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Impact of time to return of spontaneous circulation on neuroprotective effect of targeted temperature management at 33 or 36 degrees in comatose survivors of out-of hospital cardiac arrest

Jesper Kjaergaard[a,*], Niklas Nielsen[b], Matilde Winther-Jensen[a], Michael Wanscher[c], Tommaso Pellis[d], Michael Kuiper[e], Jakob Hartvig Thomsen[a], Jørn Wetterslev[f], Tobias Cronberg[g], John Bro-Jeppesen[a], David Erlinge[h], Hans Friberg[i], Helle Søholm[a], Yvan Gasche[j], Janneke Horn[k], Jan Hovdenes[l], Pascal Stammet[m], Matthew P. Wise[n], Anders Åneman[o], Christian Hassager[a]

[a] Department of Cardiology B, The Heart Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[b] Department of Anesthesia and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden
[c] Department of Cardiothoracic Anesthesiology RT, The Heart Centre, Copenhagen University Hospital, Denmark
[d] Department of Intensive Care, Santa Maria degli Angeli, Pordenone, Italy
[e] Department of Intensive Care, Leeuwarden Medical Centrum, Leeuwarden, The Netherlands
[f] Copenhagen Trial Unit, Centre of Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark
[g] Department of Clinical Sciences, Division of Neurology, Lund University, Lund, Sweden
[h] Department of Cardiology, Skåne University Hospital, Lund, Sweden
[i] Department of Anesthesia and Intensive Care, Skåne University Hospital, Lund University, Lund, Sweden
[j] Department of Intensive Care, Geneva University Hospital, Geneva, Switzerland
[k] Department of Intensive Care, Academic Medical Centrum, Amsterdam, The Netherlands
[l] Department of Anesthesia and Intensive Care, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[m] Department of Anesthesia and Intensive Care, Centre Hospitalier de Luxembourg, Luxembourg
[n] Department of Intensive Care, University Hospital of Wales, Cardiff, United Kingdom
[o] Department of Intensive Care, Liverpool hospital, Sydney, New South Wales, Australia

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ABSTRACT

Aim: Time to Return of Spontaneous Circulation (ROSC) has a plausible relation to severity of hypoxic injury before and during resuscitation in Out-of-Hospital Cardiac Arrest (OHCA), and has consistently been associated with adverse outcome. The effect of Targeted Temperature Management (TTM) may not be similar over the full spectrum of time to ROSC. This study investigated the possible beneficial effect of targeting 33 °C over 36 °C on the prognostic importance of time to ROSC.
Methods: In predefined sub-study of the TTM-trial (NEJM 2013) we investigated the relationship between time to ROSC, level of TTM and mortality and neurological outcome as assessed by the Cerebral Performance Category (CPC) scale and modified Rankin Scale (mRS) after 180 days.
Results: Prolonged time to ROSC was significantly associated with increased mortality with a hazard ratio (HR) of 1.02 per minute (95% CI 1.01–1.02). Level of TTM did not modify the association of time to ROSC and mortality, $p_{interaction} = 0.85$. Prolonged time to ROSC was associated with reduced odds of surviving with a favorable neurological outcome for CPC ($p = 0.008$ for CPC 1–2) and mRS ($p = 0.17$, mRS 0–3) with no significant interaction with level of TTM.
Conclusion: Time to ROSC remains a significant prognostic factor in comatose OHCA patients with regards to risk of death and risk of adverse neurological outcome. For any time to ROSC, targeting 33 °C in TTM was not associated with benefit with regards to reducing mortality or risk of adverse neurological outcome compared to targeting 36 °C.

* Corresponding author.
E-mail address: Jesper.kjaergaard.05@regionh.dk (J. Kjaergaard).

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1. Introduction

The time from collapse to return of spontaneous circulation (ROSC) in patients resuscitated from cardiac arrest may be perceived as a marker of severity of anoxic brain injury, although pre-hospital interventions such as cardiopulmonary resuscitation may prolong the period of hypoxia that can be tolerated without irreversible brain damage. The duration of low- or no-flow is thus likely to be reflected by time to restoration of spontaneous circulation. Time to ROSC has been shown to be an important and independent predictor of mortality and adverse neurological outcome in several case series, and also in the era of advanced protocolised post-resuscitation care, including targeted temperature management.[1–3] Targeted temperature management has been reported to be beneficial in comatose patients resuscitated from shockable primary rhythm [4,5] and indications were later expanded to patients resuscitated from OHCA with non-shockable rhythm as well.[6] A previous propensity matched cohort analysis in 400 patients indicated a modest effect of hypothermia applied in patients with time to ROSC of less than 15 min,[7] and observational studies have suggested increasing mortality with increasing time to ROSC in patients with a non-shockable primary rhythm.[8] In 2013 the Target Temperature Management of out-of hospital cardiac arrest trial (TTM-trial) was published, comparing 33 °C and 36 °C as target temperature for 24 h following ROSC, showing no difference in mortality or neurological outcome.[9] Even though no significant benefit of any of the target temperature levels interacted with median time to ROSC, time to ROSC remains a robust predictor of adverse outcome, possibly acting as marker of severity of brain injury. Time to ROSC could be clinically useful in defining a subgroup of patients that may respond favorably to either of the two target temperature management regimens.[10]

This is a pre-specified sub-study of the TTM-trial aiming to determine the prognostic importance of time to ROSC in comatose survivors of OHCA of both shockable and non-shockable origin, and the potential benefit of targeting 33 °C over 36 °C in patients with longer time to ROSC as a marker of severe hypoxic brain injury.

2. Materials and methods

We assessed the prognostic importance of time to ROSC and the potential interaction of level of the target temperature as a pre-specified sub-study of the investigator-initiated, multi-center, randomized, parallel-group, and assessor-blinded clinical TTM-trial, previously reported.[9] The main study reported results from a modified intention to treat population of 939 patients after excluding patients that did not meet inclusion criteria or for whom consent was withdrawn.[9] The main TTM trial showed no difference in mortality or neurological outcome assessed by Cerebral Performance Category (CPC) [11] or modified Rankin Scale (mRS).[12] The trial included adult patients (≥18 years) resuscitated from out-of-hospital cardiac arrest of a presumed cardiac cause, who remained unconscious (Glasgow Coma Score (GCS) <8) after sustained return of spontaneous circulation (ROSC) >20 min. Eligible patients were randomized to target temperature management at 33 °C (TTM33) or 36 °C (TTM36) for 24 h after cardiac arrest. Main exclusion criteria included unwitnessed asystole as primary rhythm and refractory shock at time of admission to hospital defined as sustained systolic blood pressure less than 80 mmHg despite administration of fluids, vasopressors, inotropes and/or treatment with intra-aortic balloon pump or left ventricular assist device.[13] Pre-hospital data regarding the cardiac arrest including initial arrhythmia, witnessed arrest, administration of bystander CPR and time to ROSC were systematically collected at admission according to Utstein guidelines.[14] Time from cardiac arrest to provision of basic (bystanders or first responders) and advanced life support (BLS and ALS, respectively) was recorded. Time to ROSC was defined as time from cardiac arrest to first recorded time point of sustained spontaneous circulation.

The study was approved in each participating country, informed consent was obtained or waived according to national laws and guidelines for Good Clinical Practice (GCP) were followed and monitored.[13] GCP monitoring included key prehospital data and during data analysis of the main TTM trial outliers were queried and corrected.

2.1. Post-cardiac arrest care

Post resuscitation care of patients in the trial included admission to an intensive care unit, sedation, mechanical ventilation and active cooling, which was initiated immediately after randomization. The protocol allowed for up to 4 h to reach target temperature, followed by 24 h at the designated target temperature and with subsequent rewarming at a rate of not more than 0.5 °C/h–37 °C in both groups. Sedation was mandatory throughout the 36 h intervention period. Active prevention of fever was mandatory for 36 h following the intervention period in patients not regaining consciousness. Patients were monitored by an arterial pressure catheter and a central venous line. Due to the pragmatic study design, no fixed protocolised treatment regimens was applied, with the exception of target temperature management and neurological prognostication which included active treatment for at least 108 h post ROSC and neurophysiological testing in patients remaining unconscious after tapering of sedation to allow for complete wash out of any sedation.[13]

2.2. Outcome

The primary outcome in the present analysis was all cause mortality and the interaction of TTM33/TTM36 and time to ROSC and mortality. Secondary endpoints included adjusted analysis of mortality, death from neurological causes and neurological outcome assessed by CPC and mRS at follow-up out-patient evaluation by a trained, blinded study nurse or similar. The CPC scale is a 5 point scale with 1 representing good cerebral performance, 2 moderate disability, 3 severe disability, 4 vegetative state and 5 death.[11] The mRS is a 7 point scale, ranging from 0 to 6 with 1 corresponding to no symptoms, 1 no clinical disability, 3 moderate disability, 4 moderate severe disability, 5 severe disability and 6 death.[12] Survival status was determined by July 2013 representing at least 180 days of follow-up in patients included in the trial.

2.3. Statistical analysis

Data are presented as mean ± standard deviation (SD) or proportions (%), and differences were assessed by Kruskal–Wallis test, Cochran–Armitage trend test or χ^2-test, as appropriate. For variables with a non-normal distribution, data are presented as median and 25th and 75th percentiles and differences were assessed by the Kruskal–Wallis test. Associations of time to ROSC and events/treatments given were analyzed by logistic regression analysis. Quartiles of time to ROSC defined four strata and were used for describing the population. Likelihood of Quartiles of time to ROSC defined four strata for survival analysis by Kaplan Meier plots, and differences were tested by the log rank test. A proportional hazard model was applied for multivariable analysis to adjust for possible confounders. An additive proportional hazard models with smoothing spline was fitted. The multivariable model was repeated after imputation of missing data was performed using random forest imputation. A p-value <0.05 was considered statistically significant. All statistical analyses were performed by R Core Team (2013). R: A language and environment for statistical computing. (R