Resuscitation 89 (2015) 142–148

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical Paper

Target temperature management of 33 °C and 36 °C in patients with out-of-hospital cardiac arrest with initial non-shockable rhythm – A TTM sub-study☆

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ARTICLE INFO

Article history:
Received 4 November 2014
Received in revised form
19 December 2014
Accepted 22 December 2014

Keywords:
Out-of-hospital cardiac arrest
Non-shockable rhythm
Targeted temperature management
Mortality
Neurologic function
SOFA score

ABSTRACT

Purpose: Despite a lack of randomized trials in comatose survivors of out-of-hospital cardiac arrest (OHCA) with an initial non-shockable rhythm (NSR), guidelines recommend induced hypothermia to be considered in these patients. We assessed the effect on outcome of two levels of induced hypothermia in comatose patient resuscitated from NSR.

Methods: Hundred and seventy-eight patients out of 950 in the TTM trial with an initial NSR were randomly assigned to targeted temperature management at either 33 °C (TTM33, $n = 96$) or 36 °C (TTM36, $n = 82$). We assessed mortality, neurologic function (Cerebral Performance Score (CPC) and modified Rankin Scale (mRS)), and organ dysfunction (Sequential Organ Failure Assessment (SOFA) score).

Results: Patients with NSR were older, had longer time to ROSC, less frequently had bystander CPR and had higher lactate levels at admission compared to patients with shockable rhythm, $p < 0.001$ for all. Mortality in patients with NSR was 84% in both temperature groups (unadjusted HR 0.92, adjusted HR 0.75; 95% CI 0.53–1.08, $p = 0.12$). In the TTM33 group 3% survived with poor neurological outcome (CPC 3–4, mRS 4–5), compared to 2% in the TTM36 group (adjusted OR 0.67; 95% CI 0.08–4.73, $p = 0.69$ for both). Thirteen percent in the TTM33 group and 15% in the TTM36 group had good neurologic outcome (CPC 1–2, mRS 0–3, OR 1.5, CI 0.21–12.5, $p = 0.69$). The SOFA-score did not differ between temperature groups.

Conclusion: Comatose patients after OHCA with initial NSR continue to have a poor prognosis. We found no effect of targeted temperature management at 33 °C compared to 36 °C in these patients.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.12.033.

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http://dx.doi.org/10.1016/j.resuscitation.2014.12.033
0300-9572/

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is associated with a high risk of dying and of neurologic impairment in survivors.[1] Even though recent data suggest an increase in survival after OHCA,[2] overall mortality remains approximately 90%. Annual incidence of OHCA is estimated to be 28–55 per 100,000 person-years with considerable variance amongst different populations.[3] Non-shockable primary rhythm as first recorded rhythm on scene is known to have major prognostic importance,[2] not only by reducing chances of obtaining return of spontaneous circulation (ROSC)[4] but also with regards to chances of surviving to hospital discharge.[2,4]

Neurological injury from anoxic brain damage remains the leading cause of death, independent of initial rhythm.[5,6] Targeted temperature management (TTM) at 32–34 °C for 12–24 h was adopted in international guidelines as being part of post-resuscitation care in patients not regaining consciousness after resuscitation from an initial shockable rhythm[7–9] and was later extrapolated to be considered in patients with cardiac arrest with initial non-shockable rhythms (NSR). Previous studies examining hypothermia in patients with NRS were mainly observational.[10–21]

Patients resuscitated from NSR are often older, have more pre-existing comorbidities, and at increased risk of developing multiple organ dysfunction, all of which may increase mortality.[2,23–25] Whether this group would benefit from or would be at greater risk of adverse events during TTM has not been thoroughly tested in clinical trials. The recent Target Temperature Management at 33 °C vs. 36 °C after Cardiac Arrest (TTM)-trial included patients resuscitated from OHCA of presumed cardiac cause regardless of primary arrhythmia.[26]

The interaction analysis between NSR and mortality has previously been published in the TTM-trial manuscript,[26] and the present analysis represents an in-depth analysis of the sub-group presenting with NSR. We aimed to assess the effect of targeted temperature management at 33 °C (TTM33) vs. 36 °C (TTM36) on mortality, neurologic outcome, and the development of multiple organ dysfunction evaluated by the SOFA score[27] in unconscious patients after OHCA with initial NSR.

2. Materials and methods

The TTM-trial was a multi-center, randomized, parallel-group, assessor-blinded, monitored, and investigator-initiated clinical trial investigating targeted temperature management of 33 °C and 36 °C, respectively in unconscious patients resuscitated from out-of-hospital cardiac arrest. Patients were centrally randomized, stratified for site, with adequate allocation sequence generation and concealment between November 2010 and January 2013.[28]

Patients at the age ≥18, comatose (Glasgow Coma Scale < 8) at hospital admission after OHCA with presumed cardiac cause were included. Eligible patients had sustained return of spontaneous circulation (ROSC) of more than 20 min. Patients were excluded if (a) randomization was not performed within 240 min after ROSC, (b) cardiac arrest with an initial rhythm of asystole was unwitnessed, and (c) the patient suffered from refractory shock. A full list of exclusion criteria has been published elsewhere.[28] Written informed consent was obtained or waived as previously described.[26]

Patients were randomized in a 1:1 ratio to either TTM33 or TTM36 for 24 h after ROSC. All patients were sedated, intubated and mechanically ventilated until the end of the intervention period. Active treatment was maintained for a predefined period of minimum 108 h after ROSC, and strict criteria for discontinuation of life support were predefined.[28]

Pre-hospital data regarding cardiac arrest including initial arrhythmia and factors traditionally associated with mortality were systematically collected at admission in accordance with the Utstein guidelines.[29]

2.1. Outcome

The primary outcome was mortality in the NSR group at the end of the trial with all patients followed-up for at least 180 days after cardiac arrest. We assessed mortality in a multivariate model of induced temperature, age, gender, pulseless electrical activity (PEA), lactate at admission, time to ROSC, bystander cardio pulmonary resuscitation (CPR), SOFA score on day one, largest 2 sites, and witnessed cardiac arrest. In 9 patients initial lactate measurements was missing and therefore excluded from the multivariate analysis. Finally we examined causes of death in the total cohort of patients with NSR. Cause of death was determined by the local physician as the most probable cause of death. The protocol had no requirement for autopsy in fatal cases.

Secondary outcome was poor neurologic function at 180 days post-CA. Neurologic function was assessed by cerebral performance category (CPC)[30] and the modified Rankin Scale (mRS).[31] Poor neurological function was defined as CPC 3–4/mRS 4–5 and good as CPC 1–2/mRS 0–3.

Thirdly we assessed the possible association between initial rhythm and the allocated target temperature on the development of multiple organ dysfunction. The Sequential Organ Failure Assessment (SOFA) score was used to assess the severity of organ dysfunction.[27] The SOFA score assesses the respiratory (PaO_2/FiO_2), coagulation (platelet count), liver (bilirubin concentration), renal (creatinine concentration), cerebral (Glasgow Coma Scale), and cardiovascular (hypotension–mean arterial pressure – need for adrenergic agent administration) functions. Each item scores from 0 to 4, with 0 being the best value. The individual organ scores are summarized. SOFA score was registered as the maximum score on day 1, 2, and 3. A possible association between initial rhythm and targeted temperature level on the cardiovascular part of the SOFA-score were also examined separately.

2.2. Ethical approval

The TTM-trial is registered at ClinicalTrials.gov (Identifier: NCT01020916) and ethical committees in each participating country approved the protocol. Informed consent was waived or obtained from all participants or relatives according to national legislations.

2.3. Statistics

Data are presented as mean ± standard deviation (SD) for normally distributed data, and median and 25th and 75th percentile for skewed data (IQR). Categorical data are presented as numbers and percentages. Differences between groups were tested by *t*-test, Kruskall-Wallis, Wilcoxon's, Cochran-Armitage's and χ^2 tests as appropriate. Differences in mortality at 30 days and at end of trial as well as neurological outcome at 180 days between strata were assessed by log-rank test, and univariable and multivariable proportional hazard ratio, the latter adjusted for potential confounding factors. Due to the limited sample size we adjusted for age, gender, PEA, lactate on admission, time to ROSC, bystander CPR, total SOFA-score on day 1, and witnessed arrest as these have previously been found to be strong predictors of outcome in OHCA patients.[24,32,33] Proportional hazard models were tested for underlying assumption of proportionality, linearity and for interactions. A comparison of the effect of targeting 36 degrees over 33 was performed by adding this variable to the model. Difference in SOFA-score and cardiovascular subscore were tested by binary linear regression with unstructured covariance and repeated measurements.