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Clinical paper

Cerebral blood flow velocity and autoregulation in paediatric patients following a global hypoxic-ischaemic insult

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ABSTRACT

Aim: To describe the cerebral blood flow velocity pattern and investigate cerebral autoregulation using transcranial Doppler ultrasonography (TCD) following a global hypoxic-ischaemic (HI) event in children.

Methods: This was a prospective, observational study in a quaternary-level paediatric intensive care unit. Intubated children, newborn to 17 years admitted to the PICU following HI injury (asphyxia, drowning, cardiac arrest) were eligible for inclusion. TCD was performed daily until post-injury day 8, discharge, or death, whichever occurred earliest.

Results: Twenty-six patients were enrolled. Median age was 3 years (0.33, 11.75), initial pH 6.95, and initial lactate 5.4. Median post-resuscitation Glasgow Coma Score was 3T. Across the entire cohort, cerebral blood flow velocity (CBFV) was near normal on day 1. Flow velocity increased to a maximum median value of 1.4 standard deviations above normal on day 3 and slowly downtrended back to baseline by the end of the study period. Median Paediatric Extended Version of the Glasgow Outcome Score was 4 at three months. No patient in the favourable outcome group had extreme CBFV on day one, and only one patient in the favourable group had extreme CBFV on PID 2. In contrast, 38% of patients in the unfavourable group had extreme CBFV on PID 1 ($p = .039$ compared to frequency in favourable group), and 55% had extreme CBFV on PID 2 ($p = .023$ compared to frequency in favourable group). No patient had consistently intact cerebral autoregulation throughout the study period.

Conclusions: Following a HI event, patients with favourable neurologic outcomes had flow velocity near normal whereas unfavourable outcomes had more extreme flow velocity. Intermittently intact cerebral autoregulation was more frequently seen in those with favourable neurologic outcomes though return to the autoregulatory baseline appears delayed.

Introduction

Global hypoxic-ischaemic (HI) events are a major cause of morbidity and mortality in children. Each year 18,000 children are at risk of developing hypoxic-ischaemic encephalopathy following a global HI event, such as asphyxia or cardiopulmonary arrest [1,2]. Children who survive their initial insult are often left with neurologic impairment. In a recent study of 295 children who suffered out-of-hospital cardiopulmonary arrest, 56% of survivors had poor neurobehavioral function at one year [3]. These impairments are devastating to the patient, their family, and to the healthcare system.

Transcranial Doppler ultrasonography (TCD) uses low-frequency ultrasound to measure cerebral blood flow velocity (CBFV) in the vessels within the circle of Willis [4]. This non-invasive method does not expose the patient to radiation and can be performed at the bedside. TCD allows the clinician to obtain real-time information regarding cerebral haemodynamics, including autoregulation [5–7]. Alvarez-Fernandez reported the predominant TCD flow pattern in comatose patients following return of spontaneous circulation, is that of low CBFV, which should resolve by 72 h [8].

Cerebral autoregulation refers to the intrinsic ability of the cerebral vasculature, specifically the arterioles, to react to changes in cerebral perfusion pressure to maintain constant cerebral blood flow. This process provides the brain protection from injury during extremes of flow. When outside the window of autoregulation, flow is pressure-passive. With low flow, the brain is at risk for ischaemia, contrary to high flow,

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when there is risk for oedema. Following HI injury, cerebrovascular responsiveness is altered and autoregulation is often impaired or absent [9,10]. In adults following cardiopulmonary arrest, 35% of patients had disturbed cerebral autoregulation; intact autoregulation was an independent predictor of good outcome [10]. Lee et al evaluated a small cohort of children for 72 h following cardiopulmonary arrest, those with impaired autoregulation more frequently required tracheostomy or gastrostomy tube prior to discharge [9].

In this prospective observational study, we aimed to describe the cerebral blood flow velocity pattern for children who suffered a global hypoxic-ischaemic insult. We hypothesized that there would be an initial reduction followed by a subsequent increase in CBFV. We hypothesized that children with abnormal CBFV would have impaired neurologic outcomes compared to those with normal CBFV. Lastly, children with intact autoregulation would have better neurologic outcomes compared to children with impaired autoregulation.

Methods

Patients

This was a single-centre, prospective observational study of children 0–17 years admitted to the paediatric intensive care unit (PICU) at a quaternary children's hospital following global HI insult, defined as cardiopulmonary arrest for any duration (in and out-of-hospital), submersion injury, or asphyxial injury. Children were excluded if they had a prior diagnosis of: hypoxic-ischaemic encephalopathy, disease processes known to alter cerebral blood flow (sickle cell disease or moyamoya), central nervous system structural abnormality (intracranial mass or arteriovenous malformation), seizures, traumatic brain injury, cyanotic heart disease, or moderate-severe developmental delay. Demographic data (age, gender, past medical history and mechanism leading to HI insult) were recorded. Clinical and laboratory data routinely collected during patient care were recorded (vital signs, head imaging, sodium, haematocrit, and blood gas results). Values recorded were those closest to the time of TCD. This study was approved by the Nationwide Children's Hospital Institutional Review Board and informed consent was obtained prior to enrolment.

Patient care was at the discretion of the treating intensivist, whom was not aware of study results. Within our institution, standard goals for a patient that has suffered a HI insult include: normotension, normoventilation, avoidance of hypoxemia, normonatremia, normothermia, and rapid protocolized seizure treatment. Imaging and electroencephalograms were at the discretion of the intensivist and neurology consultant.

Transcranial Doppler (TCD) examinations

TCD was performed using a commercially available 2-MHz transducer (Sonara Digital TCD, CareFusion). Initial TCD was performed within 24 h of PICU admission. Daily ultrasounds were continued through post-injury day (PID) eight, discharge, or death, whichever occurred earliest. The bilateral middle cerebral arteries (MCA) were insonated. The depth and angle of insonation giving the highest mean flow velocity and best waveform was chosen. Peak systolic, diastolic, and mean flow velocity were recorded.

Cerebral autoregulation was interrogated using the transient hyperaemic response ratio (THRR). Reported by Giller, the THRR is a dynamic method involving a direct challenge to the cerebral vasculature [11]. During continuous MCA insonation, the ipsilateral carotid artery is compressed for 5 s. Flow velocity must be reduced by 30–50% during compression. After release, THRR is calculated per the method described by Smielewski et al. [12].

$$\text{THRR} = \text{systolic FV}_{\text{hyperaemia}}/\text{systolic FV}_{\text{baseline}}$$

The systolic $FV_{hypaeremia}$ is the average systolic value of the two waveforms following carotid artery release. Systolic $FV_{baseline}$ is the average of the five waveforms preceding occlusion.

Transient hyperaemic response ratio comparisons

Intact autoregulation in healthy adults is defined as THRR ≥ 1.1 [11–13]. There are no previously published normative THRR data for children. Therefore, children in this study were compared to the normative value for healthy adults, as well as the median value of a local cohort of critically ill, intubated, and sedated children with no evidence of shock or neurologic injury (THRR controls).

Children eligible for inclusion as THRR controls were aged 0–17, admitted to the PICU, intubated, and sedated. Children were excluded if they had shock (defined as active fluid resuscitation or ongoing titration of vasoactive medications within the prior four hours), were sedated with dexmedetomidine, had developmental delay, seizures, central nervous system structural abnormalities, traumatic brain injury, or suffered a global HI event.

Clinical outcome

Short-term neurologic outcome was assessed at 3 months using the Paediatric Extended Version of the Glasgow Outcome Score (GOS-E Peds) [14]. This structured interview was performed via phone with the patient's primary caregiver/legal guardian, and provides an age-appropriate, valid measurement of neurologic outcome. Outcome categories include: 1) upper good recovery, 2) lower good recovery, 3) upper moderate disability, 4) lower moderate disability, 5) upper severe disability, 6) lower severe disability, 7) vegetative state, and 8) death. Favourable neurologic outcome defined a priori, was GOS-E Peds ≤ 4 and unfavourable outcome was GOS-E Peds ≥ 5.

Statistical analysis

Cerebral blood flow velocities were reported as standard deviations (SD) from previously published normative values for children of similar age and gender. Intubated patients were compared to critically ill, intubated and sedated children without neurologic illness or injury [15]. After extubation, patients were compared to healthy children of similar age and gender [15]. Extreme CBFV was defined as a value greater than or less than two standard deviations from normative. Mean arterial blood pressures were compared to normative data for children of similar age and gender [16]. If blood pressure fell within the age-appropriate range (5–95%), it was deemed normal.

Descriptive continuous data were reported as median with interquartile range, and categorical data were reported as percentage. Univariate analysis was performed using Mann-Whitney for continuous variables. Statistical significance was assumed with $p \leq 0.05$. Statistical analysis was performed using GraphPad, Prism (LaJolla, CA).

Results

From June 2015 to April 2017, 31 patients met inclusion criteria. Two patients were not approached per request of the treating intensivist, and three declined enrolment, leaving a sample size of 26 patients. Median age was 3 years (0.33, 11.75). The aetiology of the HI insult varied (Table 1). The unspecified cardiopulmonary arrest group included children that arrested at home, without clear, inciting aetiology.