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## Clinical paper

Time to awakening after cardiac arrest and the association with target temperature management<sup>☆</sup>

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## ABSTRACT

**Aim:** Target temperature management (TTM) at 32–36 °C is recommended in unconscious survivors of cardiac arrest. This study reports awakening in the TTM-trial. Our predefined hypotheses were that time until awakening correlates with long-term neurological outcome and is not affected by level of TTM.

**Methods:** Post-hoc analysis of time until awakening after cardiac arrest, its association with long-term (180-days) neurological outcome and predictors of late awakening (day 5 or later). The trial randomized 939 comatose survivors to TTM at 33 °C or 36 °C with strict criteria for withdrawal of life-sustaining therapies. Administered sedation in the treatment groups was compared. Awakening was defined as a Glasgow Coma Scale motor score 6.

**Results:** 496 patients had registered day of awakening in the ICU, another 43 awoke after ICU discharge. Good neurological outcome was more common in early (275/308, 89%) vs late awakening (142/188, 76%),  $p < 0.001$ . Awakening occurred later in TTM33 than in TTM36 ( $p = 0.002$ ) with no difference in neurological outcome, or cumulative doses of sedative drugs at 12, 24 or 48 h. TTM33 ( $p = 0.006$ ), clinical seizures ( $p = 0.004$ ), and lower GCS-M on admission ( $p = 0.03$ ) were independent predictors of late awakening.

**Conclusion:** Late awakening is common and often has a good neurological outcome. Time to awakening was longer in TTM33 than in TTM36, this difference could not be attributed to differences in sedative drugs administered during the first 48 h.

## Introduction

At cardiac arrest the brain suffers a period of diminished blood flow with subsequent immediate loss of consciousness. After successful resuscitation most survivors will remain comatose due to ischaemic brain injury. Current guidelines recommend treating these patients with

target temperature management (TTM) at 32–36 °C  $\geq 24$  h as a neuro-protective strategy [1,2]. In order for the patient to tolerate a lowered body temperature and to reduce shivering, sedation is required for the duration of TTM.

Drug metabolism is slower and more variable in the critically ill as compared to healthy volunteers [3] and a lowering of the body

**Abbreviations:** BMI, body mass index; CPC, cerebral performance category; CPR, Cardiopulmonary resuscitation; GCS, Glasgow Coma Scale; ICU, intensive care unit; ROSC, return of spontaneous circulation; SSEP, somatosensory evoked potentials; TTM, target temperature management; TTM33, TTM at 33 °C; TTM36, TTM at 36 °C; WLST, withdrawal of life-sustaining treatments

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temperature decreases drug elimination [4,5]. Hence, sedation may linger after rewarming from TTM and discontinuation of sedation, and possibly delay awakening.

Previous studies performed before the introduction of TTM showed that awakening generally occurs within three days of cardiac arrest [6–8]. Subsequent studies on TTM-treated patients have reported longer times until awakening [9–12], with reported awakening as late as several weeks after cardiac arrest [13]. These studies were all small, retrospective and lacked comparable control groups.

Previous studies were equivocal regarding the association between early awakening and better neurological outcome, but all agree that good outcomes frequently occur after late awakening [10,11,14–17]. One study measured neurological outcome at 90 days post-arrest [10], the remainder at ICU or hospital discharge when neurological recovery is unlikely to be complete. Importantly, all but one [14] published studies on time until awakening after cardiac arrest lacked protocols for withdrawal of life sustaining therapy (WLST), increasing the risk of premature WLST leading to poor outcome, the so-called self-fulfilling prophecy [18].

This post hoc analysis of the Target Temperature Management trial (TTM-trial) [19] was predefined before the randomisation code was broken. It reports time until awakening after cardiac arrest and its correlation with long-term neurological outcome in the two intervention arms (TTM33 °C and TTM36 °C). Our pre-defined hypotheses were that time until awakening would not be affected by level of TTM and that time until awakening would correlate with long-term neurological outcome. In addition we decided to investigate whether predictors of time until awakening can be identified already at ICU admission, as suggested in recent publications [11,14].

## Materials and methods

### Study population

The TTM-trial was an international, randomized, parallel group, assessor-blinded trial designed to evaluate outcome after temperature management at either 33 °C (TTM33) or 36 °C (TTM36) in unconscious patients after out-of-hospital cardiac arrest of presumed cardiac origin [19]. It enrolled 950 adult ( $\geq 18$  years) patients in 26 months 2010–2013. The modified intention to treat group included 473 patients at 33 °C and 476 at 36 °C. Trial data were obtained from 36 intensive care units in Europe and Australia with no difference in end-of-trial mortality or 180-day neurological outcome between the intervention arms.

All patients were sedated, endotracheally intubated and mechanically ventilated. Sedation and neuromuscular blocking agents were not defined in the study protocol but sites were instructed to follow their local routines and provide equal treatment for both intervention groups. After ROSC (defined as 20 min of spontaneous circulation) there was a 4 h inclusion window. The intervention period was divided into 3 periods: (a) achievement of target temperature (4 h), (b) maintenance of target temperature (24 h) and (c) rewarming to 37 °C (8 h). After 36 h, sedation was stopped unless continued for medical reasons, at the discretion of the treating physician.

### Data collection and definitions

Primary objective was time until awakening, secondary objective was neurological outcome at 180-days according to the Cerebral performance category (CPC) scale. Good outcome was defined as: good cerebral performance (CPC 1); or moderate cerebral disability (CPC 2). Poor outcome was defined as: awake with severe disability (CPC 3); vegetative state (CPC 4); or death (CPC 5). Awakening in the intensive care unit (ICU) was defined as Glasgow Coma Scale (GCS) Motor score 6, i.e. obeying command, which was registered daily in the ICU. In patients who awoke after ICU discharge, no exact day of awakening was

available. Instead, the CPC score collected at hospital discharge and at 180-days were used, CPC 1–3 was considered awake. Early awakening was defined as awakening on day 1–4, based on previous studies [10,11,14,15,17] and before the time of the scheduled neurological prognostication [19]. Awakening on day 5 or later was defined as late awakening. Data on sedative drugs and use of sedation monitoring scales were retrospectively collected from trial sites via online questionnaires (2015–2016). Cumulative doses of sedative drugs were collected at 12, 24 and 48 h.

Potential predictors of late awakening included in the analysis were: age; sex; obesity (BMI > 25); arrest characteristics (place, witnessed, bystander CPR, time to ROSC); GCS-M on admission; shock on admission; renal failure (eGFR < 60) on admission; level of TTM; clinical seizures before awakening; and renal replacement therapy before awakening.

The day of study inclusion was named “day 1”. Study inclusion may have taken place at any hour, hence the duration of “day 1” varies from 0 to 24 h. 180-day neurological outcome was assessed by a face-to-face interview. Survival status was obtained from hospital or civil registers.

Neuroprognostication according to study protocol was scheduled at 72 h after rewarming (108 h after ROSC) in patients who remained unconscious [19] with strict criteria for WLST. WLST was allowed in persistent coma with absent or extensor motor responses to pain and bilaterally absent somatosensory evoked cortical N20-responses (SSEP) or treatment-refractory status epilepticus. WLST was also allowed for patients with early status myoclonus and absent SSEP N20 potentials after rewarming from TTM, in brain death, and for ethical reasons [20,21]. If the criteria for WLST were not fulfilled, intensive care was continued, patients re-examined daily and WLST considered if their level of consciousness did not improve and metabolic and pharmacological effects were ruled out.

### Statistical analyses

Continuous data are reported as medians and interquartile ranges. Continuous variables were compared by Mann–Whitney-*U* test (GraphPad PRISM). Categorical data were compared using Fisher’s exact test or Chi-square as appropriate (GraphPad PRISM). The frequency of awakening in the two temperature groups were compared using a cumulative incidence function with death as a competing event (R). Correlation between day of awakening and 180-day neurological outcome was performed using Spearman’s correlation (GraphPad PRISM). Predictors of late awakening were assessed by univariate and multivariate logistic regression analysis. In a first multivariate analysis, all potential predictive variables were included, predictors with *p*-value > 0.1 were then excluded from the analysis in a step-wise manner if other predictors were unaffected by their removal (SPSS). Missing data (awakening and sedation) were analysed by comparison of background variables with non-missing data. A *p*-value of < 0.05 was considered significant. Statistical analyses were performed using: GraphPad PRISM 7.0a GraphPad Software Inc, La Jolla, CA, USA; SPSS Statistics 24, IBM, Armonk, NY, USA; and R: A language and environment for statistical computing, version 3.2.5, Vienna, Austria.

## Results

### Pre-randomisation characteristics

A total number of 539 patients awoke (262 managed at TTM33 and 277 at TTM36), of whom 496 patients had registered day of awakening in the primary ICU (235 managed at TTM33 and 261 at TTM36). Forty-three patients awoke after discharge from the primary ICU according to the CPC scale, with no exact day of awakening available. There were no significant differences in the pre-randomisation characteristics between the intervention arms, with the exception of body mass index (BMI), which was higher in the group managed at TTM33 (Table 1). There was

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