Pediatric RESEARCH

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COMMENT

Intraventricular hemorrhage and white matter injury: is persistent cerebral desaturation a missing link?

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Extremely preterm infants are at high risk of mortality and neurodevelopmental impairment. Many studies have evaluated factors associated with severe intraventricular hemorrhage (IVH) among preterm infants (Fig. 1), including lower gestational age, male sex, lack of antenatal steroid exposure, lower Apgar score, umbilical cord milking, mechanical ventilation, neonatal transport, hypotension, hypercapnia, fluctuations in PCO_2, hypoxemia, pneumothorax, and specific gene mutations.[1–9] Severe IVH is associated with death, ventricular dilatation, and need for ventriculo-peritoneal shunt, as well as neurodevelopmental impairment, such as cerebral palsy and intellectual disability.[10,11]

The mechanisms of neurodevelopmental impairment in relation to the severity and location of IVH are not well understood. Direct neuronal injury, ventricular dilatation, ventriculo-peritoneal shunt complications, and white matter injury (WMI) may be the mediators for neurodevelopmental impairment. In this issue of *Pediatric Research*, Vesoulis et al.[12] report cerebral tissue oxygen saturation (StO_2) and fractional tissue oxygen extraction (FTOE) by postnatal age in relation to IVH and WMI.

While systemic hypoxia has been shown to be associated with the development of IVH,[13,14] little is known regarding the magnitude and duration of the effect of various grades of IVH on cerebral oxygenation. Vesoulis and colleagues[12] evaluated the impact of various grades of IVH as well as WMI on brain oxygenation. In this prospective observational study, they included 185 preterm infants born <30 weeks of gestation (Fig. 2). A total of 1237 near-infrared spectroscopy (NIRS) recordings were obtained from within 48 h of birth until 36 weeks' postmenstrual age. Mean StO_2 and FTOE were examined by postnatal age and by the occurrence of IVH or WMI. IVH of any grade was associated with an acute drop in StO_2 that persisted till 68 days of age. The effect was more pronounced among patients with severe IVH. The authors suggest that prolonged low cerebral oxygen saturations after IVH may predispose these infants to repeated cerebral insults. Notably, patients with WMI also had early and persistent elevations of FTOE.

The results reported here by Vesoulis et al.[12] are both novel and highly informative as the focus of prior investigations has primarily been on cerebral oxygenation and autoregulation during the development of IVH in the first few days of life.[14–22] These studies have implicated low cerebral oxygenation levels[14,15,17,19,21] and impaired cerebral autoregulatory measures[18–21] in preterm infants with severe IVH. Threshold cerebral saturation measures <50–55% have been associated with adverse IVH outcomes.[21,23] Moreover, the odds ratio was 1.02 (95% confidence interval, 1.01–1.03) for severe IVH for every 1% time in the first 72 h spent below threshold saturation.[23] However, it remains unclear whether low cerebral oxygenation contributes to the pathogenesis of IVH or reflects the mechanical consequence of the hemorrhage itself. It has been postulated that a transient increase in cerebral saturation may precede IVH due to a short-term increase in cerebral blood flow and under-utilization of oxygen.[23] Real-time measures of cerebral oxygenation and autoregulation both before, during, and after the development of IVH are difficult to capture, but necessary to establish patterns of causality. Unless such studies are performed, we should be cautious in our interpretation of changes in cerebral oxygenation and oxygen extraction in relation to IVH.

A striking finding in this study is that the elevation in cerebral tissue oxygen extraction after IVH was associated with WMI in 30 infants. The authors speculate that cerebral desaturation and increased oxygen utilization related to changes in brain metabolism after a hemorrhagic injury may play a role in the pathogenesis of WMI (Fig. 2). However, as acknowledged by the authors, increased FTOE is probably related to lower cerebral blood flow and oxygen delivery. IVH may also lead to cerebral injury and hydrocephalus by other mechanisms. In a rodent model, Chen et al.[24] noted persistent iron accumulation in the brain after intracerebral and IVH, with an increased risk of hydrocephalus, brain edema, and disruption of the blood–brain barrier. Administration of intramuscular deferoxamine was noted to attenuate the occurrence of brain edema, suggesting an additional role for iron accumulation in brain injury.

The current study has several limitations. The authors did not measure cerebral blood flow, an important determinant of oxygen delivery. In addition, consistent MRI diagnostic criteria for WMI was not part of the original study design, and it is unclear how many infants were instead diagnosed by cranial ultrasound, a modality less robust for detecting WMI. Data on IVH and WMI were extracted from the clinical radiology report, although designating a central or single-blinded reader would have strengthened the study. As Vesoulis and others have speculated, an increased collection of extravascular venous blood skews measurement of cerebral NIRS measures to lower values and can erroneously increase FTOE. Nonetheless, exploration of WMI with longitudinal cerebral oxygenation and autoregulation monitoring deserves further investigation.

This paper also highlights the need for clinical guidelines for NIRS monitoring of cerebral oxygenation in at-risk preterm infants. Changes in NIRS parameters from baseline, particularly a sustained

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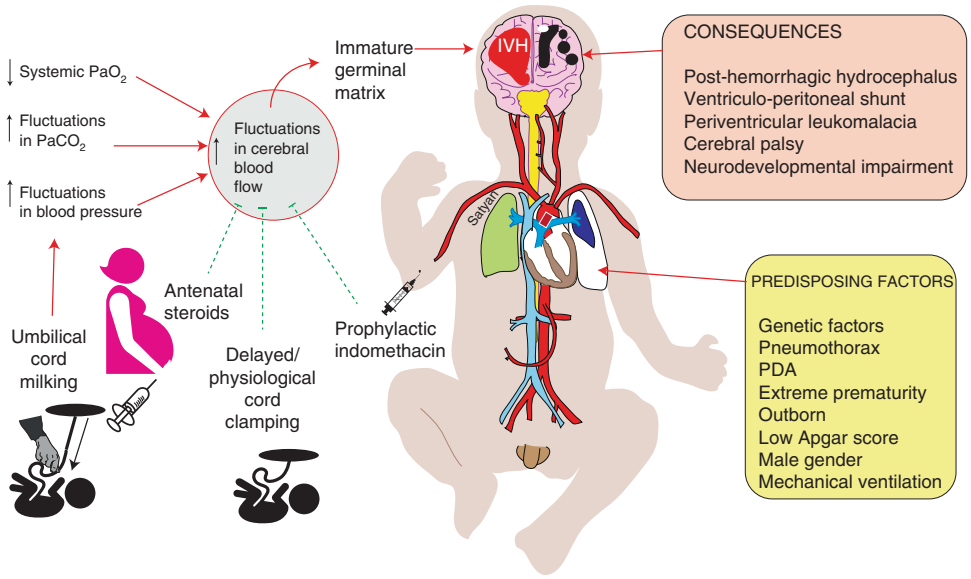

Fig. 1 Predisposing factors, pathogenesis, and consequences of intraventricular hemorrhage (IVH) in preterm infants. Solid red lines suggest a direct relationship and hyphenated, green lines suggest an inhibitory or attenuating effect. PVL periventricular leukomalacia, PDA patent ductus arteriosus. Copyright Satyan Lakshminrusimha.

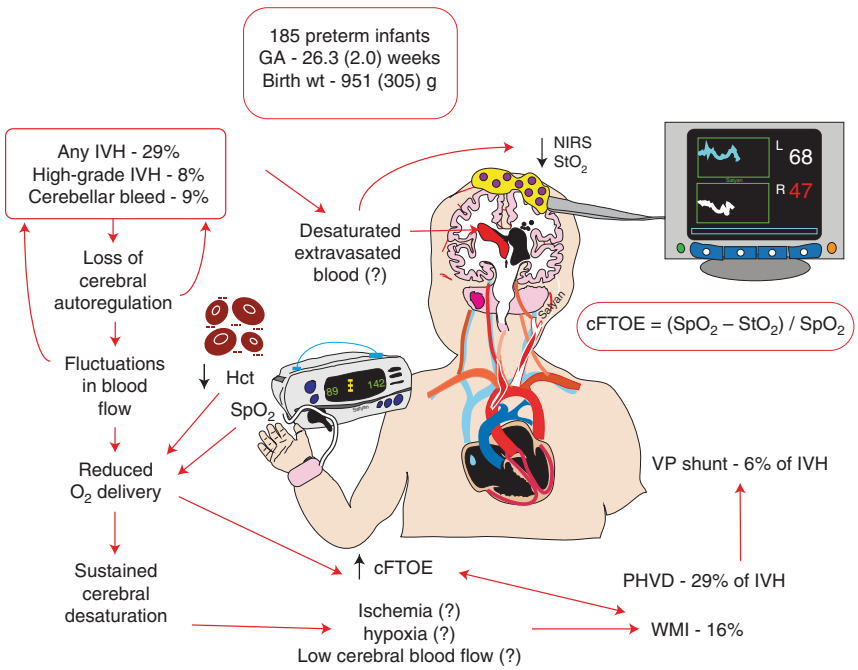

Fig. 2 Graphic abstract of Vesoulis et al.[12] This prospective, observational study evaluated 185 extremely preterm infants and monitored cerebral near-infrared spectroscopy (NIRS) measurements longitudinally and correlated these trends to the presence of IVH and development of white matter injury (WMI). IVH intraventricular hemorrhage, GA gestational age, VP shunt ventriculo-peritoneal shunt, PHVD post-hemorrhagic ventricular dilation. Numbers shown within parentheses are standard deviation. Copyright Satyan Lakshminrusimha.

decrease in StO_2 <55% should alert clinicians to perform a further evaluation. This evaluation should include a bedside clinical examination and review of changes in activity, vital signs, blood gas parameters, hemoglobin, and consideration of head ultrasonogram and electroencephalogram as needed. In patients with IVH with prolonged cerebral desaturation and elevated cFTOE, further investigation is needed into whether aiming for a higher hemoglobin target, different SpO_2 alarms, and higher blood pressure targets to increase cerebral blood flow and increase oxygen delivery may improve neurodevelopmental outcome.

There have been studies that used clinical risk factors among extremely preterm infants to generate the risk prediction models for severe IVH.[4,25] Based on data from the Vermont Oxford Network, Singh et al. developed a prediction model for severe IVH among preterm infants (gestational age (GA), 23–34 weeks, $n = 2917$).[25] GA, sex, birth weight, any antenatal steroid exposure, mode of delivery, Apgar score at 5 min, and inborn versus outborn status were associated with severe IVH. Luque et al.[4] developed a risk prediction model for severe IVH in preterm infants ($n = 6538$; birth weight, 500–1249 g) born at the NEOCOSUR Network centers

between 2001 and 2010. Gestational age, mechanical ventilation, antenatal steroid exposure, 1-min Apgar score, sex, and respiratory distress syndrome were associated with severe IVH.

In addition to the clinical variables mentioned above, low cerebral NIRS values should be considered as another important marker for identifying the risk of IVH in the extremely preterm infant. Preventing cerebral desaturation by monitoring brain NIRS may potentially be a therapeutic strategy to reduce WMI following IVH. More longitudinal studies simultaneously measuring cerebral blood flow, SpO_2, and StO_2 by NIRS before, during, and after the development of IVH are needed to confirm the important findings reported by Vesoulis et al.[12] in this issue of *Pediatric Research*.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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