Incidence of intraventricular haemorrhage in very low-birthweight infants in a group of private hospitals in Johannesburg, South Africa, 2018 - 2022

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Background. Intraventricular haemorrhage (IVH) is a common complication among very low-birthweight infants (VLBWIs), affecting ~20 - 30% of VLBWIs. Most published reports on the incidence of IVH in South Africa (SA) come from public sector hospitals, with few studies having been conducted in private sector hospitals.
Objectives. To determine the incidence of IVH and factors associated with moderate to severe IVH in VLBWIs admitted to private sector hospitals.
Methods. This was a retrospective study of VLBWIs admitted to neonatal intensive care units in three private hospitals in Johannesburg, SA, from 2018 to 2022. The study was a secondary analysis of data provided by the Vermont Oxford Network. VLBWIs admitted in three hospitals that gave permission for their data to be used were analysed. Incidence was determined based on all VLBWIs who had cranial ultrasound scans performed during admission. Comparisons were performed between VLBWIs with normal findings or mild IVH and those with moderate to severe IVH.
Results. A total of 186 VLBWIs were admitted to the three private hospitals during the study period, of whom 135 (72.6%) had cranial ultrasound scans performed. Of these VLBWIs, 34 had some degree of IVH and 18 had moderate to severe IVH, giving an incidence of 25.2% for any IVH and 13.3% for moderate to severe IVH. The odds of having moderate to severe IVH were lower if birth was via caesarean section (CS) v. vaginal (adjusted odds ratio (aOR) 0.09; 95% confidence interval (CI) 0.02 - 0.45; p=0.004) and gestational age was ≥28 weeks (aOR 0.08; 95% CI 0.01 - 0.86; p=0.037), while odds were higher for neonates born to mothers who received antenatal magnesium sulphate (aOR 8.60; 95% CI 1.64 - 44.87; p=0.011).
Conclusion. The incidence of IVH in VLBWIs admitted to certain private hospitals was comparable to the incidence reported in high-income countries. The odds of VLBWIs having moderate to severe IVH were lower when infants were born by CS or were of higher gestational age, but higher if the mother received antenatal magnesium sulphate. Although routine CS cannot be recommended for delivery of VLBWIs based on the study findings, as we did not review the indications for CS, some VLBWIs may benefit from being delivered by CS. The unexpected finding of magnesium sulphate being associated with high odds of moderate to severe IVH needs to be studied further.

Keywords. very low-birthweight infants; non-invasive ventilation; intraventricular haemorrhage.

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In sub-Saharan Africa (SSA), the prevalence of premature delivery, i.e. birth of an infant before 37 weeks' gestation, is 10.1%.[1] In South Africa (SA), the prevalence is 13%, which is the highest among countries in the SSA region. With advances in neonatal care, survival of premature infants has improved significantly over the past three decades. Intraventricular haemorrhage (IVH) is a common comorbidity in very low-birthweight infants (VLBWIs), affecting 20 - 30% of this group of preterm infants.[2] In high-income countries (HICs), the incidences of any IVH and moderate to severe IVH in VLBWIs are reported to be 32% and 12%, respectively.[3] The high incidence of IVH in premature infants presents a significant challenge for low- to middle-income countries (LMICs), where prematurity rates are relatively elevated. Reports from studies conducted in LMICs indicate that the incidence of IVH was 34.2% in Zambia, while in SA, the incidence ranged from 26.7% to 44%.[4-6]

Factors associated with IVH can be categorised into maternal and neonatal factors. Maternal factors include intrauterine infection, lack of antenatal steroids, premature rupture of the membranes, and vaginal delivery.[7,8] Neonatal factors are male sex, low Apgar score, metabolic acidosis, coagulation abnormalities, fluctuating blood pressure, blood transfusions, the use of hydrocortisone for hypotension treatment, neonatal sepsis, patent ductus arteriosus, respiratory distress syndrome (RDS), birthweight, and gestational age.[9-11] Factors that have been associated with a decreased risk of IVH include the use of antenatal steroids and magnesium sulphate for mothers.[12] Rates of IVH have reportedly decreased from 18.9% to 4.4% with the use of magnesium sulphate.

In SA, VLBWIs are delivered and managed in different types of hospitals. SA has a two-tier healthcare system consisting of the private and public sectors, with the private sector being relatively well resourced. For example, a 2007 study by Bhagwanjee *et al.*[13] revealed that 23% of public hospitals had intensive care units (ICUs) or high-care units (HCUs), compared with 84% of private hospitals. Access to ICU and HCU beds in public sector hospitals is therefore limited. Additionally, each infant in a neonatal ICU (NICU) in the private sector is assigned one nurse, whereas in the public sector, each nurse may attend to two to three infants. The incidence of comorbidities such as IVH in preterm infants admitted to private sector hospitals would therefore be expected to be lower than that observed in public sector hospitals and similar to that reported in HICs, as private sector hospitals are relatively well resourced.

To date, there have been no published studies from the private sector in SA specifically addressing the incidence of and factors associated with IVH in VLBWIs. Understanding the incidence of comorbidities in preterm infants is crucial for the private healthcare sector, as it seeks to enhance the quality of care and management of these high-risk infants. The aim of this study was to determine the incidence of any and moderate to severe IVH, as well as the factors associated with moderate to severe IVH, in VLBWIs admitted to private sector hospitals.

Methods

Study design

This study involved a retrospective secondary analysis of data from the Vermont Oxford Network (VON) database, collected from three private sector hospitals in Gauteng Province, SA.

Study setting and population

The analysis reviewed data on all VLBWIs recorded in the VON database in the NICUs of three private hospitals in Johannesburg, SA, from January 2018 to December 2022. These hospitals are part of a private hospital group affiliated with the VON, a non-profit collaboration of over 1 200 hospitals worldwide that aims to enhance neonatal care through data-driven quality improvement. The VON database contains information on maternal and neonatal characteristics, clinical management, interventions and diagnoses. Only VLBWIs with available cranial ultrasound data (including results) were included in the study. Cranial ultrasound scans were performed by either radiologists or neonatologists, depending on whether the caregiving doctors were comfortable with regard to performing their own scans. Infants without cranial ultrasound data or results were excluded. A sample size of 196 was calculated based on an assumed incidence of moderate to severe IVH of 15%, similar to rates observed in HICs, with a margin of error of 5% and 95% confidence limits.

Statistical analysis

Statistical analysis was conducted using Stata 18 (StataCorp, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test and histogram plots with an overlaid normal curve. Normally distributed continuous variables were summarised using means and standard deviations (SDs), while non-normally distributed variables were summarised with medians and interquartile ranges (IQRs). Categorical variables were summarised using frequencies and percentages. Cranial ultrasound results were classified as normal or according to grades of IVH using the Papile classification system.[14] Infants with cranial ultrasound findings classified as Papile grades III or IV were categorised as having moderate to severe IVH, while those with grades I or II were classified as having mild IVH. The incidence of IVH was reported as a percentage. Univariate logistic regression analysis was performed to identify factors associated with moderate to severe IVH, with results presented as odds ratios (ORs), 95% confidence intervals (CIs) and *p*-values. For the multivariate logistic regression analysis, stepwise variable selection was applied to identify significant variables for inclusion, setting a liberal *p*-value threshold of 10%. Adjusted ORs, 95% CIs and *p*-values were reported for these results. In all inferential analyses, statistical significance was established at a *p*-value of 0.05.

Ethical considerations

This was a retrospective study, and the information was stored in a database, so informed consent from parents was not needed before collecting data.

Permission to use data from the VON system was obtained from the research department of the private hospital group. Data were collected after approval was obtained from the hospital, and a clearance certificate was received from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M230438 MED23-03-134). Each patient received a study number. To maintain confidentiality, names and case numbers/hospital numbers remained separate.

Results

Maternal characteristics

A total of 186 VLBWIs were admitted to the NICUs of the three private hospitals over the study period. Most of the mothers were black Africans (*n*=128), 182 mothers had attended antenatal care, and 35 had multiple gestations. Pregnancy complications included hypertension in 52 mothers and chorioamnionitis in 3. About two-thirds of the mothers (*n*=122) received antenatal steroids to promote neonatal lung maturity, and 24 mothers received antenatal magnesium sulphate. Most of the mothers, 166 in total, delivered via caesarean section (CS) (Table 1).

Neonatal characteristics at delivery

The median (IQR) weight of the neonates was 1 140 (901 - 1 330) g. The mean (SD) gestational age was 29.0 (2.6) weeks. Most neonates (*n*=150) were diagnosed with RDS.

Approximately one-third of the neonates (*n*=58) were treated with nasal continuous positive airway pressure (nCPAP) shortly after delivery, while 127 required intubation for conventional ventilation. In total, 136 neonates received surfactant treatment, which included those on both nCPAP and conventional ventilation (Table 2).

Incidence of IVH

Of the 186 VLBWIs admitted to the NICUs at the three private hospitals, 135 underwent cranial ultrasound imaging. Of these, 101 infants had no IVH, while 34 infants exhibited some grade of IVH. The grades of IVH were distributed as follows: grade I in 11 infants, grade II in 5 infants, grade III in 7 infants, and grade IV in 11 infants. A total of 16 infants therefore had mild IVH, and 18 infants had moderate to severe IVH (Fig. 1).

Comparing characteristics of infants who had no to mild IVH with those who had moderate to severe IVH

In the univariate analysis, VLBWIs with moderate to severe IVH were more likely to come from multiple gestations, to be extremely premature (gestational age <28 weeks), to be of extremely low birthweight (<1 000 g), to have received invasive mechanical ventilation, to have received surfactant and to have developed necrotising enterocolitis, and were more likely to die (Table 3). Conversely, these infants were less likely to have been born via CS.

In the multivariate analysis, after adjusting for potential confounding factors, the odds of VLBWIs having moderate to severe IVH were high if they were born to mothers who had received antenatal magnesium sulphate and low if they were born via CS and were of gestational age ≥28 weeks (Table 4).

Table 1. Maternal characteristics in the very low-birthweight group analysed (*N*=187)

Variable	*n* (%)
Maternal ethnic group	
Black	128 (68.8)
White	29 (15.6)
Asian	26 (14.0)
Unknown	3 (1.6)
Attended antenatal care	182 (97.9)
Had multiple gestation	35 (18.8)
Maternal hypertension	52 (28.0)
Mother received magnesium sulphate	24 (12.9)
Mother received antenatal steroids	122 (65.6)
Mode of delivery caesarean section	166 (89.2)

Table 2. Neonatal characteristics of very low-birthweight infants

Variable	*n* (%)*
Gestational age (weeks), median (IQR)	29 (26.4 - 31.6)
<28	53 (28.5)
28 - 30	77 (41.4)
>30	56 (30.1)
Birthweight (g), median (IQR)	1 140 (901 - 1 330)
<1 000	63 (33.9)
1 000 - 1 499	123 (66.1)
Apgar score <7 at 5 minutes	27 (14.5)
Respiratory distress syndrome	150 (81.1)
Required nCPAP	58 (31.5)
Required intubation for ventilation	127 (68.7)
Surfactant administration	136 (76.0)

IQR = interquartile range; nCPAP = nasal continuous positive airway pressure.
*Except where otherwise indicated.

Discussion

This study is one of the first to examine the incidence of IVH and associated risk factors in VBWIs in the private hospital sector in Johannesburg, SA. In this study, the incidences of any IVH and moderate to severe IVH were found to be 25.2% and 13.3%, respectively. This incidence of any IVH is lower compared with both HICs (incidence 32%) and LMICs in SSA (incidence 27 - 44%).[4-6,15] For the period 2018 - 2022, VON reported overall incidences of any IVH and moderate to severe IVH in VLBWIs of 22 - 24% and 6.5 - 8%, respectively, in HICs. These figures are lower than those observed in our study. Private healthcare accounts for ~41.8% of SA's health expenditure while only serving 17% of the population; it also accounts for 26% of total bed capacity in SA while being serviced by 55% of SA's health professionals.[16] SA medical schemes offer duplication and supplementary health insurance, as opposed to HICs, where the focus is primarily supplementary coverage to public healthcare.

The incidence of moderate to severe IVH was significantly reduced in neonates delivered via CS, aligning with other studies supporting the notion that vaginal delivery may contribute to factors related to development of IVH such as raised intracranial venous return and elevated mechanical stress on cerebral blood vessels.[17,18] In contrast, Magann *et al.*[19] did not observe a significant decrease in the severity of IVH in preterm infants delivered via CS compared with vaginal delivery. Improved outcomes in infants delivered via CS may also be due to management bias, as these mothers often receive antibiotics, antenatal steroids and antenatal magnesium, which assist in improving neonatal outcomes.[20]

The univariate analysis found an association between lower gestational age, lower birthweight, and an increased incidence of moderate to severe IVH; however, only lower gestational age was demonstrated to be a significant risk factor in the multivariate model, findings also found in other studies.[21]

Many studies have reported prevention strategies for IVH, including antenatal steroids, which assist in improving cerebral autoregulation and accelerating lung development and are associated with a reduced risk of IVH development in premature neonates.[22] However, in our study antenatal steroids had no statistically significant effect in the prevention of IVH. This could be because well-resourced hospitals typically have advanced NICUs with sophisticated support systems, experienced staff and established protocols, which in themselves reduce the incidence of IVH, thus potentially decreasing the additional

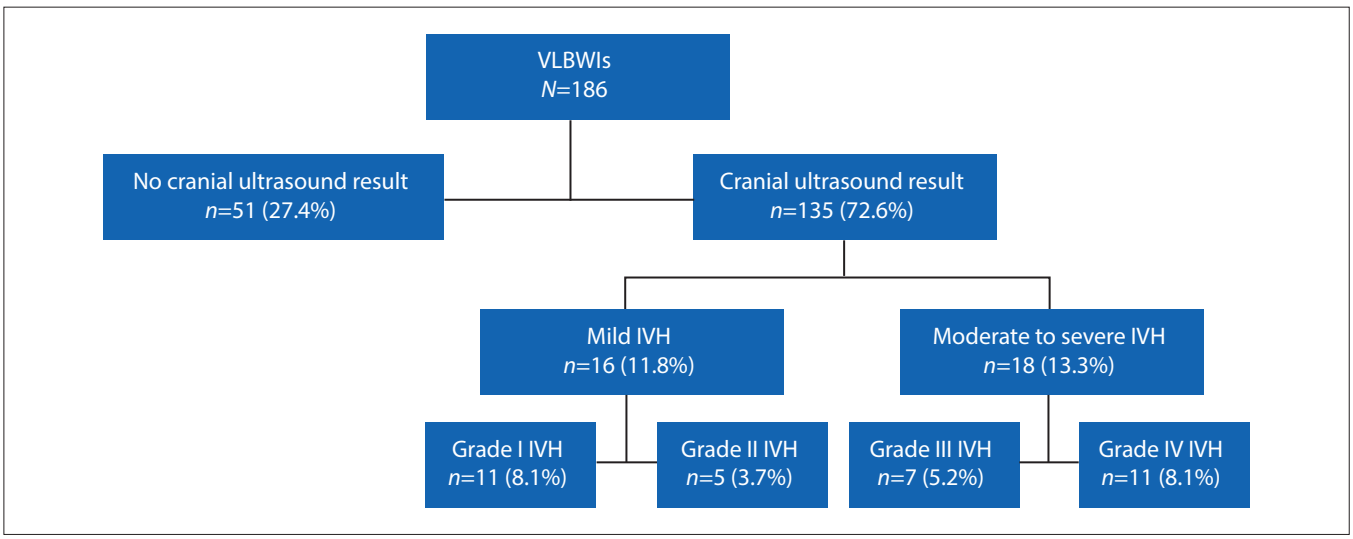

Fig. 1. Number of patients enrolled, and presence and severity of IVH. (IVH = intraventricular haemorrhage; VLBWI = very low-birthweight infant.)

Table 3. Univariate analysis comparing characteristics of very low-birthweight infants who had no or mild IVH with those who had moderate to severe IVH (*N*=135)

Variable	No to mild IVH (*n*=117), *n* (%)	Moderate to severe IVH (*n*=18), *n* (%)	*p*-value
Maternal characteristics			
Antenatal care	115 (98.9)	18 (100)	0.576
Place of birth			0.67
Inborn	92 (78.6)	15 (83.3)	
Outborn	25 (21.4)	3 (16.7)	
Multiple gestation	21 (18.0)	7 (38.9)	0.048*
Maternal hypertension	36 (31.9)	5 (31.3)	0.961
Antenatal steroids	84 (78.5)	9 (64.3)	0.236
Antenatal magnesium sulphate	14 (13.1)	5 (31.3)	0.070
Chorioamnionitis	1 (0.9)	1 (6.3)	0.106
Caesarean section	108 (93.1)	12 (66.7)	0.001*
Neonatal characteristics			
Gestational age (weeks)			0.004*
<28	53 (45.0)	17 (94.4)	
≥28	64 (54.0)	1 (5.6)	
Birthweight (g)			0.001*
<1 000	34 (29.1)	14 (77.8)	
1 000 - 1 500	83 (70.9)	4 (22.2)	
Respiratory distress syndrome	98 (84.5)	17 (94.4)	0.260
Type of ventilation after initial resuscitation			0.033*
Conventional	90 (77.6)	17 (94.4)	
nCPAP	41 (35.3)	1 (5.6)	
Surfactant at any time	88 (79.3)	18 (100)	0.033*
Patent ductus arteriosus	37 (32.2)	9 (50.0)	0.139
Pneumothorax	5 (4.3)	0	0.371
Necrotising enterocolitis	18 (15.4)	7 (38.9)	0.022*
Late neonatal infection	44 (37.9)	8 (53.3)	0.251
Chronic lung disease <33 weeks	29 (31.5)	2 (66.7)	0.201
Chromosomal abnormality	1 (0.9)	0	0.694
Died	21 (18.0)	15 (83.3)	<0.001*

IVH = intraventricular haemorrhage; nCPAP = nasal continuous positive airway pressure.
*Significant (p<0.05).

Table 4. Multivariate analysis of maternal and neonatal characteristics of very low-birthweight infants with moderate to severe IVH

Variable	Univariate analysis, OR (95% CI)	*p*- value	Multivariate analysis, aOR (95% CI)	*p*-value
Maternal characteristics				
Multiple gestation	2.90 (1.01 - 8.34)	0.048	3.73 (0.80 - 17.36)	0.094
Antenatal MgSO4	3.02 (0.91 - 9.99)	0.070	8.60 (1.64 - 44.87)	0.011*
Caesarean section	0.13 (0.04 - 0.45)	0.001	0.09 (0.02 - 0.45)	0.004*
Neonatal characteristics				
Gestational age (weeks)				
<28	Ref.			
≥28	0.05 (0.01 - 0.38)	0.004	0.08 (0.01 - 0.86)	0.037*
Birthweight (g)				
<1 000	Ref.			
1 000 - 1 500	0.14 (0.04 - 0.45)	0.001	0.66 (0.15 - 2.95)	0.588
Used nCPAP	0.11 (0.14 - 0.84)	0.033	0.30 (0.03 - 2.78)	0.286
Necrotising enterocolitis	3.50 (1.19 - 10.23)	0.022	1.70 (0.36 - 7.91)	0.505

IVH = intraventricular haemorrhage; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; MgSO4 = antenatal magnesium sulphate; nCPAP = nasal continuous positive airway pressure.
*Significant (p<0.05).

significance of antenatal steroids in these specific populations. In an SA public sector study, administration of antenatal steroids had no significance in terms of decreasing the incidence of IVH.[18] This finding was attributed to late presentation of unbooked mothers and lower rates of antenatal steroid administration, poor antenatal care attendance, and vaginal delivery.

Administration of antenatal magnesium sulphate was associated with a statistically significant increased incidence of moderate to severe IVH in our study. Contrary to the findings in this study, several studies have reported a reduction in the incidence of IVH in neonates born to mothers who received antenatal magnesium sulphate, as it reduces brain inflammation and excitotoxicity,[12] and therefore stabilises blood pressure and cerebral blood flow in the fetus. A possible reason for this contrasting finding in our study could be that the effects of hypermagnesaemia, such as lethargy and respiratory depression, often lead to an increased incidence of intubation, as suggested by Mittendorf *et al.*,[23] who found that infants born to mothers with higher serum ionised magnesium levels (0.75 mmol/L v. 0.56 mmol/L) were more likely to develop IVH. Other possible reasons could be that magnesium inhibits platelet function, affecting coagulation and thereby increasing the chance of IVH in the premature infant's immature brain, or that high serum levels of magnesium together with other factors may act as an injury promoter in the brain.[23]

Study limitations and strengths

Our study had the following limitations. It was a retrospective study, with some centres/hospitals having missing or incomplete patient data, the general reasons for which as stated by VON were death before imaging, transfer before imaging, and missing documentation or no record. VON does not have a single network-wide percentage for missing cranial ultrasound data in VLBWIs; the data vary according to registry, centre and year. Our moderate to severe IVH group was small. VON does not include maternal age and HIV status in their data collection. The study also had limitations in terms of accounting for reasons for prematurity, and timing, dosage or number of antenatal steroids and antenatal magnesium courses. With regard to use of antenatal magnesium sulphate, we were unable to ascertain whether it was for maternal hypertension or as neuroprotection for infants.

The strength of this study was the database used, the VON database being the world's largest database of VLBWIs and NICU admissions across more than 1 200 centres worldwide. The expanded database includes all NICU admissions, broader gestational age ranges, and outcomes and practices in both HICs and LMICs. VON reports include centre, group and network data, and risk-adjusted outcome data.

Conclusion

More research should be directed at determining the optimal timing and dosage of antenatal magnesium to prevent IVH in premature neonates. In the present study, infants delivered via CS experienced a significantly lower incidence of IVH, and this mode of delivery should always be considered where appropriate. More extensive studies would provide better insight into potential risk factors for IVH in VLBWIs, and the cost implications of preventive measures.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (MFK) 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 MFK's MSc (Childhood Neurodevelopment) degree at the University of the Witwatersrand.

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Author contributions. SV and TR supervised the study process**.** MFK, SV and TR designed the study and developed the methodology. MFK collected and analysed the data. MFK prepared the article. The final article was edited and reviewed by supervisors SV and TR.

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Conflicts of interest. None.

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