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Clinical paper

Association of brain metabolites with blood lactate and glucose levels with respect to neurological outcomes after out-of-hospital cardiac arrest: A preliminary microdialysis study☆

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ABSTRACT

Aim: Out-of-hospital cardiac arrest (OHCA) is associated with poor prognosis. Cerebral microdialysis (CMD) is an efficient sampling technique to detect neurochemical changes in brain interstitial tissue. In this retrospective study, we hypothesised that there are different CMD levels between patients with favourable and unfavourable neurological outcomes.
Methods: Data of patients with OHCA admitted to Kagawa University Hospital and administered therapeutic hypothermia (TH) were collected. Using a CMD probe, extracellular glucose, lactate and pyruvate levels were measured hourly along with intracranial perfusion pressure (ICP) and cerebral perfusion pressure (CPP) for the initial 72 h during TH. The lactate/pyruvate (LP) ratio was calculated. Patients were divided into favourable [Glasgow–Pittsburgh cerebral performance category 1–2 at 30 days after cardiac arrest] or unfavourable neurological outcome groups. CMD biochemical markers and blood lactate and glucose levels were compared between two groups.
Results: Ten patients were included. ICP was significantly higher in the unfavourable than in the favourable neurological outcome group; there were no significant differences with respect to CPP. The CMD LP ratio in the unfavourable outcome group progressively increased; significant differences were observed on days 2, 3 and 4 ($p < 0.01$). Significant differences in blood lactate levels were observed between the groups only on day 3.5. CMD and blood glucose levels were higher in the unfavourable than in the favourable outcome group during TH.
Conclusion: The association of CMD levels with long-term outcomes would be better defined in a large randomised prospective study.

Introduction

Out-of-hospital cardiac arrest (OHCA) is associated with poor prognosis. Predicting neurological outcomes in these patients is complicated mainly because of the uncertainty in the evaluation of brain damage.[1–3] Cerebral microdialysis (CMD) is an efficient sampling technique to detect neurochemical changes in brain interstitial tissue and has been evaluated in patients with traumatic brain injury[4–7] intracerebral haematoma[8] and subarachnoid haemorrhage to monitor brain metabolism[9,10]; however, there are only few reports of CMD studies in patients with OHCA,[11–14] and the association of CMD metabolites (i.e. brain metabolites) with blood lactate and glucose with respect to neurological outcomes in patients with non-traumatic OHCA remains unknown. The aim of this study was to examine the hypothesis that there are different CMD levels between patients with favourable and unfavourable neurological outcomes in patients with non-traumatic OHCA treated with therapeutic hypothermia (TH).

Methods

Study design and setting

This study is a retrospective analysis of prospectively collected data of patients admitted to Kagawa University Hospital who received therapeutic hypothermia (TH) after resuscitation from OHCA between 1 July, 2005 and 30 April, 2009. This study was

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approved by the institutional review board of the Kagawa University Hospital (Heisei 16-035) and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patients' legally authorised representative prior to inclusion.

The Kagawa university hospital is an academic tertiary care centre with 613 beds and 20 intensive care beds. It is also a referral centre supporting a region with a population of approximately 150,000 people. Approximately 3–5 OHCA patients are treated with TH in our ICU each year.

Study participants and inclusion criteria

Patients ≥18 years who were comatose after resuscitation from non-traumatic cardiac arrest and received TH were included. They were excluded if they received only comfort care within 24 h of admission. Further, patients without agreement from their family or who had no neurosurgeon available to perform the procedure were excluded. The attending physician was responsible in deciding whether the CMD was initiated. All patients with CMD sampling underwent complete TH without withdrawal of ICU care.

Cerebral microdialysis

In the operating room, commercially available sterile CMA 70 microdialysis catheters (CMA Microdialysis, Solna, Sweden) were placed through a burr hole. The microdialysis catheters were inserted in the right frontal subcortical white matter. After positioning, a cranial computed tomography scan was conducted to verify the location of the catheter and check for any catheter-related intracranial bleeding. The catheters were attached to a CMA 106 perfusion pump, and central nervous system sterile isotonic perfusion fluid (CMA Microdialysis) was perfused at a rate of 0.3 μL/min. After an equilibration period of 2–4 h, samples were collected hourly and immediately analysed for glucose, lactate and pyruvate using a CMA 600 microdialysis analyser (CMA Microdialysis). CMD data are presented as real sample concentrations, uncorrected for recovery. For CMD, recovery has been estimated to be approximately 70%.

Therapeutic hypothermia

Core temperature was monitored using bladder or rectal temperature upon hospital admission and monitored during the cooling period. A target core temperature of 32–34 °C was maintained for 24 h, followed by gradual rewarming for 24–48 h.

A sedative drug [midazolam (0.2–0.4 mg/kg/h)] and an analgesic [pentazocine (120 mg/day)] was usually administered. A muscle relaxant [vecuronium (0.05 mg/kg/h)] was also administered during the induction and maintenance phases, as deemed necessary. Sedatives and analgesics were usually tapered off, once patients had been rewarmed to 36 °C.

Regarding glucose control, intervention was usually initiated when the blood glucose level was >200 mg/dL. Insulin was administered and adjusted as needed by each physician.

As for ICP management, mannitol was administered by each physician as needed. CMD metabolites were just collected for research use, and the clinical decision was not changed based on the results of the CMD metabolites.

Data sampling

The following data were collected: the number of measurements, age, sex, time from collapse to recovery of spontaneous circulation (ROSC), Glasgow coma scale (GCS) score on admission, cardiac arrest of cardiac origin, density of regions of interest (ROIs) and grey/white matter ratio (GWR) on brain CT obtained within 2 h after ROSC, details of drugs used during TH and Glasgow–Pittsburgh cerebral performance category (GP-CPC) [15] at 30 days after cardiac arrest. CMD metabolite levels, including glucose, lactate and pyruvate, were measured hourly in addition to intracranial and cerebral perfusion pressure (ICP and CPP) for the initial 72 h. The lactate/pyruvate (LP) ratio was also calculated and adopted instead of the direct value of lactate due to the nature of CMD. The tentative normal value was defined as CMD glucose level of >0.7 mmol/L [4,16,17].

Density of measurement in brain CT obtained within 2 h after ROSC

As reported by Lee et al. [18], circular ROIs (9.4 mm^2) were used to measure the densities of grey matter (GM) and white matter (WM) in Hounsfield units. The average densities of GM were measured in the putamen, while those of WM were measured in the corpus callosum.

Outcome measures

The primary outcome measure was the association of CMD metabolites with blood lactate and glucose levels with respect to neurological outcomes at 30 days after cardiac arrest. The secondary outcome measure was the association of ICP with the CMD LP ratio with respect to neurological outcomes. A favourable neurological outcome was defined as GP-CPC 1–2; an unfavourable neurological outcome was defined as GP-CPC 3–5.

Statistical analysis

Patients were divided into two groups: the favourable neurological outcome group and the unfavourable neurological outcome group. The groups were compared using the Mann–Whitney *U* test or Fisher's test as appropriate.

For each patient, 12-h pooled values of CMD metabolites, blood lactate and glucose levels as well as CPP and ICP were compared between the favourable neurological outcome and unfavourable neurological outcome groups during the observation period. Furthermore, the Spearman rank correlation coefficient was calculated between ICP and the CMD LP ratio in the favourable and unfavourable neurological outcome groups. The results are presented as n (%) or medians (interquartile ranges, IQR). A p value of ≤0.05 was considered significant.

Results

Comparison of baseline characteristics

During the study period, 18 comatose patients were admitted to the ICU following cardiac arrest and were treated with TH. Eight patients who met the exclusion criteria were excluded. Of the 10 patients included in this study, four were included in the unfavourable neurological outcome group; furthermore, a total of 828 measurements were included in this study (Table 1).

There were no significant differences between the favourable neurological outcome and unfavourable neurological outcome groups with regard to age, sex, time from collapse to ROSC, initial GCS score, the rate of cardiac arrest of cardiac origin, density of ROIs and GWR in brain CT obtained with 2 h after ROSC or details of drugs used during TH.