Early Human Development 120 (2018) 17–20

Contents lists available at ScienceDirect

Early Human Development

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

Effects of caffeine on the preterm brain: An observational study

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ARTICLE INFO

Keywords:
Caffeine
Cerebral oxygenation
Near-infrared spectroscopy
Electroencephalogram
Cerebral perfusion

ABSTRACT

Background and aim: Caffeine improves neurodevelopmental outcome of preterm infants. This study analyses the effects of caffeine on the neonatal brain. We hypothesized that caffeine has a neuroprotective effect through an increase in oxygen metabolism; reflected by increased cerebral oxygen extraction, electrical function, and perfusion.

Methods: Preterm infants < 32 weeks gestation (GA) receiving their primary dose caffeine-base (10 mg/kg) were included. Ten minutes of stable monitoring were selected before, during, and every hour up to 6 h after caffeine. Near-infrared spectroscopy monitored regional cerebral oxygenation ($rScO_2$) and extraction (FTOE). Amplitude-integrated electroencephalogram (aEEG) monitored minimum, mean and maximum amplitudes. Spontaneous activity transients (SAT) rate and the interval between SATs (ISI) were calculated. Mean arterial blood pressure (MABP), heart rate (HR) and arterial oxygen saturation (SaO_2) were monitored. Arterial pCO_2's were collected before and 4 h after caffeine. Brain perfusion was assessed 1 h before and 3 h after caffeine by Doppler-measured resistance-index (RI), peak systolic velocity (PSV) and end-diastolic velocity (EDV), in the anterior cerebral artery (ACA) and internal carotid artery (ICA). Results were presented in mean ± SD.

Results: 34 infants, mean GA 28.8 ± 2.1 wk, were included. $rScO_2$ significantly decreased from 69 ± 11 to 63 ± 12 1 h after caffeine, and recovered at 6 h (66 ± 10). FTOE increased correspondingly. MABP and HR increased significantly. PSV in the ACA decreased slightly. Other Doppler variables, aEEG parameters, and SaO_2 were unaffected.

Conclusion: Caffeine increases oxygen extraction, suggesting a (transient) stimulating effect on brain metabolism. However, no substantial changes were found in brain perfusion and in electrical brain activity.

1. Introduction

Apnea of prematurity (AOP) is very common in preterm infants, with a higher incidence amongst lower gestational ages [1]. AOP is defined as a respiratory cessation of at least 20 s, or < 20 s and accompanied by a drop in arterial oxygen saturation or bradycardia. AOP is presumably caused by a relative immaturity of the central respiratory control centre. Besides general measurements such as maintaining temperature stability and airway management, methylxanthines are often used to treat AOP. Caffeine is the preferred methylxanthine due to its wide margin of safety and low incidence of side effects [2]. The drug induces respiratory hyperexcitability in several ways, including improvement of minute ventilation, improved diaphragmatic activity, and prevention of hypoxic breathing depression [3].

The efficacy of caffeine in preventing AOP has been demonstrated extensively [1]. Besides respiratory benefits, caffeine improves neurodevelopmental outcome. The “Caffeine for Apnea of Prematurity” (CAP) study, a large randomized controlled trial comparing caffeine to placebo in very low birth weight infants, showed a positive effect of caffeine on neurodevelopment [4]. At 18 to 21 months follow up, infants who received caffeine treatment showed an improved rate of survival without neurodevelopmental disability, with a lower incidence of cerebral palsy and of cognitive delay. These results were less clear at later ages, although outcome was still in favour of caffeine [5,6]. Additionally, caffeine was associated with a reduced rate of developmental coordination disorder [7]. Other studies have also shown favourable effects of early caffeine such as reduced risk of death, bronchopulmonary dysplasia, and patent ductus arteriosus, as well as less time on artificial ventilation [4,8,9].

At present in our center, caffeine is given as respiratory support to

Abbreviations: 95%CI, 95% confidence intervals; aEEG, amplitude-integrated electroencephalogram; AOP, Apnea of Prematurity; FTOE, Fractional Tissue Oxygen Extraction; ISI, Inter Spontaneous Activity Transient Interval; MABP, Mean Arterial Blood Pressure; Max, Maximum; Min, Minimum; $rScO_2$, Regional cerebral Oxygen saturation; SAT, Spontaneous Activity Transient; SaO_2, Arterial oxygen saturation

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https://doi.org/10.1016/j.earlhumdev.2018.03.008
Received 1 February 2018; Received in revised form 14 March 2018; Accepted 20 March 2018

infants born < 32 week of gestational age (GA) who are not intubated after birth, or to intubated infants who are about to be extubated. If caffeine has a neuroprotective effect, it could potentially be beneficial in other patient groups who currently do not receive caffeine treatment, such as intubated infants or moderately preterm infants born after 32 to 37 weeks of GA. In this study we addressed the effects of caffeine on cerebral oxygenation, perfusion, and electrical brain activity in preterm infants born < 32 weeks GA. We hypothesized that the beneficial effect of caffeine would be the result of an increase in oxygen metabolism of the brain.

2. Patients and methods

2.1. Patients

Preterm infants with a GA of < 32 weeks and admitted to the neonatal intensive care unit (NICU) of the Wilhelmina children's hospital Utrecht between December 2015 and September 2016 who received their first loading dose of 10 mg/kg caffeine-base intravenously, were eligible for inclusion. The two indications in our centre to start caffeine therapy were: 1) respiratory support in infants who were not intubated on admission or 2) respiratory support in intubated infants ready for extubation. Obstetric and neonatal data were obtained from hospital records. Treatment decisions were made by the attending neonatologist. Prophylactic Indomethacin is not administered in our centre. The Medical Ethical Committee of the University of Utrecht approved the study protocol and waivered parental consent, as both caffeine therapy and neuromonitoring are standard clinical care in our NICU.

2.2. Data collection

Neuromonitoring is considered to be standard care during at least the first 72 h after birth for all preterm infants born < 32 weeks GA in the Wilhelmina Children's Hospital, or longer if indicated. It includes cranial ultrasound studies, cerebral oxygenation monitoring with near-infrared spectroscopy (NIRS), and assessment of electrical brain activity with two-channel amplitude integrated electroencephalogram (aEEG). Regional cerebral oxygen saturation ($rScO_2$) was monitored with the INVOS near-infrared spectrometer (Covedien, Mansfield, MA USA) with the small adult sensor (small adult SomaSensor SAFB-SM, Covidien, Mansfield, MA, USA). Fractional tissue oxygen extraction (FTOE) was calculated with $rScO_2$ and arterial oxygen saturation (SaO_2): $(SaO_2 - rScO_2) / SaO_2$. Electrical activity was assessed with a BrainZ aEEG monitor (Natus, Seattle, WA USA). The raw EEG signal of 265 Hz was used to calculate spontaneous activity transients (SAT) and the length of intervals between SATs (ISI). The minimal, mean, and maximum amplitudes (min, mean and, max) in μV were derived from the amplitude-integrated EEG signal (aEEG). Repeated cranial ultrasound including Doppler flow assessment were performed and intra- or periventricular haemorrhages were graded according to Papile's classification [10]. Brain perfusion was assessed by the Doppler flow parameters peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistance index (RI) in the anterior cerebral artery (ACA) and internal carotid artery (ICA) before and after caffeine.

Physiological parameters were monitored on a patient monitor (IntelliVue mP70, Philips, Best, NL) and included SaO_2 (%), respiratory rate (RR, in breaths per minute), blood pressure (MABP, in mmHg) and heart rate (HR, in beats per minute). pCO_2 (mmHg) was collected from routine arterial blood gas analyses. pCO_2 from blood gas analysis had to be taken shortly before and within 4 h after caffeine intake. Neuromonitoring data and physiological parameters were simultaneously recorded with BedBase® (software designed for data compilation, University Medical Center Utrecht, The Netherlands) and analysed with SignalBase® (software designed for data analysis, University Medical Center Utrecht, The Netherlands).

2.3. Statistical analysis

Data from neuromonitoring and physiological parameters were collected prospectively. Ten minute periods of stable and representative data of neuromonitoring (NIRS and aEEG parameters) and physiological parameters were selected before caffeine intake (baseline), during the 30 min infusion period, and every hour after caffeine intake up to 6 h, and these periods were used for statistical analysis. The ten minute periods did not include any data with artefacts, such as substantial changes in the signals without physiological explanation (e.g. > 30% change in $rScO_2$), or simultaneous distortions in multiple signals indicative of handling. Cranial ultrasound data was collected at time points corresponding with baseline measurements and approximately 3 h after caffeine intake. pCO_2 data was included when available within the time inclusion criteria. Changes over time (in hours) were analysed with linear mixed effect model analysis, or paired *t*-test where appropriate. SPSS (IBM SPSS Statistics for Windows 2012 version 21, Armonk, NY, USA) and Rstudio (RStudio Team 2015 Inc., Boston, MA, USA) were used for statistical analyses, a *p*-value of < 0.05 was considered to be significant. Linear mixed effect model analysis was applied to account for missing data and to enable multiple comparisons within patients. Results are presented as mean (standard deviation).

3. Results

In total, 34 preterm infants were included in this study between December 2015 and June 2016. Infants were included only when neuromonitoring was started before administration of caffeine or if a cranial ultrasound was completed before initiation of caffeine. Of these, 32 infants had neuromonitoring data (2 infants started neuromonitoring after caffeine administration and 27 infants had repeated cranial ultrasounds. In 29 infants, repeated measurements of pCO_2 were available for analysis. All 34 infants received 10 mg/kg caffeine-base intravenously, 27 infants for respiratory support following preterm birth and 7 infants for respiratory support to prepare for extubation. The total cohort consisted of more males than females. None of the infants had a hemodynamically significant ductus arteriosus during the study period. All infants had birth weights appropriate for GA. Clinical characteristics are shown in Table 1.

Following caffeine intake $rScO_2$ decreased and cFTOE increased significantly, with partial return to baseline 6 h after caffeine intake, as shown in Fig. 1. Linear mixed effect analysis showed a significant change in $rScO_2$ and FTOE over time. Additionally, $rScO_2$ and FTOE were both associated with GA and an interaction between GA and time was found, where an increase in GA resulted in an increase in $rScO_2$ and similar decrease in FTOE. Both HR and MABP increased significantly over time following caffeine administration. Parameters and *p*-values are shown in Online Table 2 (online supplement). In the 29 infants with repeated blood gas analysis, a significant decrease was found in pCO_2 following caffeine intake (48.66 ± 6.9 mmHg before, 44.90 ± 7.6 mmHg after; p:0.02). RR and SaO_2 did not change significantly over time. Electrical brain activity was not affected by caffeine intake. SAT rate and ISI were significantly associated with GA, with an increase in SAT rate of 0.33/min per week GA ($p < 0.001$), and a decrease in ISI length of 0.42 s per GA week ($p < 0.001$). Maximal, mean, and minimal amplitude did not change significantly over time after caffeine intake, but were all significantly associated with GA. With every week GA increase, max amplitude increased with 1.44 μV ($p < 0.001$), mean amplitude increased with 0.63 μV (p:0.001), and min amplitude increased by 0.30 μV (p:0.006).

Cranial ultrasound with Doppler flow assessment was performed approximately 1 h before and 3 h after caffeine intake, results are shown in Table 3. In the ACA, there was a significant decrease in PSV and RI, while EDV did not change significantly. No changes in Doppler variables were measured in the ICA after caffeine intake.