Risk factors for developing intraventricular haemorrhage in very low-birthweight infants at Kalafong Provincial Tertiary Hospital, South Africa, 2019 - 2020

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Background. Intraventricular haemorrhage (IVH) remains a major concern as a result of the high prevalence of preterm births globally.
Objectives. To identify maternal and neonatal risk factors associated with IVH, and to assess its incidence and most frequently occurring grade in a population of very low-birthweight infants (VLBWIs) at Kalafong Provincial Tertiary Hospital, South Africa (SA).
Methods. This retrospective cohort study included all infants of birthweight <1 500 g admitted between 1 January 2019 and 31 December 2020. Associations between IVH and maternal and neonatal risk factors were analysed using Pearson's χ^2 test and Fisher's exact test. Risk factors significantly associated with IVH were included in a binary logistic regression model to identify independent predictors. Risk factors significantly associated with IVH ($p<0.05$) corresponded to a 95% confidence level.
Results. IVH was diagnosed during the first week of life in 43 out of 127 VLBWIs who met the inclusion criteria. Hypoglycaemia remained the most significant independent risk factor after adjusting for potential confounders in the multivariable logistic regression: adjusted odds ratio 4.02 (95% confidence interval (CI) 1.52 - 10.64). The incidence of IVH was 33.9% (95% CI 25.7 - 42.1). Grade I IVH occurred in 83.7% of infants, grade II in 9.3% and grades III - IV in 7.0%.
Conclusion. This study found an association between hypoglycaemia and IVH, but causality could not be established owing to the nature of the study. In this tertiary hospital in SA, a third of VLBWIs had IVH, mostly graded as mild.

Keywords. intraventricular haemorrhage; risk factors.

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In 2020, ~13.4 million infants were born prematurely worldwide, with complications of prematurity being the leading cause of death among children aged <5 years.[1] Intraventricular haemorrhage (IVH) mainly affects more premature infants, with increasing severity associated with lower gestational ages.[2] It is a common complication of prematurity and is frequently linked to long-term neurological impairment.[3-4] IVH is a brain bleed caused by compromised germinal matrix blood vessels, often due to changes in cerebral blood flow, platelet and coagulation disorders.[5]

To date, six studies on IVH in South Africa (SA) have revealed varying prevalence rates across hospitals. At Charlotte Maxeke Johannesburg Academic Hospital, a prevalence of 26.7% was reported in 2017 (study period 2013 - 2015)[6] and a prevalence of 22.6% in 2025 (study period 2016 - 2020)[7] among neonates weighing <1 500 g. The prevalence at Inkosi Albert Luthuli Central Hospital reported in 2019 (study period January - December 2012) was 44.3% in neonates weighing <2 000 g, with the rate rising to 67% among very low-birthweight infants (VLBWIs).[8] A study at Rahima Moosa Mother and Child Hospital reported in 2022 cited a 40% prevalence in infants weighing <1 500 g.[9] Additionally, research at Steve Biko Academic Hospital reported in 2019 found a 24.6% incidence of IVH among extremely low-birthweight infants and VLBWIs, linking IVH to increased neonatal morbidity.[10] Moreover, a study in Western Cape Province focusing on periviable neonates found that 92% exhibited grades I - II IVH, while 8% showed grades III - IV.[11]

Cranial ultrasonography is the gold standard for screening for and diagnosing IVH in infants born at <30 weeks' gestation. The American Academy of Pediatrics recommends imaging by days 7 - 10, with repeat imaging scheduled after 4 - 6 weeks, at 36 weeks or before discharge, and serial cranial ultrasound scans for infants with a previously abnormal cranial ultrasound scan.[12] At Kalafong Provincial Tertiary Hospital (KPTH) in Pretoria, institutional policy mandates routine cranial ultrasound screening for all infants with a birthweight <1 500 g. The neonatal unit uses the Papile classification system to grade IVH.[13] Grade I IVH is defined as haemorrhage confined to the germinal matrix, grade II involves haemorrhage within the ventricular system without ventricular dilatation, grade III is characterised by IVH with ventricular dilatation, and grade IV involves parenchymal extension of the haemorrhage. Grades I and II are classified as mild IVH, while grades III and IV are considered severe.

Risk factors

Antenatal clinic non-attendance has been proven to be associated with preterm births, and prematurity is a prerequisite for IVH.[14] Chorioamnionitis has been identified as a risk factor for IVH owing to its role in increasing inflammatory markers in the fetal brain and compromising the blood-brain barrier.[15] A retrospective cohort study by Maduray *et al.*[8] identified key risk factors linked to IVH, such as gestational age, birthweight and blood transfusion. Infants with a birthweight <1 000 g had an 87.5% prevalence of IVH, while those weighing >1 500 g showed a significantly lower prevalence of 26.3%. Gestational age and birthweight have an inverse relationship with IVH, indicating an increased risk of severe haemorrhage in preterm infants.[8] Associated conditions, including sepsis, hypotension, the use of inotropes and hypoglycaemia, have also been linked to IVH, although the connection between isolated hypoglycaemia and IVH remains infrequently documented.[16-18]

Methods

This retrospective cohort study was conducted at KPTH and included all infants with a birthweight <1 500 g admitted between 1 January 2019 and 31 December 2020. Infants with congenital anomalies, hydrocephalus or congenital intracranial haemorrhages were excluded from the analysis. A convenience sampling method was used. Baseline maternal and neonatal characteristics were collected, including mode of delivery (normal vaginal delivery v. caesarean section), antenatal care and steroid use, maternal sepsis, prelabour rupture of membranes, hypertension or diabetes, sex, birth location (inborn v. outborn), Apgar scores, need for intubation or resuscitation at birth, hypoglycaemia, hypotension, and use of inotropes. Routine cranial ultrasound screening was performed weekly by trained sonographers for all eligible infants. The LOGIQ F8 Expert sonar machine (GE Healthcare, South Korea) was used to perform the cranial ultrasound scans. Ultrasound findings were then classified using the Papile grading system for IVH.

Statistical analysis

The study analysed data using the Statistical Package for the Social Sciences (SPSS), version 30 (IBM, USA), examining the relationship between IVH and maternal and infant characteristics. It tested the association between these factors and other risk factors. Covariates were included in binary logistic regression modelling to identify significant risk factors. The incidence of IVH was determined by dividing new cases by at-risk individuals**.**

Ethical considerations

Ethical approval was obtained from the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (ref. no. 53/2023).

Permission to access patient records and publish them for research purposes was obtained from the KPTH CEO.

Results

Over a 2-year period there were 504 admissions to the neonatal unit, of which 286 were excluded from the study owing to irretrievable records. Of the 218 files retrieved, 91 were excluded because a cranial ultrasound scan was either not performed or only performed after 7 days. Of the 218 files, 127 files of eligible participants remained (Fig. 1).

The majority (n=118/127; 92.9%) of the infants were inborn, 55.1% (n=70/127) were female, and 51.2% (n=65/127) were delivered via caesarean section (Table 1). Only two infants had an Apgar score of 5 at 5 minutes; however, these infants did not have IVH. The modal Apgar score at 5 minutes was 9. Among the 41/118 infants who required resuscitation, 43.9% had IVH. Hypoglycaemia was observed in 36/127 infants, of whom 18 (50.0%) had IVH, compared with 91/127 infants without hypoglycaemia, of whom 27.5% had IVH. Among infants with culture-positive sepsis occurring after 3 days of life, 12/22 (54.5%) had IVH, compared with 31/105 (29.5%) without sepsis. All infants who experienced hypotension (n=4/127; 0.6%) developed IVH, and 80% (4/5) of those requiring inotropic support also had IVH. Prior to multivariable logistic regression, the following variables were statistically significantly associated with IVH: hypoglycaemia (p=0.017), hypotension (p=0.049), and culture-positive sepsis after 3 days (p=0.028). Hypoglycaemia was ultimately identified as a significant risk factor for IVH in the adjusted multivariable model (adjusted odds ratio 4.02; 95% confidence interval 1.52 - 10.64; p=0.005).

The majority of the mothers were booked for antenatal care (n=89/127) (Table 2). Among the minority who were not booked (n=38 mothers), 10 infants (26.3%) had IVH. However, the sample size was too small to determine whether lack of antenatal booking was a significant risk factor for IVH. Of note, 44/127 (34.6%) of the mothers did not receive antenatal steroids and 31.8% of their infants had IVH. The remaining majority had received either one (n=20/127; 15.7%) or two (n=63/127; 49.6%) doses. Of the mothers, 19/127 had premature rupture of the membranes, and only 5/19 (26.3%) of the infants born to these mothers had IVH; a similar trend was observed among mothers with hypertension (34.0%). Of mothers who had antepartum haemorrhage, only 36.4% had infants who developed IVH. Additionally, maternal sepsis was present in only one case; that infant developed IVH. Of the infants born to two mothers with gestational diabetes, one had IVH while the other did not. No maternal factors were statistically significantly associated with IVH.

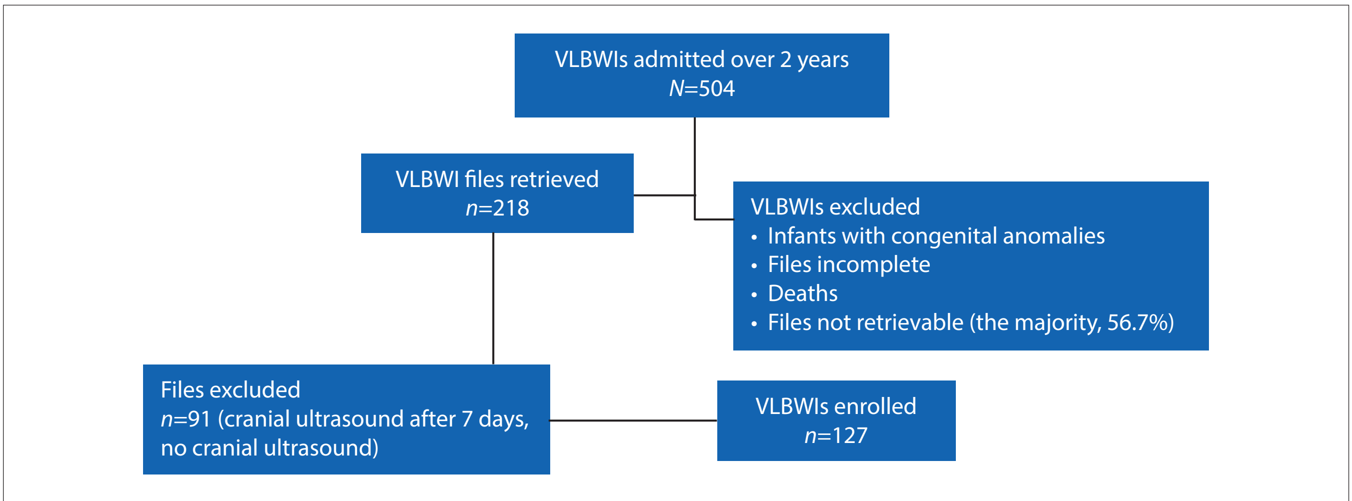

Fig. 1. The study enrolment process. (VLBWI = very low-birthweight infant.)

The study reported an incidence of IVH of 33.9%, with the majority of cases (83.7%) classified as grade I, 9.3% classified as grade II, and only 7.0% classified as grades III - IV. Severity of IVH in the different weight categories is illustrated in Fig. 2. The highest incidence of IVH was observed in infants weighing 1 300 - 1 399 g (45.5%), with the lowest incidence in those weighing 1 200 - 1 299 g (17.6%). With regard to gestational age, the highest IVH incidence occurred between 32 weeks and 32 weeks and 6 days' gestation (66.7%).

Discussion

This study reported an overall incidence of IVH in VLBWIs of 33.9%, with the majority of cases classified as grade I IVH (83.7%). There are three studies in SA that have focused specifically on the incidence of IVH in VLBWIs: Ghoor *et al.*[6] (26.7%), Tshehla *et al.*[10] (24.6%), and Akuamoah-Boateng *et al.*[7] (22.6%). All three studies were conducted in tertiary-level hospitals. An African study (Uganda) by McLeod *et al.*[19] reporting on the incidence of IVH in VLBWIs documented an incidence of 34.2%. The IVH incidence reported by McLeod *et al.*

Table 1. Baseline infant characteristics in the study population

Characteristic	With IVH (*n*=43), *n* (%)	Without IVH (*n*=84), *n* (%)	Total (*N*=127), *n*	*p*-value
Place of birth				0.486
Inborn	39 (33.1)	79 (66.9)	118	
Outborn	4 (44.4)	5 (55.6)	9	
Gender				0.707
Male	18 (31.6)	39 (68.4)	57	
Female	25 (35.7)	45 (64.3)	70	
Delivery				0.264
Vaginal delivery	18 (29.0)	44 (71.0)	62	
Caesarean section	25 (38.4)	40 (61.4)	65	
Apgar score at 5 minutes				0.435
1	1 (50.0)	1 (50.0)	2	
5	0	2 (100)	2	
6	3 (42.9)	4 (57.1)	7	
7	7 (46.7)	8 (53.8)	15	
8	9 (22.0)	32 (78.0)	41	
9	19 (38.0)	31 (62.0)	50	
10	2 (25.0)	6 (75.0)	8	
Unknown	-	-	2	
Resuscitated				0.070
Yes	18 (43.9)	23 (56.1)	41	
No	21 (27.3)	56 (72.7)	77	
Unknown	-	-	9	
Hypothermia				0.465
Yes	34 (32.4)	71 (67.6)	105	
No	9 (40.9)	13 (59.1)	22	
Intubation/ventilation				0.124
Yes	9 (50.0)	9 (50.0)	18	
No	34 (31.2)	75 (68.8)	109	
Hypoglycaemia				0.017*
Yes	18 (50.0)	18 (50.0)	36	
No	25 (27.5)	66 (72.5)	91	
Culture-positive sepsis after 3 days				0.028*
Yes	12 (54.5)	10 (45.4)	22	
No	31 (29.5)	74 (70.5)	105	
Hypotension				0.049*
Yes	4 (100)	0	4	
No	39 (31.7)	84 (68.3)	123	
Use of inotropes				0.059
Yes	4 (80.0)	1 (20.0)	5	
No	39 (32.0)	83 (68.0)	122	

*Significant (p<0.05).

Table 2. Baseline maternal characteristics in the study population

Characteristic	With IVH (n=43), n (%)	Without IVH (n=84), n (%)	Total (N=127), n	p-value
Antenatal booking				0.307
Yes	33 (37.1)	56 (62.9)	89	
No	10 (26.3)	28 (73.7)	38	
PROM				0.600
Yes	5 (26.3)	14 (73.7)	19	
No	37 (35.2)	68 (64.8)	105	
Unknown	-	-	3	
Hypertension				1.00
Yes	17 (34.0)	33 (66.0)	50	
No	26 (33.8)	51 (61.2)	77	
Antenatal steroids				0.939
2 doses completed	22 (34.9)	41 (65.1)	63	
1 dose completed	7 (35.0)	13 (65.0)	20	
No antenatal steroids	14 (31.8)	30 (68.2)	44	
Antepartum haemorrhage				1.00
Yes	4 (36.4)	7 (63.6)	11	
No	38 (33.6)	75 (66.4)	113	
Unknown	-	-	3	
Maternal sepsis				0.339
Yes	1 (100)	0	1	
No	41 (33.3)	82 (66.7)	123	
Unknown	-	-	3	
Gestational diabetes				1.00
Yes	1 (50.0)	1 (50.0)	2	
No	41 (33.6)	81 (66.4)	122	
Unknown	-	-	3	

PROM = premature rupture of the membranes.

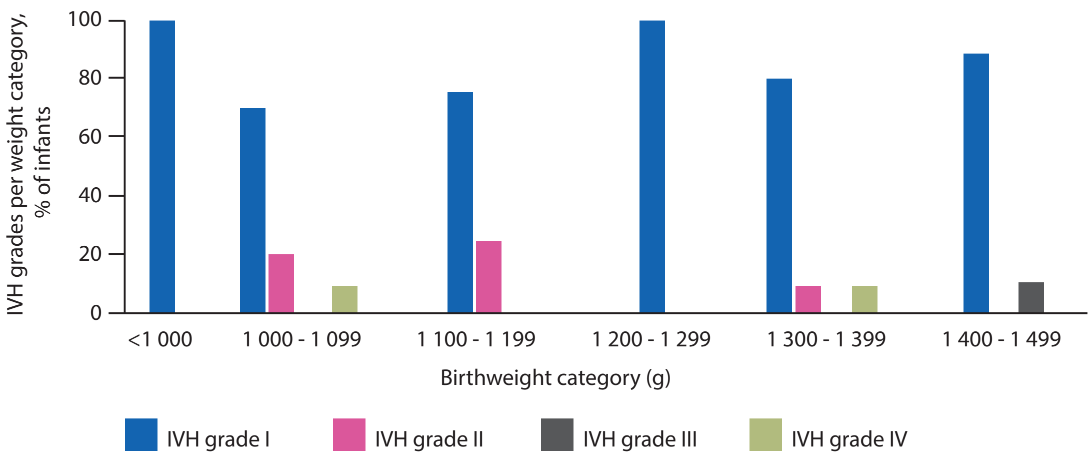

Fig. 2. Severity of IVH according to birthweight. (IVH = intraventricular haemorrhage.)

and the incidences reported by the studies in SA fall within the global range of 7 - 72%.[20] This range is wide because of differing patient groups, diagnostic tests and timing, study designs, and neonatal unit practices.[20]

The majority of mothers in our cohort were booked and received antenatal steroids. Although antenatal steroids are well documented in the literature as being protective against IVH, we found no statistically significant association between steroid administration and a reduced incidence of IVH. Notably, the absence of antenatal steroid exposure was also not identified as a statistically significant risk factor for IVH. This finding contrasts with the existing literature, which consistently reports a higher risk of IVH in the absence of antenatal steroid administration.[21] In the present study, none of the maternal conditions were statistically significantly associated with the development of IVH.

Studies demonstrate an inverse relationship between the incidence of IVH and both birthweight and gestational age.[2] In the present study, the incidence of IVH relative to gestational age was more consistent with findings reported in the existing literature than the incidence relative to birthweight.

Prior to multivariable logistic regression, hypotension, culture-positive sepsis and hypoglycaemia were identified as significant risk factors for IVH. Hypotension, defined in some studies as a mean arterial pressure <30 mmHg, has been reported to be associated with IVH.[17] However, hypotension was not explicitly defined in the present study, and although the p-value reached statistical significance, the small number of cases limited the ability to draw meaningful conclusions. Similarly, while sepsis, particularly early-onset sepsis, has been associated with an increased risk of IVH (with a reported 1.52-fold higher risk),[16] the small number of cases in our cohort limited meaningful analysis. Following multivariable logistic regression, only hypoglycaemia remained a statistically significant risk factor for IVH.

Literature on the relationship between isolated hypoglycaemia and IVH remains limited. Hypoglycaemia is more commonly described in the context of its association with long-term neurodevelopmental outcomes.[18] Studies indicate that hypoglycaemia can affect the cerebral cortex, with or without the involvement of subcortical or periventricular regions. This finding suggests that hypoglycaemia may cause injury to multiple sites within the brain, potentially contributing to broader neurological damage. Hypoglycaemia has been associated with the disruption of cerebral autoregulation and may therefore be associated with IVH, as previously mentioned.[18]

Study limitations

This study has notable limitations owing to its retrospective cohort design. The use of convenience sampling could have introduced selection bias, and as a single-centre study, the results may not be generalisable to other contexts. Additionally, the study identified associations and did not establish causality or assess temporal relationships. Other limitations include the potential for inter-observer variability due to different sonographers performing cranial ultrasound scans, which may lead to measurement bias.

Conclusion

This study found an association between hypoglycaemia and IVH; however, causality could not be established owing to the nature of the study. In this tertiary hospital in SA, a third of VLBWIs had IVH, mostly graded as mild. A better understanding of the risk factors linked to IVH in our setting could contribute to developing targeted interventions to reduce its occurrence and associated complications.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (KAM) on reasonable request. Any restrictions or additional information regarding data access can be discussed with the corresponding author.

Declaration. The research for this study was done in partial fulfilment of the requirements for KAM's MMed (Paed) degree at the University of Pretoria.

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Author contributions. KAM and NP developed the conceptual framework for the research project. KAM did the statistical planning and data collection. KAM and PM drafted the article. KAM reviewed and revised the manuscript for scientific and statistical accuracy. Both authors reviewed and approved the final manuscript for publication.

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Conflicts of interest. None.

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