

Is it feasible and safe to wake cardiac arrest patients receiving mild therapeutic hypothermia after 12 hours to enable early neuro-prognostication.

The Therapeutic Hypothermia and eArly Waking (THAW) trial protocol

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Abstract

Introduction: Mild therapeutic hypothermia (33°C MTH) post out-of-hospital cardiac arrest (OHCA) is widely accepted as standard of care. However, uncertainty remains around the dose and therapy duration. OHCA patients are normally kept sedated +/- paralysed and ventilated for the first 24 - 36 hours which allows for target temperature management (TTM), but makes neurological prognostication challenging.

Objectives: The aim of this study is to investigate the feasibility and safety of assessing the unconscious OHCA patient after 12 hours for early waking / extubation whilst continuing to provide mild therapeutic hypothermia (MTH) for 24 hours, and fever prevention for 72 hours using an intravenous temperature management (IVTM) system and established conscious MTH anti-shiver regimens.

Methods: This is a single centre, prospective, non-randomized observational study.

A total of 50 consecutive unconscious survivors of OHCA, treated with MTH, who meet the THAW inclusion criteria will be enrolled. The patient will receive MTH using IVTM. After 12 hours of MTH patients will be assessed using strict clinical criteria to determine suitability for early waking and extubation. Once awake and extubated MTH will continue for 24 hours with skin counter-warming and anti-shiver regimen followed fever prevention up to 72 hours. All patients will have serial electroencephalogram (EEG), somatic sensory potential (SSEP), and neuro-biomarkers performed on admission to ICU, 6 and 12 hours, then every 24 hours until 72 hours.

Study End Points

Primary - Patients successfully extubated whilst being treated with mild therapeutic hypothermia (33°C) following cardiac arrest.

Secondary endpoints include – i) Length of ventilation support, ii) Neurological recovery at 12 hours utilizing GCS, FOUR score and neurological assessment, iii) Assessment of Cerebral Performance Category (CPC) scale to indicate the patient’s neurological recovery on ICU and hospital discharge. iv) Length of ICU and hospital stay v) Re-intubation rate

The study has been approved by the National Research Ethics Service, Health Research Authority.

Background

Out of hospital cardiac arrest (OHCA) – a global problem

Cardiac arrest is a global problem affecting 50-100 per 100,000 in the general population, and ischaemic heart disease remains the leading cause of death in the western world (WHO, 2017; Deo et. Al., 2012). Until recently neurologically intact survival following cardiac arrest had been very poor; however with improved early cardio-pulmonary resuscitation (CPR), better access to defibrillation and coronary revascularization as well as high quality intensive care support combined with targeted temperature management (TTM) survival rates have tripled in developed healthcare systems since 2001 (Wissenberg, 2013).

OHCA - Contemporary management

When the aetiology of the cardiac arrest is assumed to be cardiac, in the majority of cases the patient will be taken to a heart attack centre (HAC) for consideration of revascularisation. Following the catheter lab, the patient is usually admitted to the Intensive Care Unit (ICU) where they will be sedated, paralysed, ventilated and receive Targeted Temperature Management (TTM) between 33-36°C. When the patient is normothermic, 24-36 hours later, sedation will be stopped to assess the patient’s neurological status and suitably appropriate patient’s would normally be extubated. When the patient no longer requires organ support they will be transferred to an appropriate step down cardiac care ward.

Targeted temperature management (TTM)

In 2013, the Targeted Temperature Management (TTM) trial showed no difference in clinical outcomes when comparing mild therapeutic hypothermia (MTH) at 33°C to maintaining a target temperature of 36°C (Nielsen et. Al., 2013).

However, MTH remains within the current guidance for the management of OHCA survivors as outlined by all major international resuscitation committees (RCUK, 2015; ERC and ESICM, 2015; ANZCOR, 2016; ILCOR, 2015; AHA, 2015). Furthermore, MTH was endorsed by the Cochrane report (2016) and the UK National Institute for Health and Care Excellence (NICE, 2011). Further hypotheses regarding the clinical utility of MTH will be tested in the upcoming TTM2 trial due to start towards the end of 2017.

Brain injury and neurological assessments

Brain injury is the most common cause of morbidity and mortality in patients with a return of spontaneous circulation who are subsequently admitted to hospital (Nichol et. al, 1999; Burke et al., 2005).

Prognostication in the unconscious cardiac arrest survivor is difficult. Patients are initially sedated and paralysed, usually for a minimum of 24 hours and only after they are re-warmed to normothermia is neuro-prognostication attempted. Without advanced multi-modal neurological testing and access to neurology and neuro-electrophysiology services, many cardiac centres rely on basic neurological clinical assessment.

The electroencephalogram (EEG) and somatosensory evoked potential (SSEP) are both thought to be useful to predict poor outcome. EEG is also helpful to assess level of consciousness as well as detecting non-convulsive seizures, which can then be treated. An isoelectric EEG at 72 hours is associated with poor outcome (Zanderbergen et. al., 2006).

SSEP has also been described as a useful bedside tool, which is not affected by sedation, paralysis (unless high doses administered) or MTH and is able to assess periphery, brainstem and cortical function (Rothstein, 2014). Upper Limb SSEP is obtained through stimulation of the median nerve at the wrist and recording the N20 cortical response. A bilateral absence of N20 at 24 hours has shown to predict poor outcome (Sandroni and Geocadin, 2015).¹⁸

Another useful predictor of neurological outcome is brain derived proteins, neuron-specific enolase (NSE) and S-100B. It has recently been described that serum concentrations of both these neuro-proteins peak within the first 24 hours in patients with a favourable to moderate neurological outcome, but continue to rise up to 3 days after cardiac arrest in patients with unfavourable outcomes (Pfeifer et al., 2014).

The problem – TTM and sedation / paralysis and ability to prognosticate

When the patient is in an induced coma, and receiving TTM / MTH clinicians have a limited ability to assess a patient's neurological function, making prognostication difficult. Furthermore, diagnosis and treatment of neurological complications such as non-convulsive seizures are difficult to detect when relying just on clinical assessment.

Conscious therapeutic hypothermia

Providing MTH in conscious patients has been demonstrated to be both feasible and safe, providing skin counter-warming and a rigorous anti-shivering regimen is concurrently employed (Georgia et. al., 2004; Lyden et. al., 2014; Dixon et. al., 2002; Erlinge et al, 2014; Götberg et. al., 2010).

At the Essex Cardiothoracic Centre (ECTC) we have considerable experience in conscious induction and management of MTH within the COOL-AMI Case series, and COOL AMI EU pilot study.^{25 26} In these studies conscious patients who presented with ST-elevation myocardial infarction (STEMI) were cooled to 32°C with an intravascular device inserted via the femoral vein into the inferior vena cava, while administering a rigorous anti-shivering strategy.

Purpose of Therapeutic Hypothermia and eArly Waking (THAW) study

The purpose of the THAW study is to assess the safety and feasibility of stopping sedation at 12 hours, whilst continuing to provide mild therapeutic hypothermia (33°C). This will allow clinicians to perform an earlier neurological assessment and discontinue mechanical ventilation as soon as practicable, whilst still allowing the patient potential benefit from MTH.

To ensure only appropriate patients are selected for early waking, patients will be assessed on their cardiovascular, respiratory and neurological stability. Patients who are considered clinically stable will be commenced on a rigorous anti-shivering regime, which allows for the continuation of therapeutic hypothermia with minimal or no discomfort to the patient. Sedation can then be stopped to enable the clinician to perform a comprehensive neurological assessment with the view to extubating suitably appropriate patients early.

The hypothesis is that THAW trial protocol will allow clinicians to prognosticate much earlier, with an emphasis on positive prognostication. Administration of sedation is minimised as well as reduction in mechanical ventilation, therefore potentially reducing intensive care and hospital length of stay.

Study Design

This is a single centre, prospective, non-randomized, safety and feasibility study. All unconscious patients who have had a return of spontaneous circulation (ROSC) after an OHCA following admission to the Essex Cardiothoracic Centre (ECTC) and are planned for MTH treatment are eligible for the study. Patients fulfilling inclusion criteria and no exclusion criteria will be enrolled. (Table 1)

50 patients will be recruited to this study, which we have judged to be appropriate to assess the feasibility and safety of the intervention, results being compared to a consecutive 50 patient historical cohort.

Table 1 - THAW Inclusion and exclusion criteria:

THAW Inclusion and Exclusion Criteria

Inclusion Criteria:

Patients are eligible if they meet all of the following criteria:

- ≥ 18 years old
- Post cardiac arrest with ROSC
- Planning to receive MTH as part of post-cardiac arrest care.

Exclusion Criteria:

Patients are not eligible if they meet one or more of the following criteria:

- Cardiac arrest caused by trauma, head injury, massive haemorrhage, drug overdose, cerebrovascular accident, drowning, electric shock or hanging.
- Do Not Attempt to Resuscitate (DNAR) orders
- Known terminal illness (e.g. malignancy in the end stages)
- Known or obvious pregnancy
- Known coagulation disorder (except those induced by medication)
- Known oxygen dependency.
- The patient has a height of <1.5 meters (4 feet 11 inches)
- The patient has a known hypersensitivity to Buspirone Hydrochloride or Pethidine.
- Patient has a known history of severe hepatic or renal impairment, untreated hypothyroidism, Addison's disease, benign prostatic hypertrophy, or urethral stricture that in the opinion of the treating consultant would be incompatible with Pethidine administration.
- The patient has an inferior Vena Cava (IVC) filter in place.
- The patient has a known, unresolved history of drug use or alcohol dependency, or lacks the ability to comprehend or follow instructions.

Methods / Study Intervention

Enrolled patients will have an Icy® catheter (Zoll Inc, USA) inserted into the femoral vein and intra-venous temperature management (IVTM) will be initiated in the catheter lab i.e. immediately prior to or following coronary imaging / revascularization. The target temperature is set to 33°C, which will continue for 24 hours from the time the patient reaches target temperature. The patient will be transferred to the ICU where physiological observations will be continuously monitored and organs supported as required. Regular neurological assessment utilising Glasgow Coma Scale (GCS) and FOUR scoring will be performed and sedatives administered to achieve a Richmond Agitation-Sedation Scale of -3 to -5. Depending on clinical stability and any evidence of shivering, preference is given to bolus administration of paralyzing agents as opposed to a continuous infusion. Figure 1 outlines the THAW intervention protocol.

Between 11-12 hours from admission to the ICU a comprehensive cardiovascular, respiratory and neurological assessment is performed to identify patients that might be suitable for early waking. This requires the patient to be cardiovascularly stable, on minimal or no inotropic support; normal gas exchange, requiring less than 50% oxygen and no evidence of adverse neurological signs. Providing these criteria are met the patient would be considered appropriate for early waking and started on a rigorous anti-shivering regime (Table 2). The patient is continuously assessed for extubation against established criteria (Table 3)

Table 2 – THAW anti-shiver guideline

Shivering Suppression Guidelines

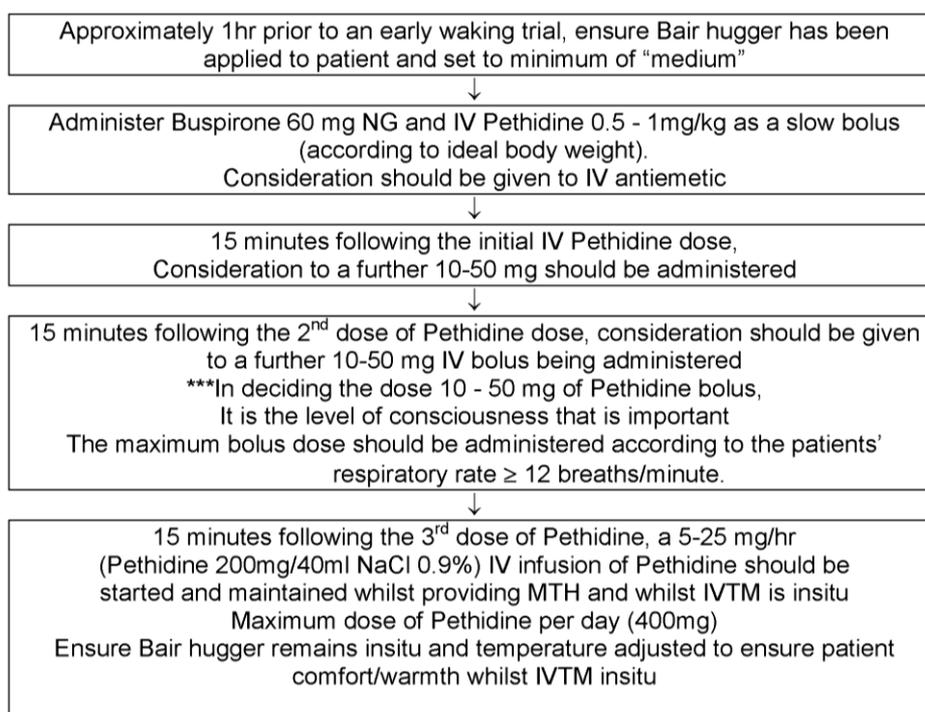


Table 3 – THAW early Extubation Criteria

Extubation Criteria

Neurology: the patient should be alert and co-operative. Adequate airway protective reflexes (cough, swallow, vocal cord movement)

Cardiovascular: the patient should be stable, with systolic blood pressure of 100 mmHg or greater. There should be minimal inotropic support and the patient should not be bleeding or have any major metabolic disturbance.

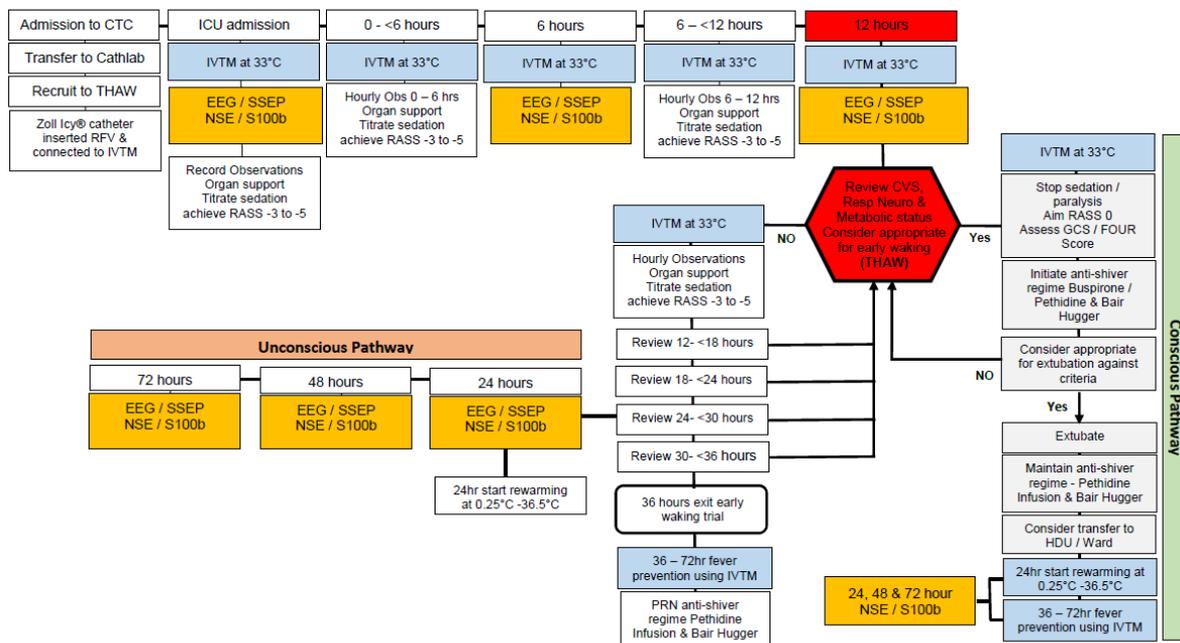
Respiratory: the patient should have an adequate cough and ability to clear secretions, satisfactory ABGs on minimal oxygen, effective spontaneous breathing and should not be tachypnoeic. The following parameters should be met.

- a. Adequately managed secretions
- b. RR < 35
- c. Vital capacity > than 10 mL/kg
- d. Tidal Volume > 5mL/kg
- e. Minute ventilation < 10L/min
- f. 30–120 minute spontaneous breathing trial with low level of CPAP (e.g. 5 cm H₂O) or low level of pressure support (e.g. 10 cm H₂O)

Pharmacology: muscle relaxants should be discontinued and the effects worn off. Sedation should usually be stopped. Pain should be adequately controlled to facilitate coughing and deep breathing.

Figure 1 The early waking and neurological prognostication protocol Study End Points

THAW protocol flow diagram – for unconscious survivors of OHCA



Primary

Patients successfully extubated whilst being treated with mild therapeutic hypothermia (33°C) following cardiac arrest.

Secondary

1. Length of ventilation support
2. Neurological recovery at 12 hours utilizing GCS, FOUR score and neurological assessment.
3. Assessment of Cerebral Performance Category (CPC) scale to indicate the patient's neurological recovery on ICU and hospital discharge.
4. Length of ICU and hospital stay
5. Re-intubation rate

Statistical analysis

Continuous variables will be presented as mean \pm standard deviation (SD), and categorical variables will be presented as absolute numbers and/or percentages.

A Shapiro-Wilks test will be performed to assess the normality of the variables investigated.

According to this, an ANOVA analysis or a Mann-Whitney test will be used, where appropriate, for univariate analysis. For categorical variables will be used a McNemar test.

Survival analysis will be performed using Kaplan-Meier's method.

A Wilcoxon signed-rank post-hoc test or a paired sample t-test will be used to assess statistically significant differences in the measured parameters within different selected times. For all tests, a p-value <0.05 will be considered statistically significant.

The SPSS software, version 23.0 (IBM Corporation, Armonk, New York), will be used for statistical analysis.

Discussion

The THAW trial will investigate whether unconscious survivors of cardiac arrest can be successfully weaned from sedation and ventilation after 12 hours whilst continuing to receive

MTH for 24 hours and temperature management to prevent fever for 72 hours. It also allows the clinician to perform a comprehensive neurological assessment using a multimodal approach and neuro-prognosticate after 12 hours.

The THAW protocol makes this feasible by utilising IVTM to achieve core temperature management, combined with a rigorous anti-shiver regime including a heated surface counter-warming air blanket, as well as oral Buspirone and intravenous Pethidine. This combination prevents or minimises the patient from shivering and experiencing discomfort.

Within the THAW protocol we have also incorporated a multimodal approach to assess neurological function. Early serial neuro-electrophysiology (EEG and SSEP), as well as biomarkers S100b and NSE have been measured on all patients at admission, 6, 12 hours, then every 24 hours for the first 72 hours or until the patient regains consciousness.

Whilst neuro-electrophysiology and biomarkers have been incorporated into the THAW trial interventions, these will retrospectively be analysed and interpreted by experts at a core lab offsite who will describe the quality of the recordings for diagnostic purposes, as well as interpret the findings. The analysis of these results will be compared to the clinical outcome of the patient at the completion of the trial, and will not be available to influence the clinical decision to wake the patient early, instead this will be determined by a strict criteria and clinical suitability as previously described. Once recruitment is complete we will determine if any of the early neuro-electrophysiology and biomarkers are helpful to predict suitable patients for early waking and a positive neurological outcome.

This study has a number of limitations. Firstly it is only a single centre trial, and one which has vast experience in providing MTH to conscious patients, therefore any safety and feasibility conclusions may not be extrapolated to other real world practice. The sample size is relatively small and there is no randomized control group instead just a consecutive historical control

group. We do however believe that for the purposes of proving feasibility and safety in this cohort the numbers are adequate.

Conclusion

A trial of early waking and prognostication in OHCA has never been performed. In this single centre study we aim to wake suitably appropriate patients early, after 12 hours whilst continuing to provide MTH for 24 hours. For this group of patients it may allow clinicians to perform a much more comprehensive neurological assessment earlier, with an emphasis on positive neurological-prognostication. It also provides an opportunity to identify suitable patients who meet established criteria to be extubated early, therefore reducing mechanical ventilation time. The ability to continue temperature management in the conscious patient using IVTM, allows fever prevention for up to 72 hours with a concurrent rigorous anti-shiver regime, ensuring patient comfort. The hypothesis being patients who are extubated and no longer require multiple organ support can then be discharged from ICU, whilst continuing to receive IVTM for fever prevention, and transferred to a high dependency or ward environment, reducing the ICU length of stay, enhancing the patient's recovery and potentially reducing their hospital stay.

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