial[13] tested therapeutic hyperthermia during OHCA and the CHEER trial[14] tested E-CPR and ECMO in patients with refractory VF. The RINSE trial included pre-hospital cooling using a bolus of intravenous saline and concluded in December 2014.[13]

TTM practice

In September 2012, The Alfred Hospital introduced a written guideline for the acute post-arrest care of the unconscious VF-OHCA patient. The guideline was available for all staff on the hospital intranet. In addition to oxygen, carbon dioxide and blood pressure targets, the guideline includes orders for temperature management.

Between September 2012 and October 2013, temperature management included sedation and neuromuscular paralysis, a 30 mL/kg bolus of intravenous ice-cold saline (if not already done by ambulance) and surface cooling using a water blanket around the torso (Meditherm3) aiming for a target temperature of 33 °C.

In November 2013, the target temperature was changed to 36 °C for 24 h, followed by 37 °C for a further 12 h, and then <37.5 °C until 72 h as per the TTM trial.[7] The guideline ordered initial cooling of patients with a core temperature >36 °C with administration of a long acting non-depolarising muscle relaxant, a 20 mL/kg bolus of intravenous ice-cold saline (if not already done by ambulance) and a cooling vest set to 36 °C with the rate of cooling set to the "rapid" setting. If cooling was not achieved, the addition of a cooling mat under the patient was recommended. If the temperature exceeded 36 °C in the first 24 h, despite surface cooling, the guideline ordered an intravenous infusion of a non-depolarising neuromuscular blocking drug.

Temperatures after hospital admission were measured by bladder temperature catheter. All other care in the post-arrest guideline remained unchanged over the study period. For patients who remained comatose, the protocol recommended prognostication be deferred until at least 108 h post-arrest.

Data collection and analysis

Patients were identified and prehospital data obtained from the Victorian Ambulance Cardiac Arrest Registry (VACAR).[15] Hospital data were obtained from auditing individual patient medical records using predefined, standardised definitions and data extraction points, undertaken by several of the investigators (JEB, JB, LS). Data collected included hourly patient temperature as documented for the first 36 h of ICU stay. In witnessed arrests, the duration of arrest was considered the time from collapse to ROSC or commencement of ECMO. In unwitnessed arrests, the duration of arrest was considered the time of emergency call to ROSC or commencement of ECMO. We calculated the number of temperatures recorded and the proportion of temperatures at or below target across the first 24 h. Patient who died or were discharged from ICU in the first 24 h were included. Cerebral performance category (CPC) scores[16] were assessed retrospectively by two investigators independently (JEB, JB).

Patient characteristics, treatment and outcomes were described using percentages, means and standard deviation (SD), or median and interquartile range (IQR) as appropriate; and were compared between the 33 °C and the 36 °C TTM period using Student's t-tests, Mann–Whitney U test and Fisher's exact test. Statistical comparisons of patient outcomes were adjusted for duration of arrest (downtime, minutes) and age (years) using logistic regression.[12] A two-sided p-value <0.05 was considered statistically significant.

Results

Over the study period, 76 VF-OHCA cases were admitted to the ICU (24 before and 52 after the TTM change). Patient demographics and cardiac arrest features were similar between the two periods (Table 1). The overall median time from cardiac arrest to return of spontaneous circulation (ROSC) was similar between the two periods (20 vs. 22 min, p = 0.98).

A similar number of patients underwent urgent cardiac catheterisation, but there were more patients treated with veno-arterial ECMO in the 33 °C period (29% vs. 14%, p = 0.12) (Table 2). ECMO was commenced intra-arrest in 9 patients and in the acute post-arrest phase for 5 patients.

More patients admitted in the 33 °C period received prehospital cooling (42% vs. 10%, p = 0.004), and on average they were slightly cooler on arrival at hospital (34.5 °C vs. 35.3 °C, p = 0.06). Active cooling was more likely to be commenced in the ED during the 33 °C period (65% vs. 2%, p < 0.001). In the 36 °C period, one extremely hypothermic patient (admission temperature 28.8 °C) and one mildly hypothermic patient (admission temperature 35.2 °C) were actively rewarmed to 36 °C in the ED.

On arrival to ICU, documented medical orders for TTM were absent in three patients in the 36 °C period (100% in the 33 °C period). All patients in the 33 °C period received active cooling

Table 1
Comparison of demographics, arrest characteristics of OHCA patients admitted to ICU for the 33 °C and 36 °C TTM periods.

	33 °C N = 24	36 °C N = 52	p-Value
Age (years), mean (SD)	59 (18)	57 (15)	0.62
Males, n (%)	20 (83)	47 (90)	0.45
Independent, n (%)	24 (100)	52 (100)	–
Arrest at home, n (%)	4 (16)	17 (32)	0.18
Unwitnessed, n (%)	3 (12)	5 (10)	0.70
Bystander witnessed, n (%)	19 (79)	47 (90)	0.45
EMS witnessed, n (%)	2 (8)	0 (0)	0.10
Bystander CPR[a], n (%)	18 (86)	48 (92)	0.54
Bystander AED, n (%)	2 (8)	7 (14)	0.71
Duration of arrest (min), median (IQR)	20 (14–30)	22 (15–45)	0.93
STEMI, n (%)	7 (29)	15 (33)	0.99

EMS: emergency medical services; CPR: cardiopulmonary resuscitation; STEMI: ST-elevation myocardial infarction.

[a] Proportion of non-EMS witnessed.

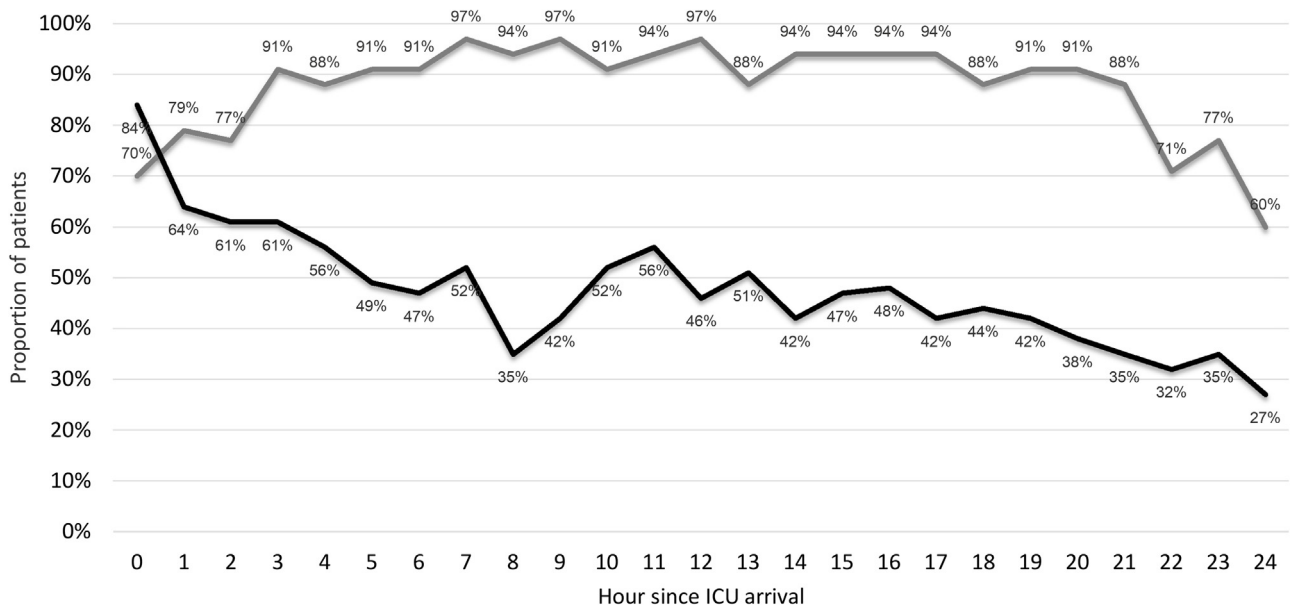

Fig. 1. The proportion of patients at target temperature for each hour of the first day of intensive care stay by the 33 °C (grey line) and 36 °C (black line) TTM periods.

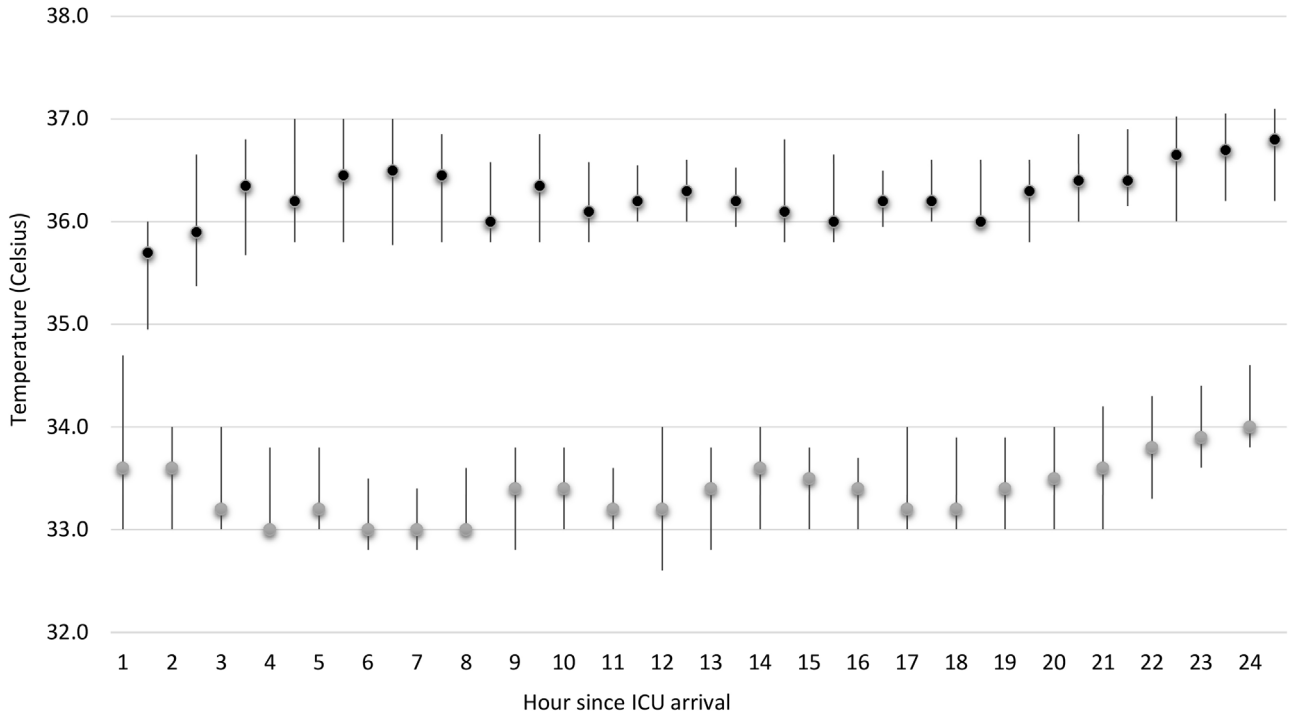

Fig. 2. The hourly median and interquartile range of temperatures over the first 24 h for the 33 °C (grey dots) and 36 °C (black dots) TTM periods.

in the ICU compared to 70% in the 36 °C period ($p < 0.001$). There was no difference in the average number of temperatures recorded between the two periods (23 vs. 22, $p = 0.13$).

Patients in the 36 °C period spent significantly less time at or below target temperature (87% vs. 50%, $p < 0.001$) (Table 2 and Fig. 1), with the majority exceeding 36 °C in each hour across the first 24 h (Fig. 2). Patients in the 36 °C period were also more likely have at least one one temperature recording ≥38.0 °C in the first 24 h (0% vs. 19%, $p = 0.03$) and 36 h following admission (8% vs. 31%, $p = 0.04$). We also found that patients admitted in the 36 °C period were less likely to receive a bolus dose of a neuromuscular blocking agent (83% vs. 64%, $p = 0.08$), and no patients in either period received this via an infusion. There was also a change in the types of sedation used between the two periods (Table 2), and on average patients in the 36 °C period had shorter durations of sedation and were more likely to have sedation ceased within the first 24 h of ICU admission (25% vs. 50%, $p = 0.002$). On average, patients in the 36 °C period were extubated almost a day earlier than those admitted in the 33 °C period (3.7 days vs. 2.4 days, $p = 0.07$). More patients in the 33 °C period experienced shivering, bleeding requiring transfusions and pneumonia.

Following the change to a target temperature of 36 °C, there was a nonsignificant trend towards a decrease in the proportion of patients who survived (71% vs. 58%, $p = 0.31$), were discharged home (82% vs. 73%, $p = 0.08$) and were discharged with a favourable

Table 2
Comparison of treatments and complications of OHCA patients admitted to ICU for the 33 °C and 36 °C TTM periods.

	33 °C N = 24	36 °C N = 52	p-Value
Angiogram, n (%)	19 (79)	42 (81)	0.99
ECMO, n (%)	7 (29)	7 (14)	0.12
Sedation ceased first 24 h, n (%)	6 (25)	26 (50)	0.002
Remifentanil, n (%)	0 (0)	33 (64)	<0.001
Propofol, n (%)	5 (21)	41 (79)	<0.001
Morphine, n (%)	21 (88)	18 (35)	<0.001
Midazolam, n (%)	21 (88)	19 (37)	<0.001
Paralysing agent bolus, n (%)	20 (83)	33 (64)	0.08
Paralysing agent infusion, n (%)	0 (0)	0 (0)	–
Number of temperature recordings first 24 h[a], mean (SD)	23 (0)	22 (2)	0.13
Active cooling prehospital, n (%)	10 (42)	5 (10)	0.004
Active cooling in ED, n (5)	11 (46)	1 (2)	<0.001
Active cooling in ICU, n (%)	24 (100)	40 (77)	0.01
Shivering, n (%)	18 (75)	8 (16)	<0.001
Bleeding requiring transfusion, n (%)	3 (13)	1 (2)	0.09
Pneumonia, n (%)	12 (50)	12 (23)	0.03
Day extubated[b], mean (SD)	3.7 (2.7)	2.4 (2.1)	0.07

ECMO: extracorporeal membrane oxygenation; ED: emergency department; ICU: intensive care unit.
[a] Excludes early deaths and discharges.
[b] Measured for surviving patients.

neurological outcome (CPC score 1-2: 71% vs. 56%, p = 0.22) (Table 3).

For all outcomes, the direction of effect did not change when patients who received ECMO were excluded from the models. Age and duration of arrest were significantly associated with all outcomes (data not shown).

Discussion

The change from a post-arrest temperature target of 33 °C to 36 °C in our ICU has been associated with significant non-compliance with achieving the target temperature and this may be associated with poorer patient outcomes. Our results are noteworthy given that many ICUs have changed TTM practice.[8–10] For example, a recent 10-year audit of ICUs in the United Kingdom reported a sudden drop in 2014 to the proportion of cardiac arrest patients with a lowest temperature recording of <34 °C (39% in 2014 compared to a peak of 60% in 2013).[10] The number of ICUs changing practice is likely to increase further following the recent guideline recommendations for TTM in 2015.[5,6]

Our temperature findings are similar to those reported by Casamento et al.,[11] who also reported high proportions of temperatures above target and fever (≥38 °C) across the first 24 h of ICU stay on the 36 °C protocol. Although in our study, more patients were at target temperature on arrival to ICU, and in the 33 °C period we found higher rates of time at target temperature. These differences are mostly likely explained by the commencement of TTM in the emergency department in our hospital and the greater use of ECMO in the 33 °C period. In contrast to our study, the Casamento et al.[11] study reported no differences in patient outcomes between the two treatment periods. However, this may be explained by the different cohorts, as their study included in-hospital cardiac arrests, arrests of all rhythms and excluded patients who did not survive the first 24-h of ICU stay.

Although our patient outcomes were not statistically different between the two protocols, most likely due to the small sample size, we believe the trend towards higher mortality and worse neurological outcomes to be clinically significant. This is supported by the similarity in our outcomes to those reported in the original hypothermia trials, which compared mild therapeutic hypothermia to normothermia.[1,2] These original trials, with high numbers of VF patients, reported similar differences in temperature and in direction of outcomes to our cohort. This may suggest that some ICU clinicians have abandoned TTM following the result of the TTM trial, and others are not adhering to the protocol or are having difficulty achieving and maintaining a target temperature of 36 °C.

It is also possible that some of our ICU staff perceived a 36 °C target as "normothermia" or that there could be less patient sedation and no muscle-relaxant required to achieve the target temperature. This may have resulted in patients waking earlier, as evident by the earlier extubation seen in the 36 °C period. This practice, combined with the change in the type of sedation agents used in the 36 °C period, differed from the TTM trial protocol. In the TTM trial, patients were sedated for the full 36-h of the intervention, although the choice of drugs was left to the treating physician and sedation agents are not reported.[7] However, the TTM protocol did recommended similar agents be used for each intervention arm, which may suggest that the sedation required to maintain 36 °C may be

Table 3
Comparison of temperatures and patient outcomes for patients admitted to ICU for the 33 °C and 36 °C TTM periods.

Outcome variables	33 °C N = 24	36 °C N = 52	Unadjusted p-value	Adjusted p-value[a]
Temperatures				
Temperature on arrival at ED, mean (SD)	34.5 (1.4)	35.2 (1.5)	0.07	–
Average temperature across first 24 h, median (IQR)	33.4 (33.1–33.5)	36.2 (36.1–36.5)	<0.001	–
Time at target temperature in first 24-h (%), mean (SD)	87 (15)	50 (31)	<0.001	–
All temperatures at or below target in first 24-h, n (%)				
Temperature ≥38.0 in first 24 h, n (%)	0 (0)	10 (19)	0.03	–
Temperature ≥38.0 in first 36 h, n (%)	2 (8)	16 (31)	0.04	–
Outcomes				
Discharge within 24 h of ICU, n (%)	0 (0)	2 (4)	0.99	–
Died within 24-h of ICU, n (%)	0 (0)	7 (14)	0.09	–
ICU survival, n (%)	17 (71)	30 (58)	0.32	0.31
Hospital survival, n (%)	17 (71)	30 (58)	0.32	0.31
Day treatment withdrawn, median (IQR)	3 (3-16)	4 (3-10)	0.99	
CPC score 1–2, n (%)	17 (71)	29 (56)	0.31	0.22
Discharged home, n (%)	14 (58)	21 (40)	0.22	0.08
Discharged to rehabilitation, n (%)	3 (18)	8 (27)	0.48	0.55
Survivors CPC 1, n (%)	<16 (94)	19 (63)		–
Survivors CPC 2, n (%)	1 (6)	10 (33)	0.02	
Survivors CPC 3, n (%)	0 (0)	1 (3)		

CPC: cerebral performance category.
[a] Adjusted for age and duration of cardiac arrest.

similar to 33 °C. This information may be important to emphasis when implementing TTM at 36 °C.

In our hospital, the evidence for the initial guideline and change to 36 °C was presented to the senior ICU medical staff, and a consensus for each recommendation was established to ensure that care would be delivered as per guideline. There was no direct education provided to staff implementing the guideline, as the junior medical and nursing staff change regularly. Other elements of the guideline (e.g. preventing early prognostication and angiogram) were unchanged between the two periods and most patients had medical orders for TTM. Therefore, it is likely that staff were familiar with the guideline and were aware of the change to 36 °C. On the basis of our current findings, we have implemented and recommend education stressing the liberal administration of sedation and muscle relaxants for the duration of TTM when implementing a 36 °C protocol. In addition, setting the target temperature at <36 °C may highlight that the treatment target of 36 °C must not be exceeded.

There are a number of limitations to this study. First, as a before and after study, there may be a number of unmeasured factors that may have affected patient outcomes. Also, the sample size was relatively small, as post-arrest care was not standardised before the guideline was introduced in August 2012. As a result, we were unable to examine subgroups or to perform fully adjusted models. Other limitations relate to the single centre setting and the retrospective collection of data, although we attempted to have standardisation of data collection.

In summary, our study highlights an important issue when changing TTM from 32–34 °C to 36 °C. ICUs considering adopting or changing their target temperature to 36 °C need to be aware that this target may in fact be more difficult to achieve and may require more sedation and muscle-relaxant to avoid fever in the first 24 h of admission.

Conflict of interest statement

None.

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