Intubation Attempts Increase the Risk for Severe Intraventricular Hemorrhage in Preterm Infants—A Retrospective Cohort Study

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Objective To evaluate whether neonates exposed to multiple intubation attempts within the first 4 days after birth have an increased incidence of intraventricular hemorrhage (IVH).

Study design This is a retrospective cohort study of infants intubated during the first 4 days after birth. Infants had birth weights (BWs) less than 1500 g and were admitted to the neonatal intensive care unit (NICU) at the University of California, San Diego, between January 1, 2005, and July 30, 2009. A subgroup analysis was done for infants with BW less than 750 g.

Results A total of 308 infants with BW <1500 g, including 102 with a BW <750 g, were intubated within the first 4 days of life. The number of intubation attempts was significantly greater in infants with a BW <750 g who had severe IVH compared with those with mild or no IVH (OR 1.395, 95% CI 1.090-1.786, $P = .008$). For infants with BW <1500 g, the number of intubation attempts in the delivery room was significantly greater for infants with severe IVH (OR 1.317, 95% CI 1.052-1.649, $P = .016$).

Conclusion Increased intubation attempts were associated with increased incidence of severe IVH in infants with BW less than 750 g and in infants less than 1500 g who were intubated only in the delivery room. Prospective studies are needed to further evaluate the relationship between intubation attempts and severe IVH. *(J Pediatr 2016;177:108-13).*

Approximately 12 000 premature infants develop intraventricular hemorrhage (IVH) every year in the US.[1-3] The incidence of IVH in very low birth weight (VLBW) infants has declined from 40% to 50% in the early 1980s to 20% in the late 1980s[1,4]; however, IVH has been reported to occur in 45% of the smallest infants weighing 500-750 g.[1,5] Unfortunately, in the last 2 decades the occurrence of IVH has remained static.[1,6]

Severe IVH profoundly decreases mental developmental index and physical developmental index scores. Grade 3-4 IVH requiring intraventricular shunt placement can reduce the mental developmental index score by 20 points and physical developmental index score by 30 points.[7] Therefore, in addition to health and wellness on a personal level, an intervention that could decrease the incidence of IVH would have a large societal impact.

The development of IVH is multifactorial and includes a complex combination of vascular and anatomic immaturity and hemodynamic factors that likely work in concert to result in the rupture of germinal matrix vessels.[8] Of particular concern, premature infants tend to experience impaired cerebral pressure autoregulation, leading to increased sensitivity to fluctuations in cerebral blood flow and increased probability of hyperperfusion, which may rupture fragile vessels.[8]

Intubation after birth has been found to be associated with IVH with an OR adjusted for lower gestational ages of 7.50 (95% CI 4.56-12.35).[9] It is unclear, however, whether the intubation procedure itself contributes to the occurrence of IVH or if intubation is a surrogate marker for illness. Intubation of the preterm infant often is accompanied by abnormal physiologic responses, especially if the infant does not receive adequate premedication. These include bradycardia, hypertension, hypotension, pulmonary hypertension, increased intracranial pressure, increased cerebral blood flow, and oxygen desaturation.[10-17]

Studies in animals involving intubation of neonatal pigs demonstrated increases in mean arterial pressure in the study group as well as significantly more hemorrhage in the basal area of the brain.[15] By measuring anterior fontanels, Friesen et al[11] showed that intracranial pressure increased by a mean of up to 197% during intubations. In their study, Millar and Bissonnette[13] reported that intracranial pressure increased 254% from baseline during unanesthetized intubation attempts. When performed under anesthesia, increased intracranial pressure did not occur.

A prospective study of 273 intubations found that an adverse event occurred in 39% of the encounters and that hypoxemia occurred 44% of the time and

BW	Birth weight
DR	Delivery room
IVH	Intraventricular hemorrhage
NICU	Neonatal intensive care unit
VLBW	Very low birth weight

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Funded by University of California, San Diego. The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.06.051

bradycardia occurred 24% of the time.[18] In a retrospective chart review of 88 extremely low birth weight infants who were intubated in the delivery room (DR) during the first 10 minutes after birth, those who needed more than 1 attempt at intubation had a greater likelihood of death or neurodevelopmental impairment.[19] It is possible that systemic hemodynamic instability and inadequate cerebral pressure autoregulation occur during intubation, resulting in cerebral pressure passivity, which in turn is associated with the development of IVH.[20] We hypothesized an association between increasing number of intubation attempts and severe IVH and evaluated this relationship in a population of VLBW (<1500 g) infants.

Methods

This was a retrospective cohort analysis of a prospectively collected database of inborn, VLBW, infants who were intubated in the first 4 days after birth and admitted to the neonatal intensive care unit (NICU) at the University of California, San Diego, between January 1, 2005, and July 30, 2009. The population was chosen because 90% of IVH occurs within the first 4 days after birth and 50% occurs within 24 hours after birth.[8] Infants with any known grade of IVH before the first intubation attempt were excluded from the study. Data collection began in 2009, and we evaluated all eligible VLBW infants admitted to our unit in the previous 4.5 years.

It is unit procedure for an observer (usually a respiratory therapist) to record all intubation attempts for each infant into a dedicated respiratory database. From this database, we collected the following information: the location of each attempt (DR or NICU), date and time of each attempt within the first 4 days after birth, the operator classification (1, medical student/intern/resident; 2, neonatal fellow; 3, attending physician; 4, neonatal nurse practitioner), and the use of premedications (if any). An intubation attempt was defined as any time the laryngoscope was placed in the infant's mouth. Unit procedure dictates that each attempt should be limited to a maximum of 30 seconds.

In addition, our NICU has data collectors that gather medical history from the patient charts to report to the California Perinatal Quality Care Collaborative. We used these data to gather medical history, including the occurrence and highest grade of IVH, complications during NICU stay, and demographic data. The study authors also reviewed the medical charts to verify and obtain any missing data. IVH on ultrasound scan or magnetic resonance imaging was graded by the radiologist by use of the Papile classification: Grade I, subependymal hemorrhage; Grade II, IVH without ventricular dilatation; Grade III, IVH with ventricular dilatation; Grade IV, IVH with intraparenchymal hemorrhage.[21] Mild or no IVH were defined as IVH Grade 0, 1, and/or 2; severe IVH was defined as Grades 3 or 4 IVH. In the first 4 days after birth, some extubated infants (whether intentional or accidental) required reintubation. The number of attempts was recorded as total attempts from all episodes of intubation. Each grouping of attempts that led to a successful intubation was defined as an episode of intubation, and the numbers of episodes also were recorded.

During the study period, it was unit procedure to premedicate infants before intubation in nonemergent situations. The choice of premedications was made by the attending physician on duty, although not all attending physicians used premedication. When it did occur, premedication typically included an analgesic (usually either morphine or fentanyl), a vagolytic agent (usually atropine), and a muscle relaxant (usually cisatracurium or mivacurium).

The primary outcome variable was severe IVH, defined as IVH Grades 3-4. Univariable analyses were performed for intubation related potential confounding factors: number of attempts, use of premedications, type of operator, and location of intubation DR vs NICU. In addition, intrinsic confounding factors potentially associated with IVH were analyzed, including birth weight (BW), gestational age, sex, antenatal steroid exposure, maternal chorioamnionitis, other maternal infections, mode of delivery, Apgar scores at 1 and 5 minutes, necrotizing enterocolitis, presence of pneumothorax, early bacterial sepsis, any postnatal steroid exposure, and postnatal steroid exposure for hypotension. The risk factors found to be significant in the univariable analyses were included in a multivariable analysis. We considered a P value < .05 as significant. Subgroup analysis was performed for infants with a BW <750 g. All analyses were performed with the R programming language (version 3.2.4). This project was approved by the University of California, San Diego Institutional Review Board.

Results

A total of 308 VLBW infants (mean gestational age 26.9± 2.2 weeks) were intubated during the first 4 days after birth, including 102 infants with a BW of less than 750 g (mean gestational age 25.1 ± 1.7 weeks). Antenatal steroids were administered to more than 90% of the mothers in both groups. Demographic data are shown in **Table I**, and the results for risk factors significantly associated with severe IVH used for the multivariable analysis are shown in **Table II**.

A total of 188 infants were only intubated in the DR, 94 infants were only intubated in the NICU, and 26 infants were intubated in both the DR and the NICU. The premedication rate was 20% for all of the infants in the study and 52% for the subgroup of infants who were only intubated in the NICU. The mean and median total intubation attempts within the first 4 days after birth was 3.045 (SD = 2.017) and 3 (range 1-13), respectively. The incidence of any IVH was 25.3%, and the incidence of severe IVH was 8.8%.

For the entire group of VLBW infants, there was no statistically significant difference in the number of intubation attempts between those with mild IVH (mean 2.99; median 3, IQR 2,4, max 13) or those with severe IVH (mean 3.59, median 3, IQR 2,4, max 13), OR 1.13, 95% CI 0.958-1.34, P = .144.

In a subgroup analysis of infants with a BW of <750 g, an increased number of intubation attempts was associated with severe IVH in both the univariable analysis (OR 1.395, 95% CI 1.090-1.786, P = .008) and multivariable analysis, adjusted for the other significant covariates listed in **Table II** (OR 1.524, 95% CI 1.109-2.092, P = .009). Those with mild or no