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Clinical paper

Head computed tomography for prognostication of poor outcome in comatose patients after cardiac arrest and targeted temperature management☆

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ABSTRACT

Introduction: A multimodal approach to prognostication of outcome after cardiac arrest (CA) is recommended. Evidence for combinations of methods is low. In this post-hoc analysis we described findings on head computed tomography (CT) after CA. We also examined whether generalised oedema on CT alone or together with the biomarker Neuron-specific enolase (NSE) could predict poor outcome.
Methods: Patients participating in the Target Temperature Management after out-of-hospital-cardiac-arrest-trial underwent CT based on clinical indications. Findings were divided into pre-specified categories according to local radiologists descriptions. Generalised oedema alone and in combination with peak NSE at either 48 h or 72 h was correlated with poor outcome at 6 months follow-up using the Cerebral Performance Category (CPC 3–5).
Results: 356/939 (37.9%) of patients underwent head CT. Initial CT ≤ 24 h after CA was normal in 174/218 (79.8%), whilst generalised oedema was diagnosed in 21/218 (9.6%). Between days 1–7, generalised oedema was seen in 65/143 (45.5%), acute/subacute infarction in 27/143 (18.9%) and bleeding in 9/143 (6.3%). Overall, generalised oedema predicted poor outcome with 33.6% sensitivity (95%CI:28.1–39.5) and 98.4% specificity (95%CI:94.3–99.6), whilst peak NSE demonstrated sensitivities of 61.5–64.8% and specificity 95.7% (95%CI:89.5–98.4). The combination of peak NSE > 38 ng/l and generalised oedema on CT predicted poor outcome with 46.0% sensitivity (95%CI:36.5–55.8) with no false positives. NSE was significantly higher in patients with generalised oedema.
Conclusion: In this study, generalised oedema was more common >24h ≤ 7d after CA. The combination of CT and NSE improved sensitivity and specificity compared to CT alone, with no false positives in this limited population.

Introduction

Brain injury is the main cause of death for patients hospitalised after cardiac arrest (CA) and most die following withdrawal of life sustaining therapy (WLST) due to a prediction of poor neurological prognosis [1]. A multimodal approach to prognostication is recommended, in which the results of a clinical neurological examination is considered together with findings of electrophysiological investigations, serum biomarkers and neuroimaging [2–4]. However, the

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evidence for specific combinations of prognostication tools is limited [2–4]. In a large and mainly European survey, head computed tomography (CT) and EEG were the most frequently used methods for prognostication to supplement a clinical neurological examination [5]. CT is widely available and, compared with magnetic resonance imaging, cheaper and easier to perform on ICU patients. CT is often performed upon admission to rule out non-cardiac causes of arrest and contraindications for targeted temperature management (TTM) [5–7].

Within minutes of cerebral ischemia, energy depletion leads to cytotoxic oedema, mainly in the grey matter. During the following days, vasogenic oedema will enhance the swelling [8]. Global hypoxic-ischemic oedema after cardiac arrest may be recognized on a non-contrast enhanced CT as a reduced differentiation between grey and white matter and effacement of the cortical sulci [9]. It is a sign that correlates with poor neurological outcome after CA, but the level of evidence is low [10–12]. In addition, data from long-term follow-up are limited and possible bias regarding selection of patients for CT examinations applies to the majority of studies [6,10,11,13–25]. To standardize image interpretation, various techniques of manual and automated measurements of density in the basal ganglia and cerebrum have been employed to calculate a grey-white-matter ratio that correlates with poor outcome, but there is currently no consensus on method nor cut-off values to use in clinical practise [6,15–22,24].

Neuron-specific enolase (NSE) is a marker of neuronal damage recommended for prognostication after CA [26]. High serum-levels of NSE 48–72 h after CA are predictive of poor neurological outcome [27]. NSE-release after CA correlates to pathologic EEG-patterns and other measures of severe brain injury such as global ischemia on MRI and histopathological examinations [28,29].

The Targeted Temperature Management After Out-of-Hospital Cardiac Arrest Trial (TTM-trial) was an international, multicentre trial randomising patients to 33 °C vs. 36 °C. In this study we described CT findings after CA and investigated whether generalised oedema alone or in combination with peak-NSE predicted poor outcome. Additionally we investigated the relationship of serum NSE levels to cerebral oedema on head CT.

Materials and methods

Patient selection

This was a pre-specified post-hoc analysis of the TTM-trial, registered at clinicaltrials.gov NCT01020916. Ethical committees in each participating country approved the trial protocol. In line with the Helsinki declaration, informed consent was waived or obtained from all patients or relatives according to national legislations [30]. Between November 2010 and January 2013, 36 sites randomised unconscious patients after out-of-hospital-cardiac-arrest to targeted temperature management of either 33 °C or 36 °C. The trial design, statistical analysis plan, primary, secondary and tertiary outcomes have been previously published [31–34].

Computed tomography

The indication of neuroimaging was made at discretion of the responsible physicians and at various time-points after cardiac arrest. The non-contrast CT images were examined by a local radiologist at each study site and the results were entered into the electronic case report form (eCRF) in pre-specified categories; normal, bleeding, infarction, bone fracture, generalised swelling/oedema and other findings specified in writing for each patient. Multiple options were possible. Information regarding timing and findings of the head CT examinations from the database were systematically extracted and examined. Site investigators were contacted for clarification of incomplete or conflicting data, which were corrected accordingly.

Neuron-specific enolase

29 of 36 TTM sites participated in the biobank. Serum blood samples were collected at 24, 48 and 72 h after return of spontaneous circulation (ROSC) and were pre-analytically processed at the site, aliquoted and frozen to −80 °C before shipment to the Integrated BioBank of Luxembourg for batch-analysis. NSE-analyses were performed 6 months after trial completion using COBAS e601 line with an Electro-Chemi-Luminescent-Immuno-Assay (ECLIA) kit (Roche Diagnostics, Rotkreuz, Switzerland). Haemolysis testing was performed on all samples using the Roche haemolysis index with measurements at 600 and 570 nm. All samples with a positive haemolysis index (≥500 mg/l of hemoglobin) were discarded. Detailed information about the data collection and measurement techniques was previously published [27]. NSE-levels at 48 and 72 h have similar predictive values for poor neurological outcome at 6 months after cardiac arrest [27]. To minimize the effect of missing samples at a single time-point, we used the highest available NSE-measurement at 48 or 72 h (peak-NSE) for the present analysis. We used a 48 ng/ml cut-off at 48 h and a 38 ng/ml cut-off at 72 h, accepting 2 false positive patients according to previously published results [27].

Outcomes

Neurological outcome was determined at a face-to-face follow-up approximately 6 months after cardiac arrest using the Cerebral Performance Category Scale (CPC). Good outcome was defined as; good cerebral performance (CPC 1); or moderate cerebral disability (CPC 2). Poor outcome was defined as: severe disability (CPC 3); vegetative state (CPC 4); or brain death (CPC 5).

Prognostication

A physician outside of the ICU team and blinded for treatment allocation made a neurological prognostication for each patient, according to the previously described protocol, resulting in a recommendation to either "continue active care", "not to escalate care" or to "withdraw life-sustaining-therapy". Decisions on the level of care were left at the discretion of the responsible physicians.

Statistical analysis

Continuous variables are expressed as median (interquartile range) and categorical variables as number of patients (percentages). Mann–Whitney U and Chi-squared tests were used to compare continuous and categorical variables respectively. Tests are two-sided and p-values <0.05 were considered statistically significant. The sensitivities and specificities for each variable to predict poor outcome are presented with 95% confidence intervals using Wilsonís method. Analyses were performed using SPSS software version 23. Groups of patients are categorised by timing of CT less than 24; between 24 h and 168 h; and >168 h after CA. NSE-values were calculated using the available peak value of measurements carried out at either 48; or 72 h after cardiac arrest.

Results

Patient demographics

Of 939 included patients, 357 (37.9%) underwent at least one head CT between CA and ICU-discharge. Among these, 36 (1.0%)