Increased incidence of intracranial hemorrhage in extremely premature infants treated with hypercapnic ventilation

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Introduction

Approximately 30,000 extremely low birth weight (ELBW) infants are born annually in the US. Many of them have respiratory distress syndrome after birth and require mechanical ventilation to appropriately ventilate and oxygenate. Permissive hypercapnia is a common ventilatory strategy used by neonatologists around the world; it allows relatively high partial pressure of arterial carbon dioxide (PaCO2: 45-60 mm Hg; normal is 35-45 mm Hg) in ventilated premature infants by using lower tidal volumes and mean airway pressures in order to avoid ventilator-induced lung injury. However, recent studies suggest that hypercapnia may be associated with increased risk of intraventricular hemorrhage (IVH) in ELBW infants (1). Besides cranial ultrasound which is the standard screening imaging modality to detect IVH in premature infants, MRI can provide more specific information on both IVH and intraparenchymal hemorrhage (IPH) because of its high resolution and high specificity to blood products in the brain (by sequences sensitive to susceptibility artifact). In addition, MRI is more sensitive to white matter injury, which is also very common in ELBW infants, and often accompanies IVH. In this study, we used a randomized controlled trial approach to assign ELBW infants to permissive hypercapnia ventilation or normocapnic ventilation during the first week of life, and compared the cranial ultrasound findings during the first week and MRI findings at term-equivalent age, to determine whether the occurrence of hemorrhage is different between the two groups.

Methods

All procedures complied with IRB regulations and consents from the parent(s) of participants were obtained prior to the study. Twenty-eight ELBW infants with birth weight 401-1000 g (gestational age < 30 weeks) were recruited and randomized to hypercapnic ventilation (50-60 mm Hg, N=14) or normocapnic ventilation (35-45 mm Hg, N=14). Bedside cranial ultrasound was performed on days of life 1, 3-4, and 6-7 to screen for IVH. The grading of IVH follows the conventional standard (from I to IV). All ELBW infants were examined by MRI prior to NICU discharge at near term-equivalent age (38–42 weeks of gestation). The MRI examinations were performed on a 1.5 Tesla Philips Achieva scanner with an 8-channel SENSE coil. A neonatal brain MRI protocol was used which included sagittal T1-weighted 3D, axial T2-weighted, and diffusion weighted sequences. In addition, axial T2*-weighted gradient echo imaging sequence (for exams performed earlier than June 2011) or susceptibility weighted imaging (SWI) sequence with minimum intensity projection (MIP) reconstruction was used. Both sequences were adequate in determining whether there were blood products in the neonatal brain. No sedation was used. The infants were fed ~30 minutes before the MRI and swaddled in warm sheets and a MRI-compatible MedVac Infant Immobilizer was used to restrict movement during the scan. The MRI results were independently evaluated by two experienced neuroradiologists to determine whether there were blood products in the brain. In addition, the overall white matter development for each subject was also scored independently and then averaged from the two investigators. The scoring consists of five components: white matter (WM) signal intensity, volume of periventricular white matter, presence of cysts, ventricular dilation, and corpus callosum thickness, with each component scored from 1 to 4, corresponding to normal, mild, moderate, and severely affected, respectively. The overall score was the sum of the five scores and is regarded as a reflection of white matter integrity. The average score between subjects with or without ultrasound diagnosis of IVH and between subjects with or without permissive hypercapnia were compared by an unpaired two-sample t-test using Matlab.

Results

Eleven subjects had IVH by cranial ultrasound, including 3 with Grade I, 2 with Grade II, and 6 subjects with Grade III or IV. Among them, 8 received hypercapnic ventilation, and 3 received normocapnic ventilation. All of these 11 subjects had blood products in their brain by MRI (an example is shown in Figure 1), which appeared to be more sensitive to hemorrhage than cranial ultrasound. In total, 19 of the 28 subjects had evidence of hemorrhage on MRI; 3 additional infants from the hypercapnic group and 5 additional from the normocapnic group. The results were listed in Table 1. The WM score results are listed in Table 2, in which subjects with ultrasound diagnosis of IVH had significant higher scores (worse development) than subjects without ultrasound diagnosis of IVH. While the overall WM scores for the groups with or without permissive hypercapnia were not significantly different, the number of subjects with abnormal WM (defined as overall score ≥6) was higher in the hypercapnic group than the normocapnic group (Table 1).

	hypercapnic	normocapnic
IVH on ultrasound	57%	21%
Blood on MRI	79%	57%
Abnormal WM	64%	43%

Table 1: Percentage of ELBW infants with hemorrhage or abnormal white matter revealed by ultrasound and/or MRI

IVH	**No IVH**	**p-value**
9.75±3.75	7.41±2.07	0.04
Blood	**No blood**	**p-value**
8.71±3.06	7.28±2.60	Not significant
hypercapnic	**normacapnic**	**p-value**
7.38±3.21	7.14±2.78	Not significant

Table 2: Comparison of white matter scores on MRI

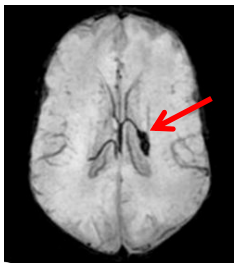

Figure 1: SWI shows blood in the lateral ventricle and periventricular white matter

Discussion

PaCO2 is a potent regulator of cerebral blood flow (CBF). Hypercapnia causes vasodilation, increases CBF, and may be detrimental to the vulnerable blood vessels in the brain of extremely premature infants. In our study, both ultrasound findings of IVH during the first week of life and MRI findings of blood products at term-equivalent age suggest that ELBW infants with hypercapnic ventilation may be at higher risk of hemorrhage in the brain, as shown in Table 1. IVH during the first week of life may be associated with poor WM development at term-equivalent age (Table 2). Although the effects of hypercapnic ventilation on cerebral WM development were not significantly different, this may be due to limited sample size or because the effects need to be investigated by advanced quantitative MRI methods which are more sensitive to subtle changes in the brain.

References

1. Kaiser JR et al, Journal of Perinatology 2006; 26: 279-285

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