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Preterm infants undergoing laparotomy for necrotizing enterocolitis or spontaneous intestinal perforation display evidence of impaired cerebrovascular autoregulation

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ABSTRACT

Background: Preterm infants requiring surgery are at risk of impaired neurocognitive development caused, possibly, by cerebral ischemia associated with impaired cerebrovascular autoregulation (CAR). We evaluated CAR before, during, and after laparotomy.
Study design: This was a hypothesis generating prospective observational cohort study.
Subjects: We included preterm infants requiring surgery for necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP). Before, during, and after surgery we measured cerebral oxygen saturation using NIRS and calculated cerebral fractional tissue oxygen extraction (cFTOE).
Outcome measures: Impaired CAR was defined if correlation coefficients (rho) between mean cFTOE and mean arterial blood pressure values were ≤ -0.30 with $P < .05$. We used logistic regression analyses to determine factors associated with impaired CAR.
Results: Nineteen infants with median (IQR) GA 27.6 weeks (26.6–31.0), birth weight 1090 g (924–1430), and postnatal age 9 days (7–12) were included. CAR was impaired more often during surgery than before (12 versus 3, $P = .02$) or after (12 versus 0, $P < .01$). A higher PCO_2 level was associated with impaired CAR during surgery (OR 3.04, 95% CI, 1.11–8.12 for every 1 kPa increase).
Conclusions: More than half of preterm infants with NEC or SIP displayed evidence of impaired CAR during laparotomy. Further research should focus on mechanisms contributing to impaired CAR in preterm infants during surgery.

1. Introduction

Preterm infants who undergo major surgery are at a greater risk of impaired neurodevelopmental outcomes than their peers [1–4]. The most common surgical conditions requiring laparotomy in preterm infants are necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP). NEC is a potentially life-threatening inflammatory disease of the intestines. It affects mainly preterm infants, of whom approximately 20% to 40% require surgery [5]. SIP is less common than NEC and always requires surgical intervention [1].

Several theories have been proposed to explain the pathogenesis of subsequent neurodevelopmental impairment in preterm infants who had undergone major surgery. One possibility is that impaired cerebrovascular autoregulation (CAR) is associated with harmful fluctuations in cerebral perfusion, because in the absence of CAR, cerebral blood flow will passively vary with blood pressure [6–10]. In this case, both hypotension and hypertension may cause neuronal injury. In case of the former there is a risk of cerebral ischemia, while in case of the latter there is a risk of cerebral hemorrhage [10–14].

Previously, CAR has been assessed non-invasively with NIRS. It is

Abbreviations: NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; CAR, cerebrovascular autoregulation; NIRS, near-infrared spectroscopy; RcSO2, regional cerebral oxygen saturation; cFTOE, cerebral fractional tissue oxygen extraction; MABP, mean arterial blood pressure; BW, birth weight; PDA, patent ductus arteriosus; GA, gestational age; IQR, inter quartile range; GMH, germinal matrix hemorrhage; IVH, intraventricular hemorrhage; TPE, transient periventricular echodensities; PVL, periventricular leukomalacia

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assessed by analyzing the relationship between cerebral oxygen saturation (r_cSO_2), as an indirect measure of cerebral perfusion, and mean arterial blood pressure (MABP), as a surrogate for cerebral perfusion pressure [14]. Regional tissue oxygen saturation (rSO_2), measured by NIRS, is commonly used to assess end-organ perfusion. While decreases in rSO2 might most commonly be caused by decreased perfusion, rSO2 can decline for reasons, such as increases in oxygen demand and consumption [15,16]. The fractional tissue oxygen extraction (FTOE) can be calculated from the rSO_2 and arterial oxygen saturation (SpO_2) values. FTOE, which reflects the balance between oxygen supply and consumption, is less dependent on SpO_2 variations and therefore perhaps a better marker for perfusion [17], assuming a stable cerebral metabolic rate. CAR is considered to be impaired when cerebral perfusion changes are parallel to changes in MABP [10,18]. On the basis of this principle the adequacy of CAR can be estimated by measuring the correlation between cerebral FTOE (cFTOE) and MABP values. A negative correlation suggests impaired CAR [10,19,20], where the correlation coefficient might be indicative of the level of impaired CAR. A coefficient of correlation between cerebral tissue oxygen saturation and MABP of > 0.3, was thought to be suggestive of impaired CAR; [21] the threshold coefficient of correlation between FTOE and MBAP should be reversed to < -0.3. Clinical and biochemical factors, such as GA, PCO_2, and the use of anesthetics, may influence autoregulatory capabilities [8–10,18,22–24].

In order to determine whether surgery and/or anesthesia increase the risk of impaired CAR in preterm infants with NEC or SIP, we evaluated CAR before, during, and after laparotomy. Secondly, we aimed to determine which clinical and biochemical variables were associated with impaired CAR during surgery. We hypothesized that preterm infants have an increased rate of impaired CAR during surgery in comparison to the rates of impaired CAR before and after surgery.

2. Methods

2.1. Study design

We performed a prospective observational study. All preterm infants with suspected NEC (Bell's classification Stage ≥ 2) or SIP, who required laparotomy between September 2010 and November 2015 and who were admitted to our NICU, were eligible for inclusion.

Indications for laparotomy were radiographic signs of free abdominal air or clinical deterioration in conservatively treated NEC infants. The definitive diagnosis, either NEC or SIP, was based on surgical as well as pathological findings.

The study was approved by the local ethical review board.

2.2. Data collection on cerebral perfusion and MABP measurements

We used an INVOS 5100C near-infrared spectrometer in combination with neonatal SomaSensors (Medtronic, Dublin, Ireland) to measure r_cSO_2. To keep the sensor in place and to protect the vulnerable skin of the preterm infants we placed Mepitel® (Mölnlycke, Sweden) below each sensor. Previous reports stated that Mepitel does not adversely affect INVOS integrity or validity [25]. We placed the sensor on the left or right frontoparietal side of the head and measured r_cSO_2 continuously every 6 s. Simultaneously, we measured transcutaneous SpO_2 using Nellcor (Medtronic), every 5 s. The cFTOE value was calculated as follows: $cFTOE = (SpO_2 - rSO_2) / SpO_2$ for every 30 s that both parameters (r_cSO_2 and SpO_2) were present at the exact same time.

We aimed to collect MABP values every 5 s from those infants who had an indwelling arterial catheter, although we managed to maintain MABP data in several patients once every minute due to software limitations. The infants who did not have an indwelling arterial catheter could participate if they had noninvasive blood pressure measurements at a frequency of at least once every 5 min. We collected MABP and r_cSO_2 values simultaneously from a minimum of 30 min up to 8 h before surgery, during surgery, and up to 8 h after surgery. We defined the period 'during surgery' as the period from the start of anesthetic administration until the moment that the abdomen was closed. To determine whether an infant had impaired CAR we used the Spearman rank correlation test to calculate the correlation coefficients between the MABP and cFTOE values using all the data from the period of maximal 8 h preoperatively, the period during surgery, and for the period of maximal 8 h postoperatively. Next, impaired CAR was defined as rho ≤ -0.30 and the statistical significance as $P < .05$. For the purpose of this study, infants that did not fulfil these criteria (all correlation coefficients > -0.3) were considered as having no evidence for impaired CAR, from here onward referred to as supposedly adequate CAR. Given the relatively low sample rate of simultaneously collected and stored data (synchronized data of FTOE and MABP every 1–5 min), we were not able to perform sophisticated dynamic CAR measurements.

2.3. Demographic and clinical variables

Prospectively, we recorded characteristics of the infants including GA, birth weight (BW), gender, Apgar scores at 5 min, hemodynamically significant PDA –defined as a PDA that needed treatment according to the attending neonatologist and cardiologist on both clinical and echocardiographic grounds-, postnatal day of diagnosis, either NEC or SIP, postnatal day of surgery, and mortality. Furthermore, we analyzed the last cranial ultrasound before surgery and the first cranial ultrasound after surgery to identify any new cerebral pathology, such as transient periventricular echodensities, germinal matrix hemorrhages, intraventricular hemorrhages, or periventricular leukomalacia. Additionally, we collected data on respiratory support, PCO_2 values collected from blood gases (obtained if clinically indicated) of which we used the last before and the first after surgery. During surgery we averaged the two or three PCO_2 values collected. Furthermore, we collected data on Hb values, lactate values, C-reactive protein, platelet concentrations, volumes of red blood cell transfusions, and need for (saline) volume expansion or inotropes for circulatory support.

2.4. Surgical procedure and anesthesia

All included infants underwent an exploratory laparotomy, in supine position, via a transverse upper abdominal incision just above the umbilicus, according to a standardized surgical protocol. We collected data on the time of incision, of opening the abdomen, of resection, of forming a stoma or performing primary anastomosis, and on the time of closing the abdomen. Furthermore, we recorded any medication and fluid therapy that was administered during surgery. Anesthesia was performed by the pediatric anesthesiologist in charge. For the induction and maintenance of anesthesia we used sevoflurane. Analgesia was achieved with fentanyl and muscle relaxation with rocuronium. Postoperative analgesia in the NICU consisted of acetaminophen and morphine. PCO_2 was measured for clinical reasons as ordered by the attending pediatric anesthesiologist. For this study we chose not to use the data on end tidal CO_2 measurements.

2.5. Data and statistical analysis

For the statistical analyses we used SPSS 23.0 (IBM Corp., Armonk, NY, USA). To describe the patient characteristics we used median (IQR) values. To evaluate differences between infants with supposedly adequate CAR and infants with impaired CAR we used the Mann-Whitney test or the chi-square test.

We used the McNemar test to compare the presence or absence of CAR (categorized as adequate or impaired) before and during surgery, as well as during surgery and afterwards. Comparisons were made using the Mann-Whitney test or the Friedman test, followed by Wilcoxon signed rank test if statistically significant, whichever was appropriate given the number of measurements and distribution of the data.