Feasibility of early waking cardiac arrest patients whilst receiving therapeutic hypothermia: The therapeutic hypothermia and early waking (THAW) trial.

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Structured abstract

Aim: To determine the safety and feasibility of an early (12 hours) waking and extubation protocol for out-of-hospital cardiac arrest (OHCA) patients receiving targeted temperature management (TTM).

Methods: This was a single-centre, prospective, non-randomised, observational, safety and feasibility pilot study which included successfully resuscitated OHCA patients, of presumed cardiac cause. Inclusion criteria were: OHCA patients aged over 18 years with a return of spontaneous circulation, who were going to receive TTM33 (TTM at 33°C for 24 hours and prevention of hyperthermia for 72 hours) as part of their post cardiac arrest care. Clinical stability was measured against physiological and neurological parameters as well as clinical assessment.

Results: 50 consecutive patients were included (median age 65.5 years, 82% male) in the study. Four (8%) patients died within the first twelve hours and were excluded from the final cohort (n=46). Twenty-three patients (46%) were considered clinically stable and suitable for early waking based on the intention to treat analysis; 12 patients were extubated early based on a variety of clinical factors (21.4 ± 8.6 hours) whilst continuing to receive TTM33 with a mean core temperature of 34.2°C when extubated. Of these, five patients were discharged from the intensive care unit (ICU) <48 hours after admission with a mean ICU length of stay 1.8 ± 0.4 days. Twenty-eight patients (56%) were discharged from the ICU with a modified Rankin Score of 0-2. The overall intra-hospital mortality was 50% (n=25).

Conclusions: It is safe and feasible to wake selected comatose OHCA patients at 12 hours, allowing for earlier positive neuro-prognostication and reduced ICU stay.

Introduction

Approximately half of the patients admitted to hospital following an out-of-hospital cardiac arrest (OHCA) will not survive[1], with brain injury considered the most common cause of morbidity and mortality[2]. Targeted temperature management (TTM), previously known as mild therapeutic hypothermia, is a medical treatment which aims at lowering core body temperature while a person recovers from an OHCA. Neurological prognostication remains challenging and the use of multiple prognostic modalities such as electrophysiological examinations, biochemical marker assessment, clinical examination and neuroimaging is needed for assessing the prognosis of patients undergoing TTM[2–4]. There is an emphasis on early recognition of patients who are likely to have a poor prognosis, such that patients with a possible positive early outcome are less of a focus.

Guidelines support patients to be treated with TTM for 24 hours followed by slow re-warming (at a rate of ~0.25°C per hour) to normothermia. Sedative and neuromuscular blocking (NMB) agents can be stopped during this period to allow for an accurate neurological assessment to be performed[5]. TTM can be delivered to awake patients using an endovascular device, demonstrated to be feasible and safe in heart attack and stroke patients, with appropriate anti-shiver therapies. [6–8].

The aim of this study was to test whether appropriate OHCA patients can be awoken early (12 hours after admission to ICU) while receiving TTM33 (TTM at 33°C for 24 hours and prevention of hyperthermia for 72 hours) and if that can further allow for earlier positive neuro-prognostication and reduced ICU stay.

Materials and Methods

Study design

The Therapeutic Hypothermia and eArly Waking (THAW) trial was a single-centre, prospective, non-randomized safety and feasibility study of adult OHCA patients, treated with TTM33. From February 2017 until January 2018, 50 consecutive adult patients were recruited to the study who fulfilled the inclusion criteria and who were considered appropriate to assess the feasibility and safety of the intervention.

Inclusion criteria were: OHCA patients aged over 18 years with a return of spontaneous circulation (ROSC), who were going to receive therapeutic hypothermia as part of their post cardiac arrest care. The time to achieve ROSC was based on initial time recorded by the ambulance service when from when CPR was commenced until a sustained ROSC of >10min was achieved.

Exclusion criteria included: non-cardiac related cause, pre-existing 'do not attempt resuscitation' order, terminal illness, pregnancy, coagulation disorder, oxygen dependency, height <1.5m, known hypersensitivity to buspirone or meperidine, inferior vena cava filter in place (prevents use of intravascular cooling catheter insertion) or unresolved drug dependency.

Approval for the study was obtained locally by the Institutional Review Board of the Basildon and Thurrock University Hospital (BTUH) Foundation Trust's Research and Development Department and from the National Health Service (Health Research Authority, United Kingdom - reference 15/EE/0173, NCT03065946). Patients were treated at the cardiac catheter laboratory of the Essex Cardiothoracic Centre (ECTC) at BTUH. Since the patients were comatose, the closest available relatives were requested for consent about trial enrolment. Once a patient regained consciousness and capacity, the patient was appropriately consented. Patients with no available next of kin / relative were initially included in the trial with the consent of 2

independent physicians not involved in the research study. The patient was then approached and consented as soon as he / she regained consciousness and capacity.

Protocol description

The detailed protocol of the study has been previously published and is described in the Supplement (**Supplement Figure 1**)[9]. As a designated Cardiothoracic Centre, OHCA patients with a presumed cardiac cause were admitted directly to the cardiac catheter laboratory where they were initially assessed for coronary intervention and appropriateness for TTM to be delivered using an endovascular catheter. Suitable patients had an ICY® catheter (Zoll Medical Corp, Chelmsford, MA, USA) inserted into the femoral vein, and intravenous temperature management (IVTM) was initiated in the catheter lab, immediately before or after coronary angiography / revascularization. The core temperature was taken from a bladder probe which was continuously monitored using an indwelling urinary catheter with an incorporated temperature probe. The target temperature was set to 33°C using the Thermogard XP™ temperature management system (Zoll Medical Corp, Chelmsford, MA, USA) for 24 hours. Patients were then slowly re-warmed at a rate of 0.25°C per hour until 36.5°C was reached and prevention of hyperthermia was maintained for 72 hours. Early extubation was considered as any patient extubated <36 hours. Suitable patients could be discharged to the ward from the ICU while receiving TTM.

Pharmacotherapy

Patients were sedated using a combination of propofol and fentanyl, which were titrated to achieve a sedation level between -3 (moderate sedation) to -5 (unarousable sedation) of the Richmond Agitation Sedation Scale (RASS) Score[10,11]. Intermittent boluses of a NMB agent was administered (rocuronium or atracurium) when indicated to avoid shivering. The decision to give a NMB agent was based on signs of patient shivering and/or an unintentional

increase in the patient's core temperature of more than 0.3°C. No patients received dexmedetomidine as this medication was not available at that time at our Institution.

Early waking assessment and neurological assessment

At 11 hours post ICU admission patients were clinically assessed in order to determine appropriateness and clinical stability to be woken early (**Supplement Figure 2**). The clinical assessment comprised assessment of the cardiovascular system, respiratory function, neurological status and metabolic requirement. If all the parameters were within normal range, sedation was reduced to achieve a RASS of -3 or lower. To assess the neurological function of the patients and to determine appropriateness for extubation a combination of the Glasgow Coma Scale (GCS)[12,13] and the Full Outline of UnResponsiveness (FOUR) score[14] were used. Patients considered neurologically appropriate for extubation needed to achieve GCS ≥ 8 or FOUR score of 13[15]. The neurological outcome at discharge was not blinded and all neurological outcomes were recorded by both the attending consultant-led intensive care and cardiology teams.

Anti-shivering regimen

All patients who met the early waking criteria had a surface air-warming blanket applied and set to a max temperature of 42°C. In addition, in all successfully awakened patients the sedation agents and NMBs were stopped and a loading dose of buspirone (60mg via the nasogastric tube) and meperidine 0.5-1.0mg/kg (intravenously over 15 minutes) were administered. Following the initial loading dose of meperidine, a maximum of three bolus doses of intravenous meperidine 10-50mg (according to patient's ideal body weight and patient responsiveness) was given at 15-minute intervals, then a continuous intravenous infusion of meperidine was started at 5-25mg/hr. The meperidine infusion was titrated to maintain patient comfort and prevent shivering as the patient continued to be treated with TTM33. Detailed

description of the shivering suppression guidelines can be found on the Supplement (**Supplement Figure 3**).

Outcome assessment

The primary end point was the number of patients successfully woken and extubated within the first 24 hours post cardiac arrest and at the same time being treated with TTM33. Neurological recovery in terms of suitability for extubation was initially assessed at 11 hours post admission and then reassessed at 6-hourly intervals, utilising the GCS and FOUR scores for patients who were considered clinically stable according to the early waking criteria. The neurological outcome was assessed during the ICU stay and at hospital discharge, categorised according to the Glasgow-Pittsburgh Cerebral Performance Categories [(CPC); with CPC 1 to 2 defined as favourable and 3 to 5 defined as poor neurologic outcome] and the Modified Rankin Score (mRS) (mRS = 0, 1, and 2 is considered a favourable outcome and MRS = 3, 4 or 5 is considered an unfavourable outcome)[16–18].

Statistical analysis

Intention-to-treat analysis was performed. The intention-to-treat analysis included all patients who fulfilled the study's criteria. Continuous variables are presented as mean ± one standard deviation. The analysis was performed with SPSS 25 statistical software (SPSS Inc., Armonk, NY, USA).

Results

Baseline characteristics

The demographics and clinical characteristics of the study cohort are shown in **Table 1**. Fifty patients were enrolled in the study, four patients (8%) were excluded from the final cohort as they died within 12 hours of admission to the ICU (**Figure 1**). Median age of the final cohort

was 65.8 ± 11.5 years and 82% (n=41) were male. Median time to achieve ROSC was 29 ± 24.1 minutes, 88% of patients (n=44) presented with a shockable rhythm and 68% of patients (n=34) received bystander cardiopulmonary resuscitation.

Primary endpoint

All patients were assessed at 11 hours to determine clinical suitability for early waking. Twenty-three patients (46%) were considered clinically appropriate to attempt early waking (**Figure 2**). Twelve patients (24%) were extubated early with a mean extubation time of 21.4 ± 8.6 hours (following admission to ICU) whilst continuing to receive TTM33 with a mean core temperature of 34.2 ± 1.28°C when extubated (**Table 2**). Of these 12 patients that were successfully extubated early, none required re-intubation and only one required non-invasive ventilation**.** Of the remaining 11 patients (22%), 2 patients remained intubated due to respiratory instability, 2 patients due to agitation, 5 patients due to need for multiple-organ support and 2 patients were unable to follow commands.

Secondary endpoints

From the twelve patients (24%) that were successfully extubated early: 8 (16%) patients were extubated ≤24 hours and 4 (8%) patients were extubated ≤36 hours from ICU admission. Six-teen patients out of the total cohort of 50 patients (32%) were extubated >36 hours from ICU admission; 4 of these patients were extubated <72 hours with an IVTM catheter in-situ, receiving active temperature management for fever prevention. No complications related to the IVTM catheter.

Of the 12 patients successfully extubated early, 5 patients (10%) were discharged from the ICU < 48 hours after admission. All the patients who survived (n=28) until being discharged from the ICU had favourable CPC and mRS scores. Three patients still requiring critical care were repatriated to their local hospital where they were discharged from the ICU with favourable

CPC/mRS scores. The overall intra-hospital mortality was 50% (n=25). Three patients who survived until discharge from the ICU died prior to hospital discharge: the first patient died awaiting cardiac surgery, the second patient died from complications associated with necrotizing fasciitis due to a Bartholin abscess and the third patient died of complications following cardiac surgery. The mean hospital LOS for the total cohort was 24.1± 20.6 days.

Four patients who were woken and extubated early had their IVTM discontinued after receiving 24 hours of TTM33. One patient became confused and agitated dislodging the IVTM catheter therefore the catheter was removed after 24 hours for safety reasons. The three remaining patients had their IVTM catheter removed between 33-45 hours. This was at the request of the treating physician, and was deemed for clinical reasons to enable the patient to mobilise and receive physiotherapy, which was considered more of a clinical priority. Seven patients (14%) were transferred from the ICU to the ward within 72 hours from admission and 4 of these patients continued to receive IVTM on the ward. The remaining 3 patients were able to complete the 72 hours of IVTM in the ward environment.

Incidence of shivering

The majority of the patients had minimal shivering; however, 3 patients did experience significant shivering. One patient was in the early waking group. The other two who experienced shivering did so during the normothermic phase.

Discussion

The principal findings of the study were:

- First, therapeutic hypothermia and early waking is safe and feasible in selective OHCA patients leading to an early ICU discharge.

- Second, none of the early waking patients required re-intubation or suffered any significant clinical sequelae and all had a positive neurological outcome.
- Lastly, early waking provides an opportunity to neurologically prognosticate and to clinically detect seizure activity if EEG is not available.

Feasibility of the study. Previous studies have demonstrated that endovascular cooling can be successfully delivered to awake patients[8,19–22], but this has been limited to a maximum of 24 hours and not in patients who are being woken from coma. In the present study, when patients reached normothermia, the IVTM catheter remained in-situ for up to 72 hours to enable fever prevention.

Positive neuroprognostication. The THAW study explored whether it was safe and feasible to wake suitably appropriate OHCA survivors after 12 hours whilst continuing to be treated with TTM33. In total 23 patients (46%) were considered clinically stable and appropriate to cease sedation at 12 hours and assess their neurological function. This study focused on positive prognostication, so no NMB agents were initiated unless clinically indicated, for gas exchange purposes (ventilator synchronisation) or shivering, when bolus doses were ineffective. Hence, it was possible to perform a more comprehensive neurological examination and assessment and start anti-seizure medication, which in other circumstances it would have not been possible in patients being treated with TTM33 who were sedated and paralysed.

TTM dose. The optimal therapeutic duration of targeted temperature management remains unclear. The dose of TTM is also unclear raising the on-going question about the dose of targeted temperature management. In our study we were able to demonstrate the safety and feasibility of providing TTM33 continuously with IVTM during the rewarming and prevention of hyperthermia in awake patients. Although this was achievable it was a challenge in the awake patient, balancing the demands of providing critical care to the patient requiring

multiorgan system optimization who has also recently been extubated, at the same time having to titrate the meperidine infusion to prevent shivering without over sedating the patient.

ICU utilisation. The ability to transfer OHCA patients from the ICU early is important from a clinical and a financial perspective. In our study we were able to demonstrate that patients who wake early and extubated can be transferred to the ward and continue to receive TTM33. Even though no formal financial data were collected during this study, lesser time in an ICU bed may prospectively translate into lesser expenditure.

Clinical implications

Waking OHCA patients early and being able to prognosticate their neurological status is imperative, since it can translate to less ICU stay and decrease hospitalizations costs.

Study Limitations

This was a single-centre, prospective, non-randomized feasibility study that had no comparator arm. However, our centre is experienced with conscious cooling, having been a large recruiter to the COOL AMI Pilot trial[23]. In addition, the small number of the study's participants does not allow for generalizability of the results and so bigger studies are needed in order to replicate this study's results. Also, it should be taken into consideration that the optimal duration and target temperature of TTM period is still under investigation. Finally, the purpose of the study was to identify whether patients could be woken early while continuing to provide TTM, and not to examine whether discontinuing TTM in the awake patient was of benefit. However, this was also considered by the researchers and for the purposes of this study the decision was to limit significant changes to standard practice, hence reducing variability.

Conclusion

The THAW trial demonstrated the safety and feasibility of waking appropriate OHCA patients at 12 hours whilst continuing to be treated with TTM33 for 24 hours. Accordingly, early

waking may lead to early neuroprognostication of patients and prompt management or prevention of neurological adverse events, early extubation and potentially a shorter ICU stay. The demonstrated feasibility of our early waking protocol prompts further assessment in randomised controlled trial settings, which could include early assessment of all patients and randomising to continuing TTM or not.

Conflicts of interest

Dr Thomas Keeble has received travel support and research grant funding from ZOLL Medical corporation as well as lecture fees from BD.

Prof Marko Noc has received consultation fees from ZOLL Medical corporation.

Prof Kees Polderman has participated in sponsored lectures and received travel support from various companies involved in TTM, including from ZOLL corporation.

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Figure legends

Figure 1. The THAW study flowchart.

*Footnote – 16 patients not recruited due to logistical reasons which included:

IVTM not available (4)

Research team not available to recruit patient and perform interventions (12)

Figure 2. Patients eligible for early waking

Supplement figure legends

Supplement Figure 1. The detailed protocol of the study.

Supplement Figure 2. Early waking and assessment criteria used in the study.

Supplement Figure 3: Shivering suppression guidelines.

370 Tables

371 Table 1. Baseline characteristics of the cohort (n= 50).

Demographic data	Mean	EARLY	LATE
Age	65.5 ± 11.5	66.2 ± 7.9	65.5 ± 13.8
Weight	91.5 ± 24.9	92.5 ± 28.8	90.9 ± 22.5
BMI	28.1 ± 4.3	27.6 ± 3.6	28.7 ± 4.8
Sex - Male (%)	82	82	82
Race (%)			
White British	90	87	93
Black British	1 (2)	1 (4.3)	0
Asian	3 (6)	2 (8.7)	1 (3.7)
European	1 (2)	0	1 (3.7)
Comorbidity			
AF	2 (4)	2 (8.7)	0
Asthma	6 (12)	2 (8.7)	4 (14.8)
COPD	5 (10)	1 (4.3)	4 (14.8)
Coronary Artery Disease	13 (26)	3 (13)	10 (37)
CKD	5 (10)	3 (13)	2 (7.4)
Diabetes	8 (16)	1 (4.3)	7 (25.9)
Hypertension	22 (44)	9 (39.1)	13 (48.1)
Peripheral Vascular Disease	5 (10)	0	5 (18.5)
Previous Stroke / TIA	0	0	0
Current Smoker	11 (22)	4 (17.4)	7 (25.9)
Bystander CPR (%)	34 (68)	16 (69.6)	19 (70.4)
Total downtime	29.4 ± 24.1	17.3 ± 10.6	39.1 ± 27.5
VF / pulseless VT	44 (88)	23 (100)	21 (77.8)
PEA	2 (4)	0	2 (7.4)
Asystole	4 (8)	0	4 (14.8)
Temperature			
at 12hr	33.27 ± 0.43	33.25 ± 0.35	33.31 ± 0.55
at 24h	33.56 ± 0.75	33.65 ± 0.60	33.43 ± 0.70
at 36h	35.81 ± 0.77	36.18 ± 0.49	35.76 ± 0.61
at extubation		34.24 ± 1.28	

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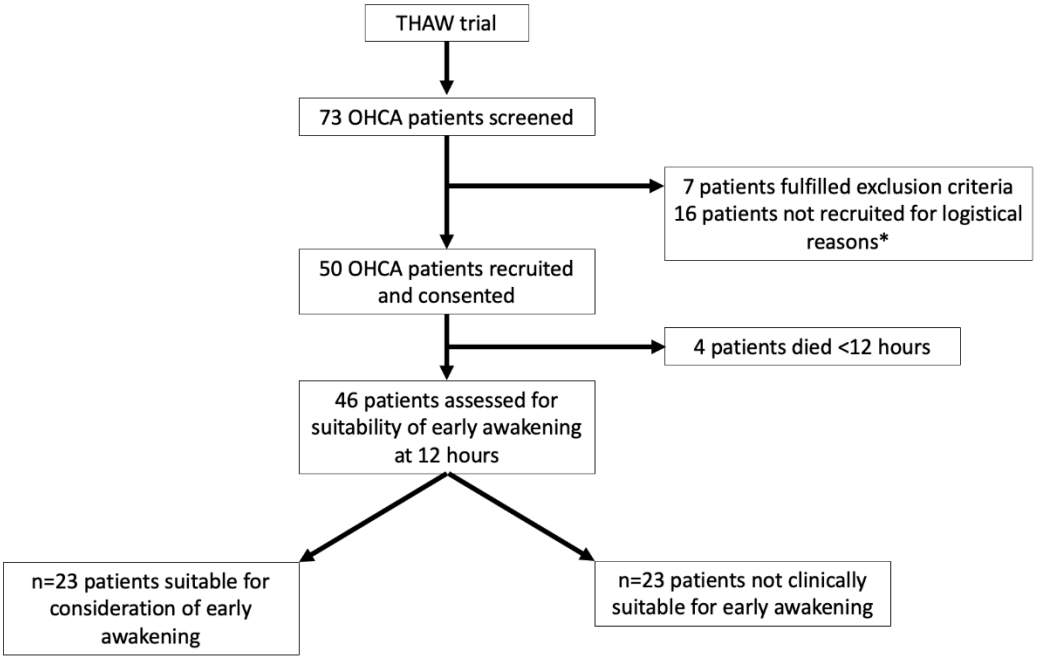
All values are n(%), unless stated otherwise. COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; CPR: cardiopulmonary resuscitation; VT: ventricular tachycardia.

* down time refers to: no flow time plus CPR time.

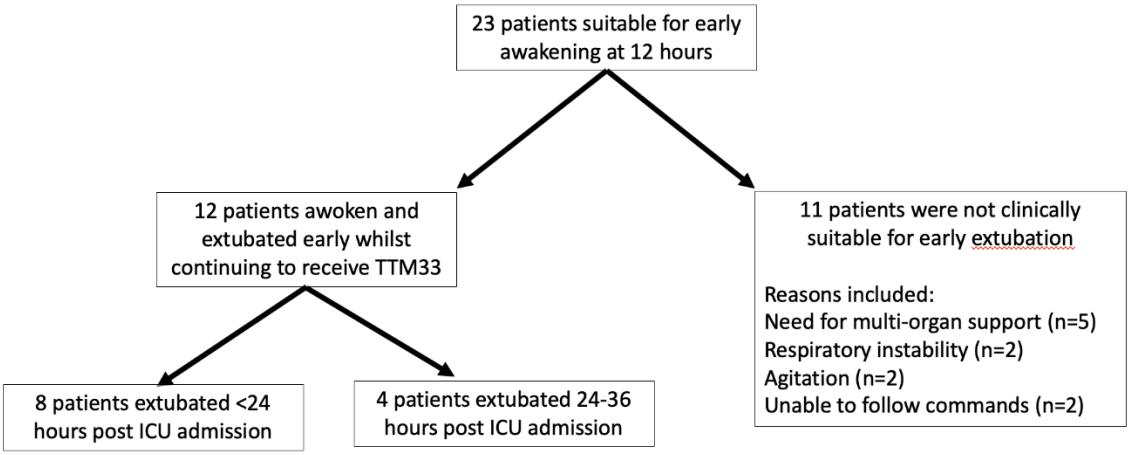
Table 2. Recorded temperatures (measured as °C) at 12 hours and at extubation, as well as ventilation time for patients woken early (n=12).

Patient	Temp (°C) at 12 hours	Temp (°C) at extubation	Ventilation time (hr)
3	33.60	36.10	36
6	33.40	33.90	19
7	33.00	33.00	16
9	34.20	33.40	12
11	33.00	35.10	28
12	33.10	33.00	16
13	33.20	35.80	36
14	33.10	33.20	14
16	33.10	35.00	24
30	33.10	33.20	13
32	33.10	33.10	15
50	33.10	36.10	27

Figure 1:



402 **Figure 2:**



All 12 patients were extubated <36 hours from ICU admission

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