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INCIDENCE AND RISK FACTORS FOR DEVELOPMENT OF PERIVENTRICULAR-INTRAVENTRICULAR HAEMORRHAGE IN THE VERY PRETERM BABY IN THE NEWBORN UNIT AT KENYATTA NATIONAL HOSPITAL

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ABSTRACT

Background: **Periventricular-intraventricular haemorrhage (PV-IVH), is bleeding into the brain's ventricular system and involves the periventricular motor tracts. Prevalence/incidence of 9.5-45% has been reported with the highest incidence being in babies born before 32weeks gestation. Overall incidence has declined over time. Clinical presentation varies, and diagnosis is mostly made on surveillance cranial ultrasonography as is the recommendation globally. This study evaluated the contribution of periventricular-intraventricular haemorrhage to preterm morbidity and mortality within the New-Born Unit at the study facility, in the context of improved new-born care.**

Objectives: **The study objective was to determine incidence and describe risk factors for intraventricular haemorrhage in very preterm babies within the first 7 days of life.**

Participants and Methods: **Consecutive sampling of neonates born at ≤ 32weeks gestation was performed in this cohort study where two cranial sonography scans were carried out in the first week of life – initially within 72 hours of life, and then at day 7.**

Results and Conclusion: **Of the 195 participants, 144 (73.8%) survived to day 7 of life, with a male-to-female ratio of approximately 1:1. Median gestational-age was 31 weeks (IQR 29 – 32), and median birthweight was 1440g. Overall incidence of PV-IVH was 8% (95% CI 4 to 12%), with majority (60%) being grade I haemorrhage and 40% being grade II haemorrhage. Statistical analysis revealed significant risk factors for PV-IVH as being severe RDS (p = 0.005), male gender (p = 0.035) and being small for gestational age (p = 0.001).**

INTRODUCTION

Germinal matrix-intraventricular haemorrhage (GM-IVH) is a major complication of prematurity and is defined as bleeding into the brain ventricular system, originating from the capillary network of the primitive germinal matrix [1]. Also termed periventricular-intraventricular haemorrhage (PV-IVH), germinal matrix-intraventricular haemorrhage involves the periventricular white matter (motor tracts) and may extend into the ventricular system and cerebral parenchyma. For purposes of this publication, the terms GM-IVH and PV-IVH have been used interchangeably.

The germinal matrix cells are highly metabolically active and thus rich in mitochondria. [2] This makes them highly sensitive to low oxygen states. The matrix receives its blood supply from a primitive and inherently fragile mesh-like capillary network [1],[2]. Arterial supply to the plexus is through the Heubner artery and the lateral striate arteries, both of which are within the distribution of the anterior and middle cerebral arteries. Venous drainage is via the terminal vein, which empties into the internal cerebral vein, which in turn drains into the vein of Galen [1]. This fragile capillary network is the primary site at which haemorrhage as seen in GM-IVH occurs.

PV-IVH is traditionally classified into four grades of severity, based on radiological appearance. There are two main grading systems, as defined by Papile [3], et al, and/or Volpe[4]. Both systems rely on the detection of blood in the sub-ependymal germinal matrix, and the ventricles.

Classification according to Papile et al is as follows: Grade I haemorrhage is restricted to the sub-ependymal region and/or germinal matrix. Grade II haemorrhage is sub-ependymal haemorrhage, with extension into the lateral ventricles with no ventricular enlargement. Grade III haemorrhage is as the previous, with associated ventriculomegaly (hydrocephalus). Grade IV haemorrhage – the most severe form – is haemorrhage into the brain parenchyma.[1],[2],[3]

There are three major pathogenic mechanisms in the neonate that are thought to lead to intraventricular haemorrhage: disturbance in cerebral blood flow (CBF), the inherent fragility of germinal matrix vasculature and platelet/coagulation disturbances.[2]

Periventricular-intraventricular haemorrhage has been shown to be inversely related to gestational age, and birth weight. Apart from the male gender most risk factors reported are those that are associated with pathogenic mechanisms namely severe respiratory problems, haemodynamic instability (PDA), sepsis and haemostatic failure [1],[2],[6],[7] Advanced maternal age and use of antenatal steroids have been associated with lower incidence of PV-IVH. [8]

Diagnosis

PV-IVH is diagnosed primarily through the use of brain imaging studies, with cranial (trans-fontanelle) ultrasonography being the imaging modality of choice.[1],[9] Computed tomography and magnetic resonance imaging have been used as supplementary tools.[9],[10]

Because PV-IVH can be asymptomatic, serial schedules for routine screening of the very preterm neonate is recommended for the diagnosis.[1] An initial trans-fontanelle ultrasound (TFU) within 72 hours of life, with a second TFU on day 5 to 7 of life.[12],[13] Frequency of subsequent sonography is then determined on a case-by-case basis.

Though studies point toward a general decline in incidence of PV-IVH, it remains a major problem of modern neonatal intensive care units globally.[2]

The aim of this study was therefore to evaluate the contribution of PV-IVH to preterm morbidity and mortality in the context of improved new-born care, as the last study within the same new-born unit was carried out about 27 years ago.

METHODOLOGY

Study Design and Setting: The cohort study was conducted within the New-Born Unit at the Kenyatta National Hospital (KNH) – the largest and oldest public, tertiary referral hospital in Kenya which also serves as the teaching hospital for the University of Nairobi (UoN).

Sample Size: The sample size was calculated using a simple formula for sample size determination in incidence studies (*Daniel, 1999)* [20], thus:

$$n = \frac{Z^2 P(1-P)}{d^2} = \frac{1.96^2 \times 0.2\ (1-0.2)}{0.06^2} \approx 195$$

Where:

n = sample size

Z = normal standard deviation taken with a 95% confidence interval, set at 1.96

P = expected prevalence of PV-IVH in study population, estimated at 24%

d = study precision, taken at 6%

Participant Selection: All preterm babies meeting the inclusion criteria of gestational age of ⊚32 weeks, admission within 72 hours of life as well as documented informed consent were recruited from the Newborn Unit. Participant recruitment was through consecutive sampling from within 72 hours of life, and they were followed up to day 7 of life.

Study Procedures: Upon enrolment, data was collected and entered into a predesigned questionnaire. Collected data included demographic data, antenatal and perinatal history, anthropometric measurements, and clinical details of each participant including presence or absence of known risk factors for PV-IVH, working diagnosis, laboratory results and treatment measures undertaken.

Data sources primarily included the neonatal admission record (which includes maternal antenatal history) and subsequent clinical notes from the neonates' medical files. No data was collected from mother's obstetric notes.

Cranial Ultrasound Scanning and Management of Data: Sonography was done via the anterior fontanelle, in the coronal and sagittal planes using a 5-7MHz (megahertz) curvilinear transducer. Anterior, mid and posterior coronal plane images were obtained by swiping the ultrasound probe in a fronto-occipital and then an occipito-frontal direction. Mid sagittal and bilateral (right and left) parasagittal plane images were obtained by swiping the probe right to left, then left to right at the midline. All ultrasounds were carried out using these standard techniques, and any observed haemorrhage was recorded in the described planes. These were all point of care ultrasounds, carried out within the new-born unit.

All images obtained were saved and presented to a blind panel of at least three experienced radiologists for verification and validation of findings. Confirmed diagnosis was then entered into the predesigned questionnaire.

Data was entered into customised Microsoft Access® database and analysed using STATA® software.

Statistical Analysis: Descriptive univariate analysis was used to summarise the sample characteristics. Both maternal and newborn demographic characteristics measured using continuous variables such as gestational age and birth weight were summarised using a measure of central tendency (either mean or median) and a measure of variation (either SD or range) depending on whether the data showed a normal or skewed distribution. For categorical variables including presence or absence of specific maternal or neonatal conditions, frequencies were reported along with percentages. The dependent variable was calculated by counting all neonates with radiological evidence of PV-IVH, using this as a numerator in calculating incidence of the same.

To determine factors associated with PV-IVH and categorical variables, bivariate cross tabulation for each factor versus PV-IVH incidence was conducted and the Chi square test for independence performed. Bivariate associations between numerical variables and PV-IVH was analysed using the student t test. Statistical significance was determined using a p value of 0.06. Multivariable logistic regression analysis was then conducted with PV-IVH incidence as the dependent variable and all the covariates showing significant associations in the bivariate analysis as independent variables. Findings were then summarised using tables and charts.

Ethical Issues: Written consent was obtained from parents or legal guardians of the babies before data collection. The study was conducted after approval from the Ethics and Research Committee of Kenyatta National Hospital and the University of Nairobi.

RESULTS

Descriptive Characteristics

Infant Characteristics: A total of 195 neonates born at ≤32 weeks were recruited. The mean age at the time of recruitment was 2 days (SD ± 0.8), with 72 (37%) neonates recruited on the day of delivery (Table 1). There were 99 (51%) males giving a male to female ratio of approximately 1:1. Out of the 195 neonates, there were 126 (65%) VLBW babies and 26 (13%) ELBW babies. The median gestation ages (IQR) were 31 weeks (29-32) and 32 weeks (29-32) based on the Ballard score and gestation by estimated date of delivery (EDD), respectively.

Of the 195 recruited neonates, 51 (26.2%) died before reaching day 7 of life. They however were not followed to autopsy. Therefore, a total of 144 neonates were followed up to day 7 of life and received 2 cranial ultrasounds within this period.

Table 1

Demographic Characteristics of Study Participants

	Frequency (%)
Age on admission	
Day 1	72 (37)
Day 2	54 (28)
Day 3	69 (35)
Gender	
Male	99 (51)
Female	96 (49)
Birth weight	
ELBW (≤1000 g)	26 (13)
VLBW (≤1500g)	169 (87)
Median gestation age	
Ballard score*	31 (IQR 29 to 32)

Maternal Characteristics: The mean age of mothers was 29.9 years (SD ±5.8) with a range between 20 and 44 years. Of these mothers 73 (37%) were aged 25 to 29 years (Table 4). Hypertension and gestational diabetes occurred in 58 (30%) and 3 (2%) of mothers, respectively. There were 17 (9%) HIV positive mothers. Antenatal steroids were administered in 7 (4%) of the mothers.

Table 2
Maternal Antenatal and Demographic Characteristics

	Frequency (%)
Maternal age	
20-24 years	30 (15.4)
25-29 years	73 (37.4)
30-34 years	56 (28.7)
⊚35 years	36 (18.5)
Antenatal Steroids Given	7 (4)
Hypertension	58 (30)
VDRL Positive	7 (4)
HIV Positive	17 (9)
Gestational Diabetes	3 (2)

Incidence of IVH: Sixteen babies had periventricular-intraventricular haemorrhage within the first 7 days of life was giving an overall incidence of 8% (95% CI 4 to 12%).

The incidence of periventricular-intraventricular haemorrhage of any grade was 4% (95% CI 1 to 7%) within 72 hours, and 5% (2 to 9%) at day 7 follow up.

There was no evidence of a significant difference in incidence of PV-IVH within 72 hours versus at day 7 follow up (McNemar Chi-square P value = 0.248).

Risk Factors

The infant factors associated with the development of periventricular-intraventricular haemorrhage within the first 7 days of life were male gender (p = 0.043) and being small for gestational age (p = 0.041). Three-quarters of all neonates with PV-IVH were male.

Of the twenty neonates who were small for gestational age, 25% were found to have PV-IVH (p=0.041). There was no significant association between PV-IVH and the remaining infant factors: mode of delivery (p = 0.949), resuscitation at birth (p = 0.108) presence of PDA (p=0.06), or sepsis (p=0.698)

Among the maternal factors, HIV status (p = 0.016) showed significant associations with PV-IVH. Antenatal steroid administration (p = 0.420), gestational diabetes (p = 0.602),

hypertension (p = 0.191) and VDRL (p = 0.420) were not significantly associated with PV-IVH.

The mean haemoglobin among neonates with PV-IVH was 12g/dl (SD 0.5) compared to 15g/dl (SD 2) in those without PV-IVH (p<0.001).

Severe RDS occurred in 8 (50%) of the neonates with PV-IVH and 32 (18%) of those without (p = 0.005). Oxygen and continuous positive airway pressure were also more frequently administered in the neonates with PV-IVH (100% and 50%, respectively) as opposed to those without PV-IVH (75% and 15%, respectively).

A multivariate logistic regression model of PV-IVH as the dependent variable was carried out considering gender, small for gestational age (SGA) status and HIV status. This showed that both gender (p = 0.035) and SGA (p = 0.001) were significantly associated with PV-IVH, but HIV status was not (p = 0.072). The odds of PV-IVH among female neonates was 79% lower than in males (OR = 0.12, 95% CI 0.05-0.9), while neonates who were small for gestational age had 13.5 times greater odds of PV-IVH compared to neonates with appropriate or large size for gestational age (OR = 13.5, 95% CI 2.72-67).

Table 3

Infant Factors Associated with PV-IVH

	PV-IVH		
	Yes (n=16)	**No (n=179)**	**P value**
	n (%)	**n (%)**	
Gender			
Male	12(75)	87(49)	0.043*
Female	4(25)	92(51)	
Birth Weight			
⊚1000g	0(0)	26(15)	0.102
1000 – 1499g	8(50)	92(51)	0.915
⊚1500 g	8(50)	61(34)	0.202
Size for Gestational Age			
Small	4(25)	16(9)	0.041*
Appropriate	12(75)	156(87)	0.178
Large	0(0)	7(4)	0.420
Median gestation (Ballard) *	31 (IQR 32-32)	32 (IQR 29-32)	0.032*
Mode of delivery			
SVD	8(50)	88(49)	0.949
CS	8(50)	91(51)	

Resuscitated at birth			
Yes	12(75)	97(54)	0.108
No	4(25)	82(46)	
Presence of PDA			
Yes	0(0)	33(18)	0.06
No	16(100)	146(82)	

Table 4

Management of neonates with and without RDS

	PV-IVH		
	Yes	**No**	**P value**
	n (%)	**n (%)**	
Severe RDS	8(50)	32(18)	0.005*
Oxygen administered	16(100)	114(64)	0.01
Continuous Positive Airway Pressure	8(50)	26(15)	0.001*
Endotracheal tube in situ	0(0)	7(4)	0.407

Table 5

Multivariate Logistic Regression Model, Odds Ratio

	Odds Ratio	**95% CI**		**P value**
Male	1.0			
Female	0.21	0.05	0.90	0.035*
Appropriate/ large for gestational age	1.0			
Small for gestational age	13.50	2.72	67.00	0.001*
HIV positive	1.0			
HIV negative	0.29	0.08	1.11	0.072

DISCUSSION

Overall incidence of periventricular-intraventricular haemorrhage at any point during the first week of life was found to be 8%, which falls within the incidence range of 7-20% seen in developing nations. [2] This value is significantly lower than that recorded from previous regional studies that found rates of between 24% and 53% [6], [12], [13], [17], and a previous Kenyan study in the same institution that observed an incidence of 33%. [18] The difference in incidence across the studies, specifically, between this and the older Kenyan study may be partly attributed to improvements in newborn care but also the previous study included all low birth weight babies and, in that study, autopsies were done. Of note, too is that the current study involved minimal manipulation of the study participants as they did not have to be moved to and from the radiology department

and this may have prevented occurrence of or worsening of intraventricular haemorrhage. Frequent handling of preterm babies in the neonatal intensive care setting has been thought to be associated with development of intraventricular haemorrhage. [23]

Incidence of intraventricular haemorrhage of any grade was found to be 4% within 72 hours, and 5% on day 7 follow up. There was no observed difference in likelihood of developing PV-IVH between the first 72 hours, compared to day 7 follow up. This is not in keeping with literature that showed majority haemorrhage taking place within the first 72 hours of life. [6], [16], [17] No specific factor was identified that may explain this finding.

Fifty-one neonates (26.2%) died before a second cranial ultrasound could be performed, giving a survival rate of 73.8% among the study population up to the postnatal age of one week. Clinically, those who died had been on management for severe neonatal sepsis or severe respiratory distress. Since respiratory distress was found to be a significant risk factor for PV-IVH, it is possible that a diagnosis of the same among these was missed and would possibly have been confirmed had these neonates been followed up to autopsy.

Among the maternal factors analysed, none was found to have a significant correlation with PH-IVH development. Of note, however, was that there was inadequate documentation of maternal factors including antenatal steroid use, comorbidities, and antenatal history. Though initial analysis revealed a potential association of maternal HIV status with PV-IVH, a multivariable regression analysis was able eliminate this as a confounder, but the numbers were small. There was inadequate data to analyse antenatal steroid use as a potential protective factor for PV-IVH.

The main factors found to be significant in the causation of PV-IVH from this study were severe respiratory distress syndrome, male gender and small size for gestational age. RDS is a known neonatal factor contributing to PV-IVH development through causing fluctuations in cerebral blood flow. [1], [2], [6], [7] Male gender has previously been reported as an independent risk factor for PV-IVH and has also been found to be related to poor neurological outcome.[24] Preterm babies who are also born SGA have been observed to have an increased risk of IVH compared to those born at appropriate size for gestational age. [25] Occurrence of PV-IVH in the SGA baby has been thought to result from prenatal events (maternal disease – hypertension, infection, diabetes, etc; placental disease – placenta *praevia* or placenta *abruptio*) superimposed upon decreased supportive tissue in the infant's germinal matrix. PDA and sepsis were not found to be significant risk factors for PV-IVH. Infants with PV-IVH in this study had a lower mean haemoglobin level compared to those without, and this was thought to be more as a result of haemorrhage rather than a contributory factor to the same.

Study Limitations

Sonography is largely a subjective imaging modality as findings and interpretations of the same are investigator dependent. This limitation was minimised by having the PI doing all the scans and interpretation included at least 3 radiologists with a minimum of 3 years post qualification experience verifying and validating results from obtained images. Cranial ultrasound scans were repeated when needed, based on advice from the consultant radiologists.

Relatively high mortality rate among study participants, coupled with lack of follow up to autopsy meant that some cases of PV-IVH may have been missed.

A more conclusive analysis of risk factors could not be performed, owing to the low prevalence of intraventricular haemorrhage observed.

Most of the antenatal and obstetric history was filled from clinic records, which are

subject to clerical errors including those of omission. There was no perusal of the mothers' clinical notes, and this too was a limitation to the study as the maternal-neonate dyad was not observed.

CONCLUSION

Overall, the incidence of periventricular-intraventricular haemorrhage among very preterm babies born at or before 32 weeks' gestational age in Kenyatta National Hospital was found to be 8%. Factors found to be significant for PV-IVH were presence of respiratory distress syndrome, male gender and being small for gestational age.

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