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Cerebral blood flow and oximetry response to blood transfusion in relation to chronological age in preterm infants

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ABSTRACT

Objective: Preterm infants frequently receive blood transfusion (BT) and the aim of this study was to measure the effect of BT on cerebral blood flow and oxygenation in preterm infants in relation to chronological age.
Patients: Preterm infants undergoing intensive care recruited to three chronological age groups: 1 to 7 (Group 1; n = 20), 8 to 28 (Group 2; n = 21) & ≥29 days of life (Group 3; n = 18).
Methods: Pre and post-BT anterior cerebral artery (ACA) time averaged mean velocity (TAMV) and superior vena cava (SVC) flow were measured. Cerebral Tissue Haemoglobin Index (cTHI) and Oxygenation Index (cTOI) were measured from 15–20 min before to 15–20 min post-BT using NIRS. Vital parameters and blood pressure were measured continuously.
Results: Mean BP increased significantly, and there was no significant change in vital parameters following BT. Pre-BT ACA TAMV was higher in Group 2 and 3 compared to Group 1 ($p < 0.001$). Pre-BT ACA TAMV decreased significantly ($p \leq 0.04$) in all 3 groups; pre-BT SVC flow decreased significantly in Group 1 ($p = 0.03$) and Group 3 ($p < 0.001$) following BT. Pre-BT cTOI was significantly lower in Group 3 compared to Group 1 ($p = 0.02$). cTHI ($p < 0.001$) and cTOI ($p < 0.05$) increased significantly post-BT in all three groups. PDA had no effect on these measurements.
Conclusion: Baseline cTOI decreases and ACA TAMV increases with increasing chronological age. Blood transfusion increased cTOI and cTHI and decreased ACA TAMV in all groups. PDA had no impact on the baseline cerebral oximetry and blood flow as well as changes following blood transfusion.

1. Introduction

In neonatal intensive care units preterm infants undergo frequent blood tests to monitor their haemodynamic and oxygenation status. As a result, one of the common practices in neonatal units is to transfuse blood with an intention to maintain optimal tissue oxygenation in order to promote growth and weight gain [1]. While transfusion is beneficial in the setting of acute perinatal blood losses and severe anaemia, it has been reported to be an independent risk factor of mortality [2,3] and in the first weeks of life has been linked to progression of intra-ventricular haemorrhage [4] in preterm infants. The threshold for transfusion in preterm infants remains controversial and has led to several randomised controlled trials using liberal and restrictive thresholds for blood transfusion with conflicting reports on neurological outcomes [5–7]. Whether these thresholds were not optimal or whether haemoglobin concentration in the blood does not correlate with tissue oxygenation measurements [8–10] remains to be answered. Other studies have shown conflicting reports regarding improvement of short term effects of apnoea, tachycardia and bradycardia following transfusion [1,11,12]. Two randomised clinical trials are currently undergoing to detect whether receiving restrictive or liberal blood transfusions improves long term neurodevelopmental outcomes in preterm infants [13,14].

One of the principal objectives of blood transfusion in preterm infants is to prevent impaired tissue oxygenation in the brain and other vital organs. But the threshold at which the demands of the tissue exceed the oxygen content of the blood remains unknown. Apart from autoregulatory mechanisms of certain organs such as the brain [15], increased blood flow and increased tissue oxygen extraction are two other main processes to maintain adequate oxygenation to support metabolism in the tissues. Peripheral arterial saturation, tachycardia and serum lactate [16,17] give realistic estimates of the haemodynamic status of the systemic circulation but fail to identify specific tissue needs.

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Blood flow to various organs could be measured at the bedside using Doppler ultrasound scan of contributing arteries, and systemic haemodynamic status could be measured by left or right ventricular output [18] as well as venous return from the superior vena cava [19]. These are excellent non-invasive bedside measurements of assessing blood flow to vital organs but are not continuous and are snapshots of the state of organ perfusion in specific timeframes. It has been reported earlier that anaemic stable preterm infants could be at a clinically unrecognised high cardiac output state, which could lead to reduced oxygen delivery to brain [20]. This might in turn lead to cerebral haemorrhage and brain injury [21]. Near infra-red spectroscopy (NIRS) is a validated method of continuous measurement of cerebral tissue oxygenation [22] and cerebral blood volume in preterm infants [23,24]. NIRS has been used in various observational studies to measure cerebral tissue oxygenation in the past 20–30 years [25]. Cerebral NIRS oximetry is currently being studied to aid in newborn resuscitation in delivery room [26], to monitor cerebral autoregulation [27] and daily monitoring in neonatal units [28], and its role in management in neonatal hypotension [29,30].

Cerebral NIRS oximetry has been used in the past to assess the effect of blood transfusion in older stable preterm infants [9,10,31]. But the effect on cerebral perfusion and oximetry in pre-transfusion anaemic state and response to blood transfusion in different gestational and chronological ages remains unknown. The aim of this study was to measure the effect of blood transfusion on cerebral blood flow and oxygenation in preterm infants according to chronological age using Doppler ultrasound scan and NIRS.

2. Methods

The study was conducted at Homerton University Hospital, a tertiary level neonatal unit in London, UK from September 2012 to July 2014. Preterm infants receiving blood transfusion for clinical indication were eligible. The infants were recruited into three groups depending on their postnatal age: Group 1: day 1 to day 7, Group 2: day 8 to 28 and Group 3: more than 28 days of life. Major congenital anomalies and infants considered unstable for Doppler ultrasound or NIRS measurements by the attending clinical team were excluded. A pragmatic sample size of 20 infants per group was considered. Blood transfusion in our neonatal unit followed current British Committee for Standards in Haematology (BCSH) guidance [32] with 15 ml/kg of packed red blood cells were transfused over a period of 3 h.

2.1. Cerebral blood flow measurements

The Doppler measurements were performed using an ultrasound scanner with a 7 MHz probe (Logic P6, GE Healthcare, US). The anterior cerebral artery (ACA) peak systolic and time averaged mean velocities (TAMV) as well as pulsatility and resistance indices were measured 30–60 min pre and post blood transfusion using a range-gated pulsed wave Doppler ultrasound scan. Superior vena cava (SVC) flow was measured using the classical method. The Doppler measurements were performed by a single operator (JB) to minimise intra-operator variability and utmost care was taken to minimise the angle of insonation to the direction of flow. Cardiac morphology and presence of patent ductus arteriosus (PDA) were also recorded.

2.2. Cerebral oxygenation measurements

Cerebral oxygenation was measured using a NIRS device (NIRO 300, Hamamatsu Photonics KK. Japan), with a sample acquisition rate of six samples per second. The NIRS probe was attached to the infant's forehead and held in place by the hat used for conventional or non-invasive ventilation; utmost care was taken to minimise any movement and ambient light interference. To reduce NIRS motion artefacts the infants were minimally handled during the study period. The cerebral tissue Hb Index (cTHI) in arbitrary units and tissue oxygenation index (cTOI) in percentage were continuously measured from 15 to 20 min before, during and 15–20 min post blood transfusion, and downloaded into the research laptop.

2.3. Vital parameter measurements

The vital parameters such as heart rate (HR), respiratory rate (RR), blood pressure (BP) and arterial saturation were measured using Phillips Intellivue monitor (MP50/MP70) during NIRS measurements, and downloaded continuously using ixTrend 2.0 software (ixellence GmBH, Halle, Germany) into the research laptop.

2.4. Laboratory parameters measured

The pre and post blood transfusion laboratory parameters such as haemoglobin (Hb), haematocrit (Hct) and blood gas parameters such as pH, pCO_2 and serum lactate were also measured. Hb and Hct were measured using flow cytometry (Beckman Coulter Inc. US) in the hospital lab and the blood gas parameters were measured by a blood gas machine (GEM Premier 4000, Instrumentation Laboratory, UK) in the neonatal unit.

2.5. Additional data collected

Antenatal factors: antepartum haemorrhage (APH), maternal pre-eclampsia (PET) and intra-uterine growth restriction (IUGR), chorioamnionitis; and infant characteristics: gestational age, birth weight, Hb at birth were collected. Clinical condition on the day of transfusion: ventilation status and inotropic support were recorded.

The study was approved by the National Research Ethics Committee (REC no.12/LO/0527) and was adopted as an NIHR portfolio study

Table 1
Infant and maternal characteristics.

Characteristics	Group 1 (1–7 ds) n = 20	Group 2 (8–28 ds) n = 21	Group 3 (>28 ds) n = 18
Gestational age (completed weeks)*	26 (23–27)	25 (23–30)	26 (24–34)
Birth weight (g)*	763 (600–1180)	740 (600–1240)	793 (520–1746)
Chronological age (days)*	5 (1–7)	14 (8–27)	45 (29–93)
Haemoglobin at birth (g/dl)*	14.5 (9.8–20.7)	14.7 (10.0–17.4)	15.3 (10–18.9)
Maternal PET†	3 (15)	5 (24)	4 (22)
IUGR†	3 (15)	5 (24)	4 (22)
Chorioamnionitis†	9 (45)	8 (38)	8 (44)
Antepartum haemorrhage†	6 (30)	8 (38)	4 (22)
Antenatal steroids†	17 (85)	20 (95)	16 (89)

† Number (percentage).
* Median (range).