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Clinical paper

Prognostic value of serum biomarkers of cerebral injury in classifying neurological outcome after paediatric resuscitation☆

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ABSTRACT

Aim: To investigate if the serum biomarkers of cerebral injury, neuron-specific enolase and S100b protein, may classify unfavourable neurological outcome after paediatric cardiac arrest.
Methods: We performed a retrospective study of neuron-specific enolase and S100b measurements from 95 children treated in our paediatric cardiac intensive care unit after cardiac arrest. Neurological outcome at discharge was evaluated using the paediatric cerebral performance category scale, with unfavourable outcome defined as a change of >1 compared to pre-arrest status or death.
Results: Fifty-eight patients (61.1%) survived to discharge with 48 (50.5%) having a favourable neurological outcome. We observed significantly higher levels of both biomarkers in the unfavourable outcome group at designated time points (neuron-specific enolase at 24, 48, and 72 h and S100b at 12, 24, and 48 h after cardiac arrest, $p < 0.05$). Receiver operating characteristic areas under the curve for neuron-specific enolase were 0.83, 0.80, and 0.73 at time points 24, 48, and 72 h and 0.87, 0.81, and 0.82 for S100b at 12, 24, and 48 h after cardiac arrest, respectively. Neuron-specific enolase measurement at 24 h after cardiac arrest was an independent predictor of unfavourable outcome in a multivariable analysis.
Conclusions: Neuron-specific enolase and S100b classify unfavourable neurological outcome in this large paediatric cardiac arrest cohort. Further multi-institutional prospective studies to comprehensively evaluate the diagnostic accuracy of these biomarkers under various clinical conditions and to determine reliable cut-off values in children are warranted.

Introduction

Cardiopulmonary resuscitation (CPR) after cardiac arrest (CA) in children is associated with substantial mortality and neurological disability. Though improved over the past decades, reported survival rates after paediatric in-hospital CA (IHCA) remain low, varying between 22% and 65% [1–4]. In survivors, neurological impairment is frequent [2,3,5–7]. Survival after paediatric out-of-hospital CA (OHCA) is even more dismal with overall survival rates of 2–12% [8–10]. In children with return of spontaneous circulation (ROSC) after resuscitation, neurological cause of death accounts for up to 20% of mortality after IHCA and 69% after OHCA [5].

Early assessment of cerebral injury severity, neurological outcome and survival would be invaluable in guiding post-resuscitation therapy to avoid futile aggressive treatment and affirm therapeutic decisions such as withdrawal of support in unambiguously fatal cases. Biomarkers for cerebral injury such as neuron-specific enolase (NSE) and S100b protein are released from damaged neurons and glial cells into the blood during various types of brain injury [11–13]. Thus, their serum levels may reflect the extent of brain damage and potentially predict neurological outcome at an early stage after CA. In adults, numerous studies have demonstrated a robust association of elevated NSE and S100b serum levels with poor neurological outcome [14,15]. In children, evidence is limited but also indicates an association of biomarkers with neurological outcome [16,17]. Therefore, we investigated the correlation of both biomarkers with neurological outcome and survival after paediatric CA and their ability to discriminate between

Abbreviations: AUC, area under the curve; CA, cardiac arrest; CHD, congenital heart disease; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; IHCA, in-hospital cardiac arrest; IQR, interquartile range; MCS, mechanical circulatory support; NSE, neuron-specific enolase; OHCA, out-of-hospital cardiac arrest; PCPC, paediatric cerebral performance category; ROC, receiver operating characteristic; ROSC, return of spontaneous circulation.

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outcomes. We hypothesized that biomarkers correlate with neurological outcome and their predictive value is superior compared to conventional clinical and laboratory parameters.

Materials and methods

Study design and setting

We performed a single-centre retrospective study in the Departments of Congenital Heart Disease and Congenital Heart Surgery of a tertiary heart disease centre from February 2010 to February 2016. Reviewing our institutional database, children <18 years of age who experienced IHCA or were referred to us for CA and had either ROSC for >20 min or mechanical circulatory support (MCS) established were identified. CA was defined as external chest compression for ≥1 min. Additional inclusion criterion was a minimum of one subsequent biomarker analysis at one of the designated time points. Exclusion criteria were unclear or undocumented neurological status or neonatal asphyxia prior to CA. The study was approved by our institutional ethics committee (decision no. EA2/020/15) and requirement of individual consent was waived.

Patients

Ninety-five children met the inclusion criteria (Fig. 1). Post-resuscitation care was provided according to institutional standard procedures. Endotracheal intubation, mechanical ventilation, placement of arterial and central venous catheters and rectal or esophageal temperature probes were performed. Therapy targets included normoxia, normocapnia, normotension and normoglycaemia. Temperature management was individually decided by attending physicians and fever was treated aggressively with antipyretics and external cooling. In general, analgesics, sedatives and neuromuscular blocking agents were used as required to maintain haemodynamic stability. After stabilization, sedation and muscle relaxation medication was usually ceased to allow for clinical neurological examination. Repetitive cranial ultrasound studies in neonates and infants, and transcranial Doppler sonography in older children were routinely performed. Further diagnostic examinations, including electroencephalography, evoked potentials or cerebral imaging, were not routinely used but were initiated at attending physicians' discretion. Physicians were familiar with biomarker results.

Biomarker analysis

Blood specimens were analysed for NSE and S100b (Elecsys® NSE and Elecsys® S100, Roche Diagnostics, Mannheim, Germany) directly after sampling according to the manufacturer's specifications using an automated analyser (cobas e®, Roche Diagnostics, Mannheim, Germany) with detection limits of 0.05–370 μg/L for NSE and 0.005–39 μg/L for S100b. Sampling was performed only from existing vascular access routes. Since serial biomarker analysis after CA was gradually being adopted as routine procedure in our institution, there were several patterns of sampling time points during the study period and a varying adherence to the sampling protocol. Designated sampling time points considered in this study included initially after ROSC or establishment of extracorporeal circulatory support (termed 'initial') and with a tolerance of 2 h deviation at 12 h, 24 h, 48 h and 72 h after ROSC, corresponding to our current institutional standard time points, except for 12 h analysis. In patients with missing values, sampling had either not been conducted or sampling time differed beyond the pre-specified tolerance. Additionally, 9 patients died within 72 h after CA. Except for analyses of peak values, other sampling time points were excluded.

Outcome measurements

Primary outcome was neurological outcome at discharge as assessed by the paediatric cerebral performance category (PCPC) scale, ranging from 1 (normal neurological status) to 6 (cerebral death) [18]. Favourable neurological outcome was defined as ΔPCPC ≤1 at discharge compared to pre-arrest PCPC and unfavourable outcome as ΔPCPC >1 or death. PCPC was assigned retrospectively by three investigators independently (PK, OM, KS), two of whom were blinded to the biomarker results. In cases of discordance, majority PCPC was agreed upon. Secondary outcome was in-hospital mortality.

Statistical analysis

Statistical analysis was performed using SPSS v23.0 (IBM SPPS Inc., Chicago, IL, USA) and Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Variables are expressed as figures, percentages, median with interquartile range (IQR) or mean ± standard error as appropriate. Data distribution was tested using D'Agostino-Pearson test. Continuous variables were compared using unpaired two-tailed *t*-test for normally distributed parameters, Mann-Whitney test for non-normally distributed parameters and Fisher's exact test for categorical data. Grouped analyses were corrected for multiple comparisons using the Holm-Sidak method with alpha = 5.0%. Receiver operating characteristic (ROC) curves were employed to assess accuracy of outcome classification; curves were compared using the DeLong method. Multivariable logistic regression with backward selection based on Akaike's information criterion was used to identify predictors for unfavourable outcome. Details of model development are provided as supplemental material.

Results

Patients

Patients' characteristics are summarized in Table 1. The majority were postoperative congenital heart disease (CHD) patients who experienced IHCA. Accordingly, cardiac failure was the most frequent CA aetiology, with arrest witnessed in virtually all cases. Abnormal baseline neurological status was present in 13 patients (13.7%). Median age was 0.51 years [IQR 0.12–2.59] with a majority of neonates and infants (n = 62, 65.3%). In 59 patients (62.1%) MCS by either extracorporeal membrane oxygenation (ECMO) or ventricular assist device was established due to refractory arrest (n = 43, 45.3%) or persistent low cardiac output after ROSC (n = 16, 16.8%). Sixty-eight patients (71.6%) received targeted temperature management at 34–35 °C for 24–48 h.

Outcomes

Fifty-eight patients (61.1%) survived to discharge. Of these, 48 (50.5% of entire cohort, 82.8% of survivors) had favourable neurological outcomes, with unchanged neurological status (ΔPCPC = 0) in 33 patients (56.9% of survivors) or minor neurological deficits (ΔPCPC = 1) in 15 patients (25.9% of survivors). Unfavourable neurological outcome including cerebral death was documented in 24 patients (25.3%). All-cause mortality was 38.9% (n = 37). Cause of death was cerebral in 14 cases (37.8% of deaths). One cerebral death was unrelated to the initial CA event; the patient remained hospitalized with permanent ventricular assist device and died from acute cerebral haemorrhage 9 months afterwards. Twenty-three patients (24.2%) died from non-cerebral causes before neurological evaluation was possible and were included in the unfavourable outcome group, unless otherwise specified. Non-cerebral deaths included cardiac, respiratory, multi-organ failure and sepsis (Fig. 1).

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