Significant Intraventricular Hemorrhage is more likely in very preterm infants born by vaginal delivery: A multi-centre retrospective cohort study

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Key words

Intraventricular hemorrhage, preterm infants, vaginal delivery, cesarean section, mode of delivery.

Abstract

Objectives To determine the association between mode of delivery (vaginal delivery [VD] vs cesarean section [CS]) and the rate of significant intraventricular hemorrhage (sIVH) in preterm infants.

Methods A multi-centre retrospective cohort study, based on data collected from the Vermont Oxford Network database. Infants born between 23 and 31^{+6} weeks of gestational age between 2001 and 2014 were identified. Exposure was the mode of birth (VD vs. CS). Primary outcome was development of sIVH. Data were analyzed using univariate and multivariate statistical methods.

Results A total of 1575 infants were eligible. 902 infants were born by CS and 673 by VD. Univariable analysis showed that infants born vaginally were more likely to have sIVH ($p<0.001$), die before discharge ($p<0.001$), have a composite poor outcome (death, sIVH or PVL), need oxygen therapy at 36 weeks corrected gestation ($p=0.010$) and have a longer hospital stay ($p=0.006$). After adjusting for available confounders, multivariable analysis persistently showed that infants between 23-27 weeks born by CS were less likely to develop sIVH [OR 1.61 (1.01 to 2.58), $p=0.049$].

Conclusions sIVH is less common in very preterm infants (23-27 weeks of gestation) delivered by CS. However, neurodevelopmental risks associated with survival at this early age, as well as increased maternal morbidities must also be considered.

Introduction

Preterm infants are at high risk of poor neurodevelopmental outcomes and death. The biggest single cause of this, is the development of significant intraventricular hemorrhage (sIVH) following delivery [1]. SIVH, defined as grade 3 or 4, is predictive of major morbidity, which includes blindness, mental retardation, cerebral palsy and death. Various treatments have been tried to reduce the risk of IVH [1-6or to treat the infants following the development of sIVH, but none are routinely available or recommended [7].

The role of Cesarean Section (CS) as a protective measure against sIVH in very preterm infants has been proposed, yet the most optimal route of delivery continues to be hotly debated [8]. A recent Cochrane, systematic review and meta-analysis of interventional studies [9] found that not enough women have been recruited into trials of mode of birth at preterm gestations, and observational studies have been sparse. Observational studies demonstrated some benefit for CS in reducing neonatal mortality [10] but there is little to support its role in reducing neonatal morbidity as well, and specifically sIVH. Such evidence would be useful for informing discussions between pregnant women at risk of preterm birth and their caregivers, until evidence from randomized controlled trials becomes available.

Our observational study aimed to determine the association between the mode of delivery (vaginal delivery [VD] vs. CS) and the rate of sIVH in very preterm infants in two large perinatal centers in Bristol, UK.

Methods

This is a retrospective observational study. We used the Vermont Oxford Network (VON) database ('Nightingale') to collect our data (https://public.vtoxford.org/). The VON Database was established in 1989, prospectively recording data on all infants born below 1500g or 32 weeks as well as infants meeting other eligibility requirements: even if the infant is not admitted to neonatal unit.

Today, VON has evolved into a community of practice that includes nearly 1,000 centers around the globe that voluntarily submit data about the care and outcomes of high-risk newborn infants. While it's main aim is that of benchmarking, its high-quality data standard is also ideal for novel research. Details of the background and structure of the database are available from the website https://public.vtoxford.org/about-us/. Data for VON are entered by individual units and collated by the network. Data were then extracted from this database using predetermined criteria for this work.

All infants born in one of the two maternity units in Bristol, UK (Southmead Hospital, North Bristol NHS Trust and St Michael's Hospital, University Hospitals Bristol) between 2001 and 2014 (inclusive) were identified. Infants born between 23+0 and 31+6 weeks of gestational age were eligible (n=1,668). 93 (5.6%) infants had missing data on their IVH status, so were excluded, leaving 1575 infants for the analysis. Exposure was the mode of birth; defined as either VD or CS. The primary outcome was developing sIVH (defined as grade 3 or 4 [11), by 28 days of age, identified using any form of cranial imaging] and secondary outcomes were grade of IVH [11], periventricular leukomalacia (identified by day 28 using any form of cranial imaging), death prior to discharge, chronic lung disease (defined as oxygen requirement at 36 weeks corrected gestation) and length of stay in the level 3 neonatal unit (days) and a composite poor outcome (death, sIVH or PVL). Potential confounders were identified a-priori and categorized into two groups:

- Antenatal (gender, antenatal steroids, maternal hypertension, multiple birth).
- Intrapartum (birth weight, gestation, administration of magnesium sulphate, chorioamnionitis, early neonatal sepsis).

All measures were derived from the definitions used by the Vermont Oxford Network [https://nightingale.vtoxford.org/help/AIT/WebHelp/index.htm#4658.htm] benchmarking database and further details are available on request.

Initially the demographics and clinical characteristics of the cohorts were derived (Table 1). As data collection, and definitions, varied by year, not all measures (e.g. magnesium sulphate administration prior to delivery and delayed cord clamping) were recorded in all years. The univariable associations between vaginal delivery and CS were derived by comparing mode of delivery with the risk of sIVH and other secondary outcomes. For the regression models, a missing data technique was used to impute the missing covariates only, hence allowing all infants to be included in the adjusted regression models. Exposure and outcomes were not imputed. Details of the imputation process are shown in appendix 1. Logistic regression models were derived using sIVH as the dependent variable. Initially, an unadjusted analysis was performed, using a random effect multi-level model to allow for changes in CS rate over the 14-year period. A second model was derived after adjusting for the available confounders (above). The model was then repeated for the other, secondary outcomes. Finally, a linear regression model was derived to test the association between vaginal delivery and the length of stay.

Five sensitivity analyses were performed; in the first, the analysis was repeated using only those infants with complete data (complete case analysis). We then repeated the analysis to test if any association was modified by gestational age (categorized as <28 weeks, or 28 weeks or greater), multiple birth or gender. Finally, we repeated the analysis using small for gestational age (SGA) (defined as a birth weight two of more SD below the gestational mean) rather than absolute birthweight as a potential confounder. Given the numbers of infants in the cohort (see Results) we have over 95% power to detect a decrease in severe IVH rates from 10% (vaginal birth) to 5% (caesarian section births), with an alpha of 0.05.

Analysis was performed using STATA 14. Data is presented as n (%), median (IQR), mean (SD) or OR (95% CI) as appropriate. Ethical approval was obtained from the North Somerset and South Bristol Clinical Ethics Committee (ref: 11/sw/0209).

Results

A total of 1575 infants were eligible for the study. 902 (57.3%) infants were born by CS, and 673 (42.7%) by VD. Infants born vaginally were more premature (26.6 vs 28.0 weeks), were more likely to be SGA (6.1% vs 0.6%), had smaller head circumference (24.8 vs 25.3 cm), and were more likely to have been exposed to chorioamnionitis (38.1% vs 22.9%) and develop perinatal sepsis (3.6% vs 1.4%). They were also less likely to have received antenatal steroids (86.7% vs 92.1%) or to have been exposed to maternal hypertension (2.4% vs 28.5%). Following birth, infants born by vaginally had significantly lower Apgar scores, were more likely to be intubated (81.7% vs 71.2%), to have been given surfactant in the delivery room (73.3% vs 65.5%), and to have received more surfactant compared to infants delivered by CS (Table 1).

In table 2, a univariable analysis was performed to assess association between mode of delivery and clinical outcomes. Results showed that infants born vaginally compared to those delivered by CS had a higher incidence of sIVH (16.2% vs 6.8%, $p<0.001$). They had a different profile of IVH grade ($p<0.001$), and were more likely to die before discharge ($p<0.001$), to have a composite poor outcome (death, sIVH or PVL), to need oxygen therapy at 36 weeks corrected gestation ($p=0.010$) and had a longer hospital stay ($p=0.006$). Risk of developing PVL was not associated by the mode of delivery.

When the associations were tested in a regression model (table 3), the unadjusted results were compatible with the univariable analysis above. After adjusting for available confounders, results persistently showed that infants born vaginally had higher odds of sIVH (OR 1.61 (1.01 to 2.58), $p=0.049$). However, there were no association with the chance of death before discharge ($p=0.687$), PVL ($p=0.420$), death, sIVH or PVL ($p=0.174$), oxygen requirement at 36 weeks' gestation ($p=0.980$), or total length of neonatal hospital stay ($p=0.931$).

In the sensitivity analysis, first, a complete case analysis produced a less precise but compatible result to the main analysis (OR 3.51 (1.17 to 10.58)).

After splitting the cohort by gestational age there was evidence that the association between vaginal delivery and sIVH remained in the extremely preterm (born before 28^{+0} weeks of gestation) infants (OR 2.05 (1.29 to 3.25)), but there was little evidence for this association in the more mature infants (OR 1.18 (0.51 to 2.72)), despite lack of evidence from interaction tests that the association was modified by gestational age ($p_{interaction}$=0.244) or multiple birth ($p_{interaction}$=0.864). There was, however, some evidence that gender modified the relationship ($p_{interaction}$=0.075), with male infants having a greater risk than female infants (OR 2.48 (1.22 to 5.06) vs 1.24 (0.74 to 2.10)). Repeating the analysis controlling for IUGR (rather than birth weight) gave similar results to the main analysis (OR 1.61 (1.04 to 2.49)).

Discussion

Our analysis suggests that cesarean section was associated with a reduced incidence of sIVH for infants born at 23-27 weeks of gestation. This effect was still present even after adjusting for available confounding factors. We had limited statistical evidence from interaction tests that the effect differed by gestational age. Therefore, the attenuation of effect of CS on sIVH rates in infants born between 28-32 weeks in this study may simply be due to the smaller incidence, and hence precision, in those infants born at later gestations. In contrast, we were unable to find an association between the mode of delivery and other measures of neonatal outcome; mortality rates, periventricular leukomalacia, oxygen requirement at 36 weeks' gestation or total length of neonatal hospital stay. Interestingly, although both genders had a raised risk for sIVH (albeit with wider confidence intervals), there was possible modification of the association by gender; male infants having greater risk of sIVH compared to female infants. Further work may help clarify if the association is truly different for male compared to female babies and why.

Randomized controlled trials to assess the effect of mode of birth on perinatal outcomes in very preterm infants are limited and mostly incomplete in its data collection due to recruitment difficulties [9]. Most observational studies investigating mode of birth have assessed the association with mortality and report limited data on IVH outcomes [9,10,12]. Some work does

however use IVH as the main outcome although the results are heterogeneous and this may be in part, secondary to differences in the populations (e.g. gestational ages). A recent study investigating the impact of antenatal steroids on IVH risk, does report a potential benefit of the mode of delivery in the provisional analysis, although the association was not tested further in the adjusted regression analysis [13]. Also, another study by Dani et al [14] on 218 neonates, has found that infants with gestational age less than 28 weeks who were born vaginally compared to those born by CS, had a higher rate of grade 3 IVH (18% vs. 2%, p<0.0001) although other studies have not reported an association between the mode of birth and IVH [15-18].

Results of these analyses must be interpreted with caution; this is a retrospective observational study, and therefore, some unknown biases and confounding variables are not accounted for. This work used data collected from VON, which is a well-established database used for both research and benchmarking and although it provides detailed definitions of the data-points, clinical judgement (e.g. if the IVH was a grade II or III) will still introduce some likely non-differential bias that could attenuate any association. Furthermore, some details of potential confounders were not available to use such as stage of labour on admission, spontaneous or induced preterm labor, planned or emergency CS, the presence of antepartum haemorrhage and the infant's presenting part at time of delivery. However, it can be argued that infants with a breech presentation would have been more likely to be offered a CS [19,20], and if so, the effect seen in this work may have underestimated the benefits of CS in vertex presenting infants. The dataset has also changed over the years, and so we had missing data for some confounders (esp. antenatal magnesium sulphate) due to changes in data collection. However, this missing data is likely to be Missing Completely At Random (MCAR), so the missing data techniques used here would be appropriate. We have performed a complete case analysis which reported similar findings. Because of limitations in the data source, however, we were unable to measure maternal illness/morbidity (e.g. classical CS and its potential consequences) and did not have data on long term outcomes. Nevertheless, a reduction in sIVH rates of this magnitude is likely to have important long-term benefits [21].

SIVH is associated with motor and cognitive impairment in neonates as well as worse developmental outcomes in school and as adults, and according to the findings reported here may represent avoidable morbidity, at least to a degree. If the association seen here is true, the implications are important. IVH is now the single biggest cause of neurologic disability in the preterm population [22]. Its long-term effects can be devastating and treatment offered is very limited. Some evidence exists that rates can be reduced by delaying cord clamping [23], and antenatal delivery of vitamin K [24]. However, the hemorrhage can often cause significant damage to the surrounding white matter [11], and treatment once the condition has occurred is challenging [25]. However, prevention is more important. A reduction in IVH rates for preterm neonates would have important benefits for parents, family and society. Indeed, the observation of reduced IVH rates for infants delivered by CS between 23-28 weeks has serious implications for counselling parents regarding delivery options. At such discussions, it is vital not only to discuss with couples the likelihood of survival with each option but also the likelihood of neurodevelopmental disability, taking the gestational age into account. The likelihood of only 23-24% of neonates born at 24 weeks being unimpaired may make some families think again regarding aggressive therapy and cesarean birth. At other gestations, the balance might be different, but parental values and wishes would remain an important determinant.

Furthermore, the concept of planned CS for preterm birth implies that it is possible to diagnose preterm birth accurately and perform caesarean section prior to delivery. This is difficult and women thought to be in preterm labor may deliver weeks later, often at term. There is, therefore, a real possibility that a policy of CS may increase the number of babies born preterm if implemented too early. It might be that a planned cesarean birth should only be discussed as an option with women who are in active preterm birth, with evidence of progressive cervical change, or as an alternative to induction of labor. This however should be discussed alongside the maternal risks of preterm CS, and the chance that it might be classical, aiming for informed joint decision making compliant with Montgomery principles [26].

Conclusion

This study has shown that infants between 23-27 weeks born by CS are less likely to develop sIVH compared to those born vaginal delivery, an association which persisted after adjustment for available confounders. Therefore, potentially suggesting that some of the morbidity seen in very preterm infants may be avoidable. However, we must be cautious when interpreting the results of this analysis and that any potential neonatal benefits should be balanced with the likely increase in maternal morbidities. We believe that results of this study would be useful to inform the urgent need for future work to provide a more robust evidence to confirm or refute these findings. However, in the meantime, this study offers valuable data to assist joint decision-making in the post-Montgomery era between obstetricians, neonatologists, and parents.

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Details of Ethics approval

Ethical approval was obtained from the North Somerset and South Bristol Clinical Ethics Committee (ref: 11/sw/0209).

Disclosure of Interest

The authors have nothing to disclose

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Table 1. Population characteristics in relation to mode of delivery

Measure	N	Vaginal Birth	CS	P
Gestational age (weeks)	1575	26.6 (2.3)	28.0 (2.0)	<0.001
Birth weight	1575	988 (306)	1000 (285)	0.453
SGA (Weight 2 SD below the mean)	1575	55 (6.1%)	4 (0.6%)	<0.001
Head circumference	936	24.8 (2.7)	25.3 (2.4)	0.002
Multiple Birth	1575	194 (28.8%)	248 (27.5%)	0.561
Antenatal Steroids	1567	581 (86.7%)	826 (92.1%)	0.001
Chorioamnionitis	872	126 (38.1%)	124 (22.9%)	<0.001
Maternal Hypertension	872	8 (2.4%)	154 (28.5%)	<0.001
Male	1575	373 (55.4%)	454 (50.3%)	0.045
Antenatal magnesium	300	37 (40.2%)	90 (43.3%)	0.622
Early/Perinatal Sepsis	1575	24 (3.6%)	13 (1.4%)	0.006
Apgar scores				
1 minute	1575	5.8 (2.3)	6.3 (2.1)	<0.001
5 minute	1574	7.8 (1.8)	8.3 (1.5)	<0.001
Intubation in DR	1575	550 (81.7%)	642 (71.2%)	<0.001
Surfactant in DR	1575	494 (73.3%)	591 (65.5%)	0.001
Surfactant at any point	1575	574 (85.3%)	721 (80.0%)	0.006

Values are number (%) or mean (SD) as appropriate

DR: Delivery room

Table 2. Associations between mode of birth and clinical outcomes.

Outcome Measure	**N**	**Vaginal Birth**	**CS**	p
Severe IVH	1575	109 (16.2%)	61 (6.8%)	<0.001
IVH grade	1575			<0.001
0		394 (58.5%)	711 (78.8%)	
1		105 (15.6%)	81 (9.0%)	
2		65 (9.7%)	49 (5.4%)	
3		56 (8.3%)	32 (3.6%)	
4		53 (7.9%)	29 (3.2%)	
Death before discharge	1575	118 (17.5%)	97 (10.8%)	<0.001
PVL	1573	32 (4.8%)	32 (3.6%)	0.229
Death, sIVH or PVL	1575	196 (29.1%)	151 (16.7%)	<0.001
Length of stay				
All infants	652	104 (67)	95 (56)	0.055
Excluding those that died	603	108 (66)	95 (53)	0.006
O2 at 36 weeks	853	188 (55.5%)	239 (46.5%)	0.010

Values are number (%) or mean (SD) as appropriate

Table 3. Regression Models

Outcome Measure	N	Unadjusted		Adjusted*	
		OR (95% CI)	P	OR (95% CI)	P
Severe IVH	1575	2.67 (1.91 to 3.72)	<0.001	1.61 (1.01 to 2.58)	0.049
Death before discharge	1575	1.76 (1.32 to 2.35)	<0.001	0.92 (0.61 to 1.39)	0.687
PVL	1573	1.36 (0.82 to 2.25)	0.228	1.28 (0.70 to 2.35)	0.420
Death, sIVH or PVL	1575	2.05 (1.61 to 2.61)	<0.001	1.24 (0.91 to 1.70)	0.174
Length of stay					
All infants	652	9.23 (0.20 to 18.66)	0.055	-0.48 (-11.25 to 10.30)	0.931
Excluding those who died	605	13.3 (3.8 to 22.8)	0.006	2.2 (-8.2 to 12.6)	0.683
O2 at 36 weeks	853	1.44 (1.09 to 1.90)	0.011	1.01 (0.67 to 1.51)	0.980

Values are OR (95% confidence interval) or mean difference (95% confidence interval) as appropriate

*Adjusted for birth weight, gestation and gender, antenatal steroids, antenatal magnesium, chorioamnionitis, maternal hypertension, multiple birth, early neonatal sepsis

All models adjusted for year of birth using random-effects multi-level regression

Appendix 1. Details of Multiple Imputation Methods

All variables presented in the paper (including exposure and outcome variables) were included in the imputation model. Analysis was based on 80 imputed datasets.

Imputation Variable	n	%	Imputation Command
Gestation	0	0.0%	-
IVH status	0	0.0%	-
Birth weight	0	0.0%	-
Gender	0	0.0%	-
Antenatal Steroids	8	0.5%	logit
Antenatal Magnesium	1,275	80.9%	logit
Chorioamnionitis	703	44.6%	logit
Maternal hypertension	703	44.6%	logit
Multiple birth	0	0.0%	-
Vaginal Delivery	0	0.0%	-
Oxygen requirement at 36 weeks	722	45.8%	-
PVL	2	0.1%	logit
Early Onset Sepsis	0	0.0%	-
Length of Stay	923	58.6%	regress
Death	0	0.0%	-
Apgar at 1 minute	13	0.8%	ologit
Apgar at 5 minutes	1	0.1%	ologit
Multiple Birth X Vaginal Delivery	0	0.0%	-
Gender X Vaginal Delivery	0	0.0%	-
Gestation X Vaginal Delivery	0	0.0%	-