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Prevalence and risk factors of intraventricular hemorrhage in Very low birth weight infants at Chris Hani Baragwanath academic hospital

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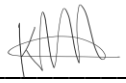
A research report Submitted to the School of Clinical Medicine Faculty of Health Sciences, University of The Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in branch of Paediatrics 2023

Declaration

I Kulani Mabasa declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the Branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University



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Signature of candidate

02_____ day of November_____ year 2023

Dedication

I dedicate this work to almighty GOD JEHOVAH ELOHIM, for in Him I live and have my being. I am able to do all things through Him who give me strength. May this gift of life that I received by His grace, brings honor and glory to His holy name throughout my days in the land of the living.

Abstract

Background: Intraventricular hemorrhage (IVH) is the commonest form of bleeding in the central nervous system (CNS) of premature neonates. Pathogenesis is attributed to germinal matrix fragility. Risk factors are multifactorial and related to various events that may happen in utero, peri-partum and postnatally.

Methods: This was a retrospective descriptive study in the neonatal unit of CHBAH. 529 VLBW infants of <1500g admitted between January 2017 to December 2018 were studied. Those with IVH were cases and those without IVH were controls.

Results: Of the 529 infants studied, 33%(n=176) had IVH, 56% (n=99) were mild IVH (grade 1 and 2) and 44% (n=77) were severe IVH (grade 3 and 4). Median gestational age (28 vs 30, p<0.001) and birthweight (1059g vs 1220g, p<0.001) were lower in those with IVH. More neonates with no IVH received steroids (40.5% vs 30.1%, p=0.020) and magnesium sulphate (11.9% vs 2.8%, p<0.001). Neonates with an Apgar score < 6 at 5 minutes (OR 8.17, 95%CI: 2.54-26.3), intubated (OR 8.822, 95%CI: 1.34-56.41) and had meningitis (OR 104.92, 95%CI: 40.10 - 274.5) were more likely to have IVH. Those with IVH had a 20-fold chance of having PHHC (OR 20.25, 95%CI: 1.21 -338.84) and a higher likelihood of dying (3.70 95% CI 1.50-9.15). PHHC was observed in neonates who had severe IVH (grade 3 and 4). Of the neonates who died IPPV (2.20, 95% CI 1.117-4.34), hypotension (10.46, 95% 2.32-47.11) and meningitis (1.13, 95% 1.016-1.26) were associated with death.

Conclusion: Incidence of IVH is consistent with those of LMIC. The significant risk factors for IVH were low Apgar score at 5 minutes, those who were intubated, and had meningitis. Steroids and magnesium sulphate were protective against developing IVH. More studies are needed to analyze risk factors associated with severe IVH (grade 3 and 4). Identifying pharmacological neuroprotective agents may be beneficial in future.

Keywords: premature, neonates, intraventricular hemorrhage (IVH), outcomes, risk factors

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Abbreviations

ANS	Antenatal Steroids
aOR	Adjusted Odds Ratio
APGAR	Appearance Pulse Grimace Activity and Respiration
BMV	Bag Mask Ventilation
BW	Birth Weight
CBF	Cerebral blood flow
CHBAH	Chris Hani Baragwanath Academic hospital
CI	Confidence Interval
CPR	Cardiopulmonary Resuscitation
CRH	Corticotropin releasing hormone
CS	Cesarean Section
DC	Discharged
DM	Diabetes Mellitus
G	Gram
GA	Gestational Age
GMH	Germinal Matrix Hemorrhage
HT	Hypertension
IPPV	Invasive Positive Pressure Ventilation
IVH	Intraventricular Hemorrhage
IQR	Inter quartile range
MGSO4	Magnesium sulphate
Min	Minute
MOD	Mode of Delivery

NCPAP	Nasal Continuous Airway Pressure
NICU	Neonatal Intensive Care
PHHC	Post Hemorrhagic Hydrocephalus
PIH	Pregnancy Induced Hypertension
p-value	Probability Value
POB	Place of Birth
REF	Reference
RDS	Respiratory Distress Syndrome
SD	Standard deviation
VLBW	Very Low Birth Weight

AUTHOR GUIDELINES FOR SOUTH AFRICAN JOURNAL OF CHILD HEALTH (SAJCH)

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Main Submission

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract

The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study

Study Methods should be described in as much detail as possible so that others would be able to replicate the study should they need to.

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Discussion section will explain interpretation of findings, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses.

The conclusion should briefly summarize the main message of the paper and provide recommendations for further study.

Tables: Tables should be constructed carefully and simply for intelligible data representation.

Structured abstract

This should be no more than 250words, with the following recommended headings:

Background: why the study is being done and how it relates to other published work.

Objectives: what the study intends to find out

Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

Conclusion: must be supported by the data, include recommendations for further study/actions. Do not include any references in the abstracts

SUBMISSABLE FORMATTED RESEARCH REPORT

Prevalence and risk factors of intraventricular hemorrhage in very low birth infants at Chris Hani Baragwanath Academic Hospital

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Introduction

Intraventricular hemorrhage (IVH) refers to a subependymal germinal matrix hemorrhage, intraventricular hemorrhage and parenchymal hemorrhage(1). It is the commonest form of bleeding in the central nervous system (CNS) in premature neonates(2). The worldwide incidence of IVH in VLBW neonates is up to 50%. It is lower in high income countries (HIC) at about 12.5%-25% compared to low middle income countries (LMIC) at 20-50%.(3) IVH is an important cause of morbidity and mortality in the preterm population (4, 5).

The risk factors for IVH are multifactorial and the pathogenesis is attributed to the germinal matrix fragility and impaired cerebral autoregulation due to immaturity in preterm neonates. The delicate vascular capillary network within the germinal matrix lacks structural support which makes it more vulnerable to injury. Impaired autoregulation contributes to this vulnerability as the sustainability of constant cerebral blood flow (CBF) during changes in systemic blood pressures is not maintained (6). Risk factors for IVH in preterm neonates are therefore related to various events that may occur in utero, peri-partum and postnatally which causes direct injury to the germinal matrix capillary network or indirectly by increased fluctuation in systemic blood pressures and cerebral blood flow resulting in bleeding. The pathogenesis of IVH support the reason that IVH is inversely proportional to gestational age and birthweight. Most bleeds occur in the first 72 hours of life which is most likely due to risk factors related to the intrapartum and immediate perinatal period (7). Studies have identified variables associated with decreased IVH such as antenatal steroids, hypertension in pregnancy, and magnesium sulphate ($MgSO_4$) therapy (8-14). The use of antenatal steroids significantly improved survival in premature neonates and had a decreased incidence of IVH (15, 16). Steroids stimulate maturation of the germinal matrix microvasculature thus making them more resistant to perinatal and postnatal events that may provoke IVH (17).

The classifications by Papile and Volpe are used to characterize IVH (1, 18). These classification systems are based on brain imaging. The commonest classification used is by Papile; where 4 grades of IVH are described: grade 1 for bleeding confined to the germinal matrix, grade 2 for

IVH without ventricular dilatation, grade 3 for IVH with ventricular dilatation and grade 4 for extension of bleeding to the brain parenchyma(1). Mild bleeds are classified as Grade 1 and 2 and they usually resolve, grade 3 and 4 are severe and associated with adverse outcomes.(1)

The improvement in neonatal care has led to an increase in survival of preterm neonates and hence preterm related complications including IVH. In this present study, we aim to determine the prevalence of IVH and identify risk factors associated with IVH at the Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods and materials

This is a retrospective, descriptive study in the neonatal unit of Chris Hani Baragwanath Academic hospital (CHBAH). The unit captures all admitted patients on REDcap data capturing system (Research electronic data capture)(19, 20). All very low birth weight (VLBW) premature neonates; both inborn and outborn, who were admitted between January 2017 to December 2018 were identified and those who had a cranial sonar, during their admission in the neonatal unit (729) were identified. Those who met study criteria were 529 and were selected as the study population. Cranial sonars are performed by neonatal consultants within the first week of life, at 14 days, 28 days and at discharge and as clinically indicated. The timing of sonars was not included in our database.

Inborn neonates were defined as those born in CHBAH and outborn were all neonates referred from another hospital, clinic or born before arrival to hospital. Neonates excluded from the study were those with severe malformations, cranial sonar abnormalities other than IVH and those with incomplete data. IVH was classified into four grades according to the Papile classification.

Maternal demographic data, neonatal characteristics and outcomes variables were extracted for each infant from the neonatal data as captured in REDCAP. These were: maternal age, maternal parity, maternal comorbidities (diabetes, hypertension) antenatal steroids, receipt of $MgSO_4$, inborn or outborn, mode of delivery, gestational age, birthweight, sex, resuscitation which includes bag mask ventilation (BMV), cardiopulmonary resuscitation (CPR), intubation

and adrenalin, Apgars at 1minute, Apgars of at 5minutes, nasal continuous positive airway pressure (nCPAP), intermittent positive pressure ventilation (IPPV), surfactant, hypotension, medication for hypotension, sepsis, meningitis, seizures, post hemorrhagic hydrocephalus (PHHC), discharge or death. The neonates were then assigned to cases (those with IVH) and controls (those without IVH).

Ethics consideration

The Human Research Ethics Committee (HREC) at the University of the Witwatersrand approved the study. (Ethics number M190739.) The Neonatal Redcap Database was approved by the HREC (M115196).

Statistical methods

Data were analyzed using Stata version 15.1 (StataCorp, USA). Continuous demographic data were represented as medians and interquartile ranges (IQR), categorical variables as means and standard deviation (SD) where appropriate. Pearson Chi-square tests and student t test were used to assess associations between outcome variables and demographic and clinical characteristics (gender, maternal parity, gestational age, birthweight, comorbidities, place of birth, mode of delivery, intubation, adrenalin, hypertension, hypotension, medication for hypotension, surfactant, $MgSO_4$, IPPV, PHHC, meningitis, seizures). Multivariable logistic regression model of the outcome variables, with a p-value<0.1, was constructed to control for confounders and identify independent predictors. Associations with these predictors are reported as adjusted odds ratios (aOR), with 95% confidence intervals and p-values. A p-value <0.05 is considered statistically significant.

Results

A total of 529 VLBW infants born between 2017 and 2018 who met the study criteria were included in the study cohort. One hundred and seventy-six (33.3%) infants had IVH (cases) and 353 (66.7%) had no IVH (controls) Figure 1. Of the 176 that had IVH 56% had mild IVH (grade 1 and 2) and 43.8% had severe IVH (grade 3 and 4). Figure1.

There were no differences in maternal age between the cases and controls. Majority of the mothers were between 20-40 years of age. Mothers in the control group had a higher parity (56% vs 47.2%; p-0.033). A quarter of the mothers in the control group had hypertension (24.9% vs 9.7%; p< 0.001). More mothers in the control group received antenatal steroids (p-0.020) and $MgSO_4$ (p<0.001). Table 2

Majority of neonates were inborn with no difference between cases and control (p=0.317). Amongst the cases there was equal distribution between vaginal and caesarean deliveries. Cases had a lower gestational age (28 vs 30weeks, p<0.001) and birthweight (1059g vs 1220g;<0.001) than controls. Seventy-seven percent of neonates in the study were between 1000-1500g; with greater proportion being in the control group. More cases were observed amongst those with birth weight <1000g (36.9% vs 15.9%, p<0.001). More males had IVH (56.8% vs 45.9%; p-0.0018). Table 3.

There were no differences in the need for resuscitation (p-0.708), use of BMV (p-0.286), CPR (p-0.294) and adrenalin administration (p-0.339). However, more cases required intubation (3.4% vs 1.1%; p-0.001). The median Apgar score at 1minute (5 vs 7; p<0.001) and 5minute (8 vs 9 p<0.001) was lower in the cases than controls. There was no difference in the use of nCPAP between the groups (p-0.706). Those with IVH required IPPV (p<0.001), surfactant (p<0.001), had hypotension (p<0.001) and required inotropes (p<0.001). Cases had a higher proportion of sepsis (66.5 vs 24.4; p<0.001) and meningitis (81.3 vs 5.4; p<0.001). Table 3

Of the 31 infants who had seizures, 26 (14.8%) had IVH (p<0.001). Eleven of the 12 neonates who developed PHHC had IVH (p<0.001). Those who developed PHHC had severe IVH (grade 3 and 4). A higher proportion of infants with no IVH were discharged (87.8% vs 46.6% p<0.001). There was no difference in outcome (discharge and death) between the mild and severe grades of IVH. (Supplementary Table 1). More neonates that had IVH died (52.3% vs 11.9%; p<0.001). There were 3 (1.1%) neonates with missing outcome information.

Neonates with an Apgar score < 6 at 5 minutes (OR 8.17, 95%CI: 2.54-26.3), those who were intubated (OR 8.822, 95%CI: 1.34-56.41) and had meningitis (OR 104.92, 95%CI: 40.10 -274.5) were more likely to have IVH. Those with IVH had a 20-fold chance of having PHHC (OR 20.25,

95%CI: 1.21 -338.84) and a higher likelihood of mortality (3.70 95% CI 1.50-9.15). Of the neonates who died; IPPV (2.20, 95% CI 1.117-4.34), hypotension (10.46, 95% 2.32-47.11) and meningitis (1.13, 95% 1.016-1.26) were associated with death. Table 5. There were no factors associated with mortality when stratified according to weight categories.

Discussion

This study shows that about a third of the study population had IVH and a third of those had grade 1 IVH. More than 50% of those who had IVH had mild forms of IVH (grade 1 and 2). There are different reports on the prevalence of IVH in very low birth weight infants (VLBW) with limited data in Africa (21). This may be due to a lack of resources, acquisition of expensive sonar machines or expertise in point of care sonars.

The current study shows the prevalence of IVH in VLBW infants to be 33% and severe IVH to be 14.5%. This is lower than the findings of 53% reported in 1992 in the same institution (22). Other LMICs, Kenya, Zambia and Uganda have reported a similar finding of about 30% (23-25). In 2 tertiary public hospitals in the same University complex, the incidence has been reported as 26% and 40%. (26). The hospital with the lower incidence of IVH had higher rates of antenatal steroid coverage(8, 26).

Though the overall incidence of IVH has declined in some birthweight and gestational age strata, the reported IVH incidence has increased due to higher survival rates of extremely preterm neonates as a result of advances and improved neonatal care(8, 27). The National Institute of Child Health and Human development (NICHD) Neonatal Research Network (NRN) reported a decline in IVH from 19% to 15% between 1993 to 2012 (28). A recent systematic review identified a lower incidence of IVH in neonates with a higher gestational age and an increase in the incidence in the lower gestational ages. Studies from Africa report on IVH in higher birthweight categories as the smaller neonates may not survive due to a lack of resources.

Maternal comorbidities of diabetes and hypertension have been associated with a lower incidence of IVH(8, 29-31) . In the current study there were no differences in IVH in infants of

diabetic mothers, the small sample size could account for this result. Neonates born to mothers with neonatal hypertension had lower rates of IVH. These results are consistent with studies that reported similar findings (8, 30, 31). Hypertensive disorders may have a protective role in IVH by accelerating maturity of the infant through endogenous steroids (30, 31) . Laatikainen et al found increased levels of corticotropin releasing hormone (CRH) in venous cord blood of women with pregnancy induced hypertension (PIH)(32). Placental release of CRH in to fetal circulation is thought to accelerate fetal maturation by stimulating fetal pituitary adrenal axis through positive feedback mechanism. (32)

In this study there were more neonates exposed to $MgSO_4$ in-utero in the control group (11.9% vs 2.8%, p<0.01). Magnesium sulphate has been reported to be neuroprotective in preterm infants(33). It is thought that $MgSO_4$ stabilizes myocardium, placental blood flow and fetal cerebral circulation (14). A recent meta-analysis showed a 20% pooled reduction in IVH with the use of $MgSO_4$ (RR 0.80; 95% CI: 0.63-1.03, p = 0.013). A meta-analysis by Zeng et al., that included 10 studies with 18655 preterm neonates, showed that $MgSO_4$ decreased moderate to severe cerebral palsy in preterm neonates (OR 0.61, 95% CI 0.42–0.89, $P < 0.01$)(34, 35). There is a need for randomized control trials to explore the association of $MgSO_4$ and IVH.

Neonates that were exposed to antenatal steroids had lower rates of IVH. Half of the mothers that received $MgSO_4$ had also received antenatal steroids in our study. Antenatal steroids stimulate maturation of the germinal matrix microvasculature thus infants are more resistant to perinatal and postnatal events that may cause IVH (17). In Kenya and Uganda where the coverage of antenatal steroids was low; there was significant reduction of IVH risk in neonates whose mothers received antenatal steroids (23, 25). A Cochrane review of antenatal steroid use (in 6093 neonates from 16 studies) reported a reduction in IVH (RR 0.55, 95% CI 0.40 to 0.76) and an improved survival in premature neonates (12). The risk of any IVH and severe IVH was two-fold, if antenatal steroids were not administered in pregnant women at risk of premature delivery (36).

In the current study there were no differences regarding place of birth and mode of delivery. Studies showed that outborn neonates who required transportation to another institution were at risk of IVH (37) (38). Cesarean section was reported as either having no association or being protective against IVH. (37-40). Mothers with planned cesarean sections received medications such as antenatal steroids, magnesium sulphate, tocolytics and antibiotics to improve neonatal outcomes which could be contributing to lower rate of IVH in cesarean section deliveries(40).

A sex difference in IVH rates among VLBW newborns was reported by Eduaedo et. al where they demonstrated that male neonates had a higher risk of IVH (26.8% vs 9.7%; p- <0.001 ; OR 3.4; 95%CI 1.8-6.4) and higher risk of severe IVH (16.1% vs 1.9%; p-<0.001; OR 9.6; 95%CI 2.9-32.5) (41). Brain maturation occurs faster in females than males, which may account for the sex difference in developing IVH(42). However, this study had a male predominance in cases.

Gestational age and lower birth weight were significant independent risk factors for IVH in our study. Studies reported that neonates with IVH were of lower gestational age and smaller birth weights (8, 17, 21, 39). With the survival of smaller neonates or micro preemies, the incidence of IVH is on the increase in LMIC and HIC. The advent of improved neonatal care and increased survival of neonates at lower gestational ages and weight bands may account for this increase.(25)

The germinal matrix has fragile microvasculature making it vulnerable to postnatal events (43). Cerebral blood flow is pressure passive, thus, events that lead to a fluctuation of cerebral blood flow, increases the risk of IVH. Resuscitation, intubation, mechanical ventilation, administration of surfactant, hypotension and the use of inotropes are some events that affect the cerebral blood flow(15, 37, 38). Low Apgar scores and perinatal asphyxia are risk factors for IVH and severe forms of IVH. (36). We report an 8-fold increased risk of IVH for VLBW neonates who require intubation at birth, cases with low Apgars of < 6 at 5minutes, those who received surfactant and required IPPV.

Haroon et. al reported a fourfold increase in IVH in neonates who received surfactant (44). A study in Turkey found no association between surfactant administration and IVH (37). Multiple

intubation attempts in the delivery room increases the risk of IVH in VLBW neonates. (45). A reduction in delivery room intubation showed a decrease in severe IVH (46). Cases who were mechanically ventilated had severe IVH and a higher mortality rate. Mechanical ventilation causes changes in intrathoracic pressure, this affects venous return and cerebral blood flow(47). Severe IVH in VLBW neonates, who underwent early mechanical ventilation, was increased to almost 3 folds (47). The timing of the development of IVH and initiating IPPV were not explored in this study, thus, it is unknown if IVH occurred before or after IPPV.

Severe IVH was noted in neonates with lower mean arterial blood pressure (MABP), fluctuations of blood pressure and those who received therapy for hypotension(15, 48). The use of inotropes had been found to be an independent risk factor for IVH(49). The current study did not demonstrate an association of severe IVH with hypotension and treatment for hypotension.

Outcome and complications

IVH is the commonest etiology of seizures in preterm infants (50). Pisani et al found seizures in a third of preterm infants with grade 2-4 IVH (51). Two thirds of those with IVH in our study had seizures. Our results showed an association of severe grades of IVH with PHHC which is consistent with other studies. (1, 52).

The odds of death were 3.7 times higher in those with IVH. We found no differences in mortality between the mild compared to severe forms of IVH (supplementary table 1). Studies have observed higher mortality rates in those with severe IVH(5). The high mortality rate in those with IVH could have been from other comorbid conditions in the neonatal course. Sepsis is still a serious concern with meningitis identified as a risk factor for late IVH and associated with mortality. Infection control measures must be reinforced to prevent late IVH. The results of a multivariable logistic analysis further revealed that infants who were hypotensive, had meningitis and those who required IPPV were more likely to die.

Study limitations

The retrospective study design was a limitation as incomplete and missing information on the database affected the cohort dataset. More than 50% of patients had no cranial sonar results documented, the lack of resources which limited the cranial ultrasound screening or related to the documentation of cranial sonar findings on the database. Neonates may have died before a cranial sonar was performed. The timing of the sonar was not documented thus cases could not be stratified to early or late IVH.

Conclusion and recommendations.

The prevalence of IVH is consistent with LMICs. The significant risk factors for IVH were low Apgar score at 5 minutes, those who were intubated, and had meningitis. Protective factors against the development of IVH include the administration of antenatal steroids and antenatal $MgSO_4$. The incidence of IVH in neonates with lower gestational age and micro preemies are on the increase as the survival rates of neonates at the borders of viability improve. Further studies that identify pharmacological neuroprotective agents that may be administered prenatally and postnatally may prove beneficial. Long term follow-up of neonates with all grades of IVH are warranted in this study and future studies.

Acknowledgements

Thank you to Professor K. Thandrayen for statistical assistance.

Conflicts of Interest

The authors have no conflicts of interests.

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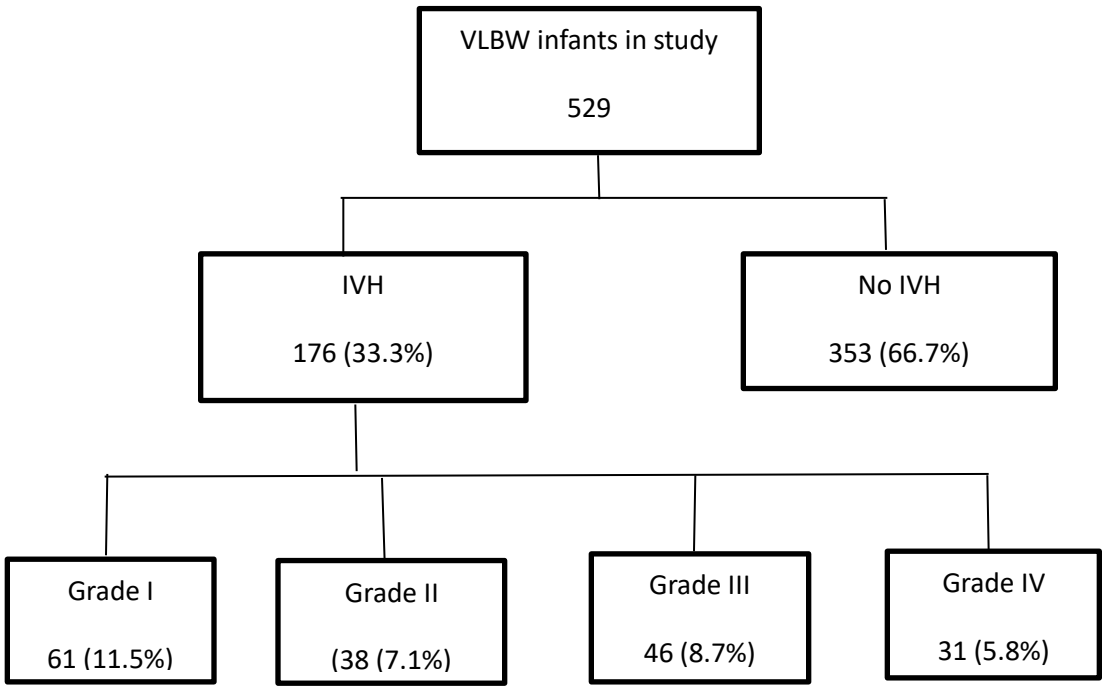

Figure 1: Consort Diagram of Neonates with Intraventricular Hemorrhage (IVH)

Table 1: Maternal Demographics of Neonates with and without IVH

		Cases n (%)	**Controls n (%)**	
	Total N=529 n (%)	**IVH n=176 (33.3) n (%)**	**No IVH n=353 (66.7) n (%)**	**P values**
Maternal age, mean (SD)	27.5 (±7.3)	27.1 (±7.8)	27.7 (±7.1)	0.405
Maternal age				
<20	60 (11.3)	18 (10.2)	42 (11.9)	0.343
20-40	447 (84.5)	148 (84.1)	299 (84.7)	
>40	16.3 (3.0)	6 (3.4)	10 (2.8)	
Undocumented age	6 (1.1)	4 (2.3)	2 (0.6)	
Maternal parity, median (SD)	2 (1-3)	2 (1-3)	1 (1-2)	0.002
Maternal parity				
0-1	243 (45.9)	93 (52.8)	152 (43.1)	0.033
>2	286 (54.1)	83 (47.2)	201 (56.9)	
Maternal Comorbidities				
Hypertension	105 (21.0)	17 (9.7)	88 (24.9)	<0.001
Diabetes Mellitus	4 (0.8)	2 (1.1)	2 (0.6)	0.603
Antenatal Steroids	196 (37.1)	53 (30.1)	143 (40.5)	0.020
$MgSO_4$	47 (8.9)	5 (2.8)	42 (11.9)	<0.001

*$MgSO_4$ – Magnesium Sulphate

Table 2: Characteristics of Neonates with and without IVH

		Cases n (%)	**Controls n (%)**	
	Total N=529 n (%)	**IVH n=176 (33.3) n(%)**	**No IVH N=353 (66.7) n(%)**	**p values**
Place of birth				
Inborn	469 (88.7)	153 (87.4)	316 (89.5)	0.317
Outborn	56 (11.3)	22 (12.6)	34 (9.7)	
Mode of delivery				0.007
Vaginal	212 (40.0)	81 (46.0)	131 (37.1)	
Caesarean	292 (55.2)	82 (46.6)	210 (59.5)	
Undocumented	25 (4.7)	13 (7.4)	12 (3.4)	
Gestational age, mean (SD)	29.4 (2.6)	29.9 (2.7)	28.4 (2.3)	<0.001
Gestational age				
<30weeks	264 (49.9)	115 (65.3)	149 (42.2)	<0.001
>30weeks	258 (49.4)	58 (33.5)	200 (57.3)	
Birthweight, mean (SD)	1156 (209)	1077 (200)	1195 (203)	<0.001
Birthweight				<0.001
<1000g	121 (22.9)	62 (36.9)	59 (15.9)	
1000g-1500g	408 (77.1)	114 (64.8)	294 (83.3)	
Male	262 (49.5)	100 (56.8)	162 (45.9)	0.018
Resuscitation	313 (59.2)	102 (58.0)	211 (59.8)	0.708
Bag mask ventilation	183 (34.6)	55 (31.3)	128 (24.2)	0.286
CPR	17 (3.2)	8 (4.5)	9 (2.5)	0.294
Intubation	16 (3.0)	12 (3.4)	4 (1.1)	0.001
Adrenalin	5 (0.009)	3 (0.017)	2 (0.0057	0.339
Apgar <6 at 1min, median (IQR)	7 (5-8)	5 (2-8)	7 (5-8)	<0.001
Apgar <6 at 1min	181 (34.2)	107 (60.8)	134 (38.0)	<0.001
Apgar <6 at 5min, median (IQR)	9 (7-10)	8 (5-9)	9 (8-10)	<0.001
Apgar <6 at 5min	61 (11.5)	58 (33)	31 (8.8)	<0.001
nCPAP	321 (60.7)	109 (61.9)	212 (60.1)	0.706
IPPV	132 (25.0)	67 (38.1)	65 (18.4)	<0.001
Surfactant	164 (31.5)	74 (42.0)	90 (26.0)	<0.001
Hypotension	77 (14.6)	45 (25.6)	32 (9.1)	<0.001
Inotropic support	66 (12.5)	40 (22.7)	26 (7.4)	<0.001
Sepsis	203 (38.8)	117 (66.5)	86 (24.4)	<0.001
Meningitis	162 (30.6)	143 (81.3)	19 (5.4)	<0.001
Seizures	31 (5.9)	26 (14.8)	5 (1.4)	<0.001

CPR – cardiopulmonary resuscitation, g-gram, min-minutes, IPPV-intermittent positive pressure ventilation, IQR-Inter quartile range, IVH- Intraventricular hemorrhage nCPAP – nasal continuous positive pressure ventilation, PHHC-post hemorrhagic hydrocephalus

Table 3: Outcomes of Neonates with and without IVH

		Cases n (%)	**Controls n (%)**	
	Total N=529 n(%)	**IVH n=176 (33.3) n(%)**	**No IVH n=353 (66.7) n(%)**	**p- values**
PHHC	12 (2.3)	11 (6.3)	1 (0.3)	<0.001
Discharge	392 (74.0)	82 (46.6)	310 (87.8)	<0.001
Death	134 (25.3)	92 (52.3)	42 (11.9)	<0.001

IVH – intraventricular haemorrhage, PHHC – post haemorrhagic hydrocephalus

Table 4: Multivariable Logistic Regression Analyses of Characteristics associated with IVH

Variable	IVH		
	Adjusted Odds Ratio (aOR)	**95% CI**	**p-value**
Maternal parity			
0-1	Ref	-	-
>2	0.801	0.380-1.689	0.560
Maternal Hypertension	0.370	0.128-1.072	0.067
Antenatal steroids	0.936	0.434-2.018	0.866
$MgSO_4$	**0.159**	**0.024-1.050**	**0.056**
Mode of delivery			
vaginal	Ref	-	-
caesarean	1.306	0.472-3.618	0.607
undocumented	1.658	0.122-22.605	0.704
Gestational age			
<30weeks	Ref	-	-
>30weeks	0.911	0.763-1.087	0.302
Birthweight			
<1000g	Ref	-	-
1000g-1500g	0.999	0.997-1.001	0.303
Sex			
Male	Ref	-	-
Female	0.575	0.277-1.194	0.138
Intubation	**8.822**	**1.379- 56.414**	**0.021**
Apgar <6 at 1min	0.710	0.304-1.661	0.430
Apgar <6 at 5min	**8.174**	**2.540-26.301**	**<0.001**
IPPV	0.845	0.332-2.155	0.725
Surfactant	1.548	0.719- 3.332	0.264
Hypotension	0.314	0.027-3.582	0.351
Sepsis	0.556	0.224-1.382	0.207
Meningitis	**104.921**	**40.103-274.502**	**<0.001**
Seizures	2.094	0.401-10.949	0.381
PHHC	**20.245**	**1.210-338.835**	**0.036**
Discharged	**Ref**	-	-
Died	**3.703**	**1.499-9.145**	**0.005**

* Logistic regression with all variables with a p-value <0.1 included. Note: All logistic regression analyses were performed at 95% CI. p-value=probability value; Ref=reference; CI=confidence interval.

Table 5: Multivariable regression analysis of factors associated with mortality

Variable	IVH		
	Adjusted Odds Ratio (aOR)	**95% CI**	**p-value**
Maternal parity			
0-1	Ref	-	-
>2	**0.547**	**0.305-0.980**	**0.043**
Hypertension	1.423	0.589-3.438	0.433
steroids	0.969	0.519-1.808	0.920
Mgso4	0.308	0.082-1.158	0.081
Mode of delivery			
Vaginal	Ref	-	-
Caesarean	0.699	0.369-1.327	0.274
Undocumented	0.654	0.144-2.966	0.582
Gestational age			
<30weeks	Ref	-	-
>30weeks	0.947	0.815-1.101	0.481
Birthweight			
<1000g	Ref	-	-
1000g-1500g	**0.996**	**0.994-0.998**	**<0.001**
Sex			
Male	Ref	-	-
Female	0.598	0.331-1.077	0.087
Intubation	0.574	0.133-2.478	0.457
Apgar <6 at 1min	1.005	0.845-1.195	0.955
Apgar <6 at 5min	0.980	0.827-1.162	0.818
IPPV	**2.203**	**1.117-4.347**	**0.023**
Surfactant	1.421	0.771- 2.618	0.260
Hypotension	**10.465**	**2.325-47.112**	**0.002**
Medication for hypotension	1.007	0.191-5.319	0.993

Sepsis	1.855	0.929-3.701	0.080
Meningitis	**1.132**	**1.016-1.261**	**0.025**
Seizures	2.079	0.622-6.950	0.235
PHHC	0.365	0.057-2.337	0.287

* Logistic regression with all variables with a p-value <0.1 included. Note: All logistic regression analyses were performed at 95% CI. p-value=probability value; Ref=reference; CI=confidence interval.

Supplementary Table 1: Table 7: Characteristics of Mild IVH compared to Severe IVH)

		Cases n (%)	**Controls n (%)**			
	Total n=529	**IVH N=176 n(%)**	**No IVH N=353 n(%)**	**Mild IVH* N=99 (56.3%) n(%)**	**Severe IVH* N=77 (43.8%) n(%)**	**p- values[#]**
Maternal age						0.159
<20	60 (11.3)	18 (10.2)	42 (11.9)	10 (10.1)	8 (10.3)	
20-40	447 (84.5)	148 (84.1)	299 (84.7)	85(85.9)	35 (45.5)	
>40	16.3 (3.0)	6 (3.4)	10 (2.8)	4 (4.0)	2 (2.6)	
Undocumented	6 (1.1)	4 (2.3)	2 (0.6)	0 (0)	4 (5.2)	
maternal parity						0.095
0-1	243 (45.9)	93 (52.8)	152 (43.1)	58 (58.6)	35 (45.5)	
>2	286 (54.1)	83 (47.2)	201 (56.9)	41 (41.4)	42 (54.5)	
Maternal comorbidities						
Hypertension	105 (21.0)	17 (9.7)	88 (24.9)	11 (11.1)	6 (7.8)	0.609
Diabetes Mellitus	4 (0.8)	2 (1.1)	2 (0.6)	0 (0)	2 (2.6)	0.190
steroids	196 (37.1)	53 (30.1)	143 (40.5)	33 (33.3)	20 (26.0)	0.295
Mgso4	47 (8.9)	5 (2.8)	42 (11.9)	3 (3.0)	2 (2.6)	0.328
Place of birth						0.502
Inborn	469 (88.7)	153 (87.4)	316 (89.5)	85 (85.6)	68 (88.3)	
Outborn	56 (11.3)	22 (12.6)	34 (9.7)	14 (14.1)	8 (10.5)	
Mode of delivery						0.690
Vaginal	212 (40.0)	81 (46.0)	131 (37.1)	43 (43.4)	38 (52.7)	
Caesarean	292 (55.2)	82 (46.6)	210 (59.5)	49 (49.5)	33 (47.3)	
Undocumented	25 (4.7)	13 (7.4)	12 (3.4)	7 (7.1)	6 (7.8)	
Gestational age						0.628
<30weeks	264 (49.9)	115 (65.3)	149 (42.2)	62 (62.6)	53 (68.8)	
>30weeks	258 (49.4)	58 (33.5)	200 (57.3)	37 (37.4)	24 (31.2)	
Birthweight						0.634
<1000g	121 (22.9)	62 (36.9)	59 (15.9)	33 (33.3)	29 (37.7)	
1000g-1500g	408 (77.1)	114 (64.8)	294 (83.3)	66 (66.7)	48 (62.3)	
Sex						0.126
Male	262 (49.5)	100 (56.8)	162 (45.9)	51 (51.5)	49 (63.6)	
Female	267 (50.5)	76 (43.2)	191 (54.1)	48 (48.5)	28 (36.4)	
Resuscitation	313 (59.2)	102 (58.0)	211 (59.8)	59 (59.6)	43 (55.8)	0.647

Bag mask ventilation	183 (34.6)	55 (31.3)	128 (24.2)	32 (32.3)	23 (29.9)	0.746
CPR	17 (3.2)	8 (4.5)	9 (2.5)	5 (5.1)	3 (3.9)	1.000
Intubation	16 (3.0)	12 (3.4)	4 (1.1)	7 (7.0)	6 (7.8)	1.000
Adrenalin	5 (0.009)	3 (0.017)	2 (0.0057	2 (2.0)	1 (1.3)	1.000
Apgar <6 at 1min	181 (34.2)	107 (60.8)	134 (38.0)	51 (51.5)	42 (54.5)	0.811
Apgar <6 at 5min	61 (11.5)	58 (33)	31 (8.8)	30 (30.3)	16 (20.8)	0.575
nCPAP	321 (60.7)	109 (61.9)	212 (60.1)	61 (61.6)	48 (62.3)	1.000
IPPV	132 (25.0)	67 (38.1)	65 (18.4)	36 (36.4)	31 (40.3)	0.640
Surfactant	164 (31.5)	74 (42.0)	90 (26.0)	44 (44.4)	30 (39)	0.540
Hypotension	77 (14.6)	45 (25.6)	32 (9.1)	23 (23.2)	22 (28.6)	0.487
Medication for hypotension	66 (12.5)	40 (22.7)	26 (7.4)	20 (20.2)	20 (26)	0.372
Sepsis	203 (38.8)	117 (66.5)	86 (24.4)	64 (64.6)	53 (68.8)	0.630
Meningitis	162 (30.6)	143 (81.3)	19 (5.4)	78 (78.8)	65 (84.4)	0.097
Seizures	31 (5.9)	26 (14.8)	6 (1.4)	13 (13.1)	13 (16.9)	0.525
PHHC	12 (2.3)	11 (6.3)	1 (0.3)	0 (0)	11 (14.5)	0.00009
Outcome						0.190
Discharge	392 (74.1)	82 (46.6)	310 (87.7)	52 (58.2)	30 (46.1)	
Death	134 (25.3)	92 (52.3)	42(11.9)	46 (46.5)	46 (59.2)	

*Mild IVH – Grade 1 and 2 IVH, Severe IVH – Grade 3 and 4, # - p-value comparison between mild and severe IVH
CPR- cardiopulmonary resuscitation, nCPAP – nasal continuous positive pressure ventilation, IPPV – intermittent positive pressure ventilation, PHHC – post haemorrhagic hydrocephalus

Supplementary Table 2: Outcome per IVH Grade

	Total IVH cases N=176 n (%)	Grade 1 N=61 n (%)	Grade 2 IVH N=38 n (%)	Grade 3 IVH N=46 n (%)	Grade 4 IVH N=31 n (%)	Total controls N=353 n (%)	p- value
Seizures	26 (14.8)	6 (3.4)	7 (4.0)	7 (4.0)	6 (3.4)	5 (1.4)	0.507
PHHC	11 (6.3)	0 (0)	0 (0)	8 (4.5)	3 (1.7)	1 (0.3)	<0.001
Discharge	82 (46.6)	36 (20.4)	16 (9.1)	16 (9.1)	14 (7.9)	310 (87.8)	0.164
Died	92 (5.1)	25 (14.2)	21 (11.9)	29 (16.5)	17 (9.7)	42 (11.9)	

Appendix A: Protocol

MMED RESEARCH PROTOCOL: PREVALENCE AND RISK FACTORS OF INTRAVENTRICULAR HEMORRRHAGE IN VERY LOW BIRTH WEIGHT INFANTS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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15. Appendix B ……

List of abbreviations

C/S - Caesarian section

CHBAH -Chris Hani Baragwanath Academic Hospital

CT - computerized tomography

GA - Gestational age

GMH -Germinal Matrix Hemorrhage

Hb- haemaglobin

HCT -haematocrit

ICD - Intercostal drain

IDM - Infant of diabetic mother

IPE - intraparenchymal lesion

IVH - Intraventricular Hemorrhage

NICU -Neonatal Intensive care

NVD - Normal vaginal delivery

PDA - patent ductus arteriosus

PHHC -Post haemorhagic Hydrocephalus

PHVD - Post haemorrhagic ventricular dilatation

PROM - Premature rapture of membranes

PVHI - Periventricular hemorrhagic infarction

RDS - respiratory distress syndrome

VLBW - Very Low Birth Weight

VP - ventricular peritoneal

VSG - ventriculo-subgaleal shunt

1.Background

Intraventricular haemorrhage (IVH) also known as germinal matrix haemorrhage (GMH-IVH) is the most common form of bleeding in the central nervous system in premature neonates. Typical GMH-IVH originates from the germinal matrix, a highly vascularized collection of neuronal glial precursor cells in the developing brain of the fetus. The germinal matrix involutes as the fetus matures; from about 28 weeks of gestation. It is usually absent by term, due to a decrease in vascularity and cellularity. The aetiology of GMH-IVH is multifactorial and its pathogenesis is attributed to the germinal matrix. Risk factors associated with GMH-IVH are related to fragility of the germinal matrix, cerebral autoregulation and haemostatic factors such as platelet and coagulation disturbances.

This fragility is due to immaturity and an unstable cerebral blood flow that is caused by impaired cerebral autoregulation. In preterm infants, the delicate vascular capillary network within the germinal matrix lacks structural support which makes it more vulnerable to injury. The cerebral blood flow is regarded as pressure passive. Impaired autoregulation makes preterm infants more vulnerable to GMH-IVH as they cannot sustain constant cerebral blood flow during changes in systemic blood pressures. An increase and fluctuation in cerebral perfusion could occur in preterm infants as a result of various factors that may occur in utero, peri-partum and postnatally in neonatal intensive care unit (NICU).

In view of the possible pathogenesis of IVH, the prevalence of IVH is higher in very premature infants and in those who are sicker; requiring resuscitation at birth, ventilator support and those with sepsis. A Study done in California reported that the rate of severe IVH was highest in the neonates at the lowest gestational age(GA), 22-23 GA at 36%, 20% in 24-25GA, 9.5% in 26-27GA,3.3% in 28-29GA and 1.2% in 30-31GA. (46) In Parkistan, a study has shown that risk of developing IVH was 3fold higher in preterm infants with respiratory distress syndrome (RDS) (OR 3.77; 95% CI 1.52-9.37; p=0.004) and those put on mechanical ventilation had 23times higher folds of IVH(OR 23.6;95% CI5.09-109.5;p<0.001).(44) In addition, other factor has been reported to be associated with increased rate of all IVH grades. These include patients with hypothermia, patent ductus arteriosus (PDA), Necrotising enterocolitis (NEC), neonatal sepsis; intercostals

drain insertion (ICD), endotracheal intubation/ventilation, umbilical venous catheterization, pneumothorax and pulmonary haemorrhage. In a cohort of premature newborns of infants with RDS, lower rates of IVH were reported in Infants of diabetic mothers (IDM), maternal hypertension, polycythaemia and Trisomy 21.(8)

2.Incidence of GMH-IVH

The incidence of GM-IVH is inversely proportional to gestational age and prematurity. The worldwide incidence is up to 50%, lower in developed countries at about 20-25% compared to developing countries at 20-50%.(3) The incidence has significantly declined, due to improved perinatal and neonatal care. A study than in South Africa Chris Hani Baragwanath Academic Hospital (CHBAH) in 1992 reported higher prevalence rate of GM-IVH at 53%, and a similar study done in 2017 at Charlotte Maxeke Johannesburg Academic Hospital in South Africa reported a lower GM-IVH prevalence of 26%.(22) (26) The National institute of child health and human development (NICHD) neonatal research network showed a decline in GMH-IVH from 19% to 15% between 1993 to 2012. (28)

The use of steroids has been reported in many studies to significantly improve survival in premature neonates and decreased incidence of IVH.(12, 15) Steroids stimulate maturation of germinal matrix microvasculature thus making them more resistant to perinatal and postnatal events that may provoke GMH-IVH.(17)

There are other risk factors that have been proposed for the development of IVH. These included low birth weight (LBW), Gestational age(GA), maternal smoking, breech delivery, gender, premature rupture of membrane(PROM), intrauterine infections, resuscitation at birth, early onset sepsis, respiratory distress syndrome, ventilation, hypotension, metabolic acidosis and rapid bicarbonate infusion.(53)

Almost all GMH-IVH occur in the first few days of life with majority in the first 24hours. In a meta-analysis done in VLBW Al-Abdi et al showed that 50% of GMH-IVH occurred in the first 6hours of life and one third occurred after 24hours.(7) In another study where cranial sonars were performed in VLBW infants within one hour of birth, GMH-IVH was detected in 20% of cases.(54) It is therefore important to identify modifiable prenatal risk factors as it has been

shown that most of the GMH-IVH is occurs early in life which could be attributed to prenatal factors and circumstances around birth.(8)

3.Clinical presentation

Papile et al(1) suggested that a presumptive diagnosis of IVH in premature infants can be made based on the following clinical features: changes in muscular activity and tone, presence of seizures, a bulging anterior fontanel, vascular hypotension, greater than 10% drop in haematocrit and presence of blood or elevated protein levels in cerebral spinal fluid. Their study demonstrated that 78% of infants with IVH had no clinical signs and 20% of infants without IVH had clinical signs suggestive of IVH.(1) although the clinical features suggestive of IVH has been described, a study by Krishnamoorthy et al failed to demonstrate evidence of IVH in infants who had clinical signs suggestive of IVH.(55)

There are clinical syndromes that describe IVH, 1) the clinically silent syndrome, 2) the salutatory syndrome, and 3) the catastrophic syndrome. The clinically silent syndrome occurs in 25-50% of preterm neonates. It is an incidental finding on routine screening, it is characterized by an unexplained drop in haematocrit (hct) or haemaglobin (hb). The salutatory syndrome occurs over hours or days, it has a stuttering evolution. The patients present with an altered consciousness, decreased movement, hypotonic, abnormal eye position and eye movement and respiratory disturbances. The catastrophic syndrome is dramatic in presentation; the deterioration is seen within minutes to hours. The patients present with respiratory abnormalities that include hypoventilation and apneas, cardiovascular abnormalities e.g arrhythmias and hypotension and central nervous system abnormalities such as decerebrate posture, eyes fixed to vestibular stimulation, seizures, and flaccid quadrapesis, deep stupor and coma.

IVH is characterized according to 2classification systems as described by Papile and Volpe. These classification systems are based on brain imaging.(1)

Papile et al describe IVH in four grades based on computerized tomography (CT) brain and post mortem of the brain.

Grade1: subependymal hemorrhage

Grade2: intraventricular hemorrhage without ventricular dilatation

Grade 3: intraventricular hemorrhage with ventricular dilatation

Grade4: intraventricular hemorrhage with parenchymal hemorrhage

Volpe's grading system is similar to Papile but more emphasis on the percentage of bleed as visualized on intracranial imaging.(18)

Grade 1: germinal matrix hemorrhage with no IVH or IVH occupying <10% of the ventricular area in parasagittal view.

Grade 2: IVH occupying 10-50% of ventricular area on parasagittal view.

Grade3: IVH occupying >50% of ventricular area on parasagittal view. Periventricular hemorrhagic infarction (PVHI) is noted differently as is a consequence of IVH not continuum but most authors including Volpe consider it as grade 4.(22)

In a study done by Franco et al where they looked at the relationship between IVH and periventricular intraparenchymal lesions (IPE) observed on cranial ultrasound. IPE was defined as sonographic appearance of periventricular echodensities with one dimension greater than 1cm on the coronal or the parasagittal plane. It was found that 81% of cases of IPE were associated with grade 3 IVH and only 4% of cases of IPE occurred in the absence of IVH.(56)

4.Treatment modalities

Currently no absolute treatment for GMH-IVH available and no specific therapy, neither to limit the extensions of the haemorrhage once it has occurred nor to prevent the complications of posthemorrhagic ventricular dilatation (PHVD). Management is mainly supportive and is aimed at reducing brain injury by maintaining good cerebral perfusion and oxygenation. Post haemorrhagic ventricular dilatation is the most common complication of GM-IVH and ongoing monitoring with cranial sonar is required to detect early signs of dilatation prior to onset of symptoms.

Infants are categorized in one of the 3groups 1) The arrested group, 2) The slowly progressive group and 3) The rapidly progressive group. The treatment modalities depend on the group in which the patient is categorized into. The patients with arrested ventricular dilatation would need monitoring for neurodevelopmental impairment. Medical management includes drugs such as acetazolamide and furosemide. Serial lumber puntures are one of the strategies employed for the slowly progressive group. For those with rapid rapidly progressive ventricular dilatation a ventriculo-peritoneal (VP) shunt will need to be inserted. In patients that are too small for a VP shunt other ventricular access devices may be considered. Eg, Ommaya shunt and ventriculo subgaleal shunt (VSG). These are temporizing measures until a definitive shunt may be placed. In a study done in Netherlands, patients where temporizing shunts that were placed sooner (early intervention group), there was an improved neurodevelopment (DQ 97(87-107) vs 60(55-84), p=0.03) and cognitive outcome (DQ 95(87-106) vs 60(55-90), p=0.002). In addition, there were less patients (10(25%) vs 15(94%) p=0.001, with cerebral palsy in the early vs late intervention groups respectively. (57)

5. Complications and outcome

Occurrence of GMH-IVH in very low birth weight infants significantly increases morbidity and mortality in these VLBW infants.(58) Improved perinatal and neonatal care has improved survival in premature neonates, hence increased survivors with this condition with short and long term complications.(53) Seizures, post hemorrhagic hydrocephalus, development impairment, cognitive impairment, cerebral palsy and death are amongst the serious complications that can occur in severe GM-IVH.

Post haemorrhagic hydrocephalus (PHH) is one of the major complications of GMH-IVH and increases mortality and neurodevelopmental impairment. Patients with grade 3 and 4 IVH are most likely to progress to PHH.(58) About two thirds of severe IVH survivors develop post haemorrhagic ventricular dilatation.(59) Developmental impairment is proportional to the increasing grade of IVH.(60) sixty percent (60%) of patients with grade 3 and 4 GMH-IVH will have neurodevelopmental disability. In a population-based study, of infants with a gestational age of less than 33weeks who had IVH and were diagnosed with cerebral palsy at the age of 5years

reported that those with severe grades (grade 3 and 4) of IVH had 18-50% risk of cerebral palsy and those with milder grades (grade 1 and 2) between 11-19%. (61)

Mortality is higher in infants with severe forms of GM-IVH.(58) In a study by Franco et al infants with IPE had a 59% mortality , 87% exhibited major motor deficits with 73% with cognitive function less than normal(56). In the same study the close relationship of severe IVH and IPE was demonstrated. A study from the Netherlands showed a 30% and 40% mortality in IVH grade 3 and IVH grade 4 respectively.(59)

In this study we aim to identify risk factors for GMH-IVH in our unit, to describe the morbidity and the outcomes in VLBW infants with IVH.

6. Study Objective

6.1 To determine the prevalence of GMH- IVH in VLBW premature neonates in CHBAH neonatal unit

6.2To describe the demographics of VLBW premature infants with various grades of IVH

6.3To analyze the risk factors associated with IVH in VLBW neonates

6.4 To compare characteristics, risk factors and outcomes of different grades of IVH

6.5To describe and discuss morbidity and mortality in patients with all grades of IVH

6.6 To describe outcome of all VLBW neonates with IVH according to severity

7. Methods and materials

This will be a retrospective descriptive study. The study will be conducted in the Neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH) Paediatrics department. The unit captures all admitted patients on a Redcap data capturing system. All very low birth weight patients from January 2017 to December 2018 will be identified by the Redcap database. Those with IVH will be cases. A total of 128 VLBW neonates with GM-IVH were captured from January 2017 to December 2018 on the Redcap database. This number might change slightly as data

capturers add patients to the database before the study commence. The medical records of the patients identified on Redcap database will be retrieved and reviewed. Data will be extracted as per data sheet (Appendix A)

Maternal variables, perinatal factors, mode of delivery, details of resuscitation at birth, the main medical diagnosis and any medical interventions during the time of diagnosis of GMH-IVH will be extracted from the medical records. Patients have cranial ultrasound performed according to the protocol in the CHBAH neonatal unit: screening cranial ultrasound in the first 7 days of life, at the 10-14 days and beyond 28 weeks before discharge. (Appendix B)

The cranial ultrasound findings will be captured as documented in the files. All GMH-IVH of all grades will be cases. The grade of IVH will be classified according to the Papille classification. Those without GM-IVH and those without cranial ultrasound investigation performed will be excluded.

Inclusion criteria: The study population will include all inborn and outborn VLBW infants of less than 1500g with IVH of any grade. Inborn infants are defined as babies born in CHBAH and outborn are all infants referred from another hospital, clinic or born at home or before arrival to hospital.

Exclusion criteria: All neonates with severe malformations and incomplete data will be excluded from the study

8. Data and analysis

The demographics of neonatal and maternal characteristics will be collected and captured on excel spreadsheet. The data will be imported in to the statistical program Statistica or STATA for data analysis. Categorical variables will be reported as proportions. Comparison between categorical variables will be done using the Chi-squared or Fishers' exact test where appropriate. Continuous variables will be reported as means or medians depending on the distribution of the data. The students t-test will be used to compare data that are normally distributed whereas the Mann-Whitney U test will be used to compare data that is not normally distributed. A p-value of $p<0.05$ will be considered statistically significant.

9. Ethics

Ethics approval will be sought from the Human Research Ethics Committee (HREC) of the University of Witwatersrand. Consent will also be obtained from the NDoH and the CEO of CHBAH to conduct the study in neonatal unit. Permission will be obtained to access the neonatal unit Redcap database from the head of neonatal unit and the head of paediatrics. All data and medical records of patients that will be used for the study will be anonymized; identifiers will be kept separately from the dataset. The data collected will only be used for the purpose of study.

10. Funding

The study will be self-funded and any expenses incurred will be borne by the researcher.

11. Timeline

	July2018-december 2018	January 2019-June 2019	July 2019-October 2019	November 2019-March 2020	April 2020-April 2021	May 2021 - May 2022	June 2022-June 2023
Literature review					Covid 19 Pandemic Lockdown		
Preparation of protocol		.					
Submission of protocol							
Submission to ethics							
Data collection							
Data analysis							
Write up							

10. References

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Appendix B

Data collection form

Study no:

Maternal details

Age_____ parity_____ gravity_____

Maternal medical condition:

Antenatal care: yes____,no____;Steroids:yes_____, no_____; Magnesium sulphate: yes_____, no____

Hypertension:_____, Diabetes:_____, cardiac_____,

Infant details

Place of birth: inborn/other hospital/clinic/BBA, Mode of delivery: NVD/C/S/ Breech/Vacuum

Resuscitation at birth:yes_____, no_____

BMV_____,CPR_____, Intubation_____, _Adrenaline

ABG: pH_____, pO2_____, pCO2_____, lactate_____, HCO3_____, BE_____

APGAR score: 1 min _____, 5 min _____, 10 min _____

Date at admission: _____/_____/_____

Gestational age: _____ weeks, Gender Male/Female/Ambiguous

Birth weight: -_____g, HC: _____cm, Length: _____cm

Main diagnosis: 1) _____, 2)_____, 3) _____

Other diagnosis: 4) _____, 5) _____, 6) _____

Sepsis: yes_____, no, _____ Date of Sepsis: _____/_____/_____

Early onset sepsis:_____, late onset sepsis: _____, Organism cultured: _____

Intervention

Ventilated: yes_____, no_____. Type of ventilation:HFOV, _____IPPV_____, CPAP_____,

Surfactant: yes_____, no_____.

Fluid boluses: yes_____, no_____, Saline -_____, FFP_____, Blood_____

Sodium bicarbonate boluses: yes_____, no _____.

Hypotension: yes_____, no_____; Inotropes: yes_____, no_____

Dopamine _____, Dobutamine_____, Adrenaline_____, Hydrocortisone _____

Imaging:

Cranial sonar: yes_____, no_____

Date of 1st cranial ultrasound_____/_____/_____ head circumference_____cm

IVH: yes_____, no_____Age of diagnosis of IVH: _____

Grade of IVH: I_____, II_____, III _____, IV_____, PHH_____

Repeat cranial sonar: yes_____, no_____

Date of 2nd cranial ultrasound_____/_____/_____ head circumference_____

IVH: yes_____, no_____ Age of diagnosis of IVH: _____

Grade of IVH: I_____, II_____, III _____, IV_____, PHH_____

Repeat cranial sonar: yes_____no_____

Date of 3rd cranial ultrasound_____ head circumference_____

IVH: yes_____, no_____ Age of diagnosis of IVH: _____

Grade of IVH: I_____, II_____, III _____, IV_____, PHH_____

Repeat cranial sonar: yes_____, no_____

Date of 4th cranial ultrasound_____ head circumference_____

IVH: yes_____, no_____ Age of diagnosis of IVH: _____

Grade of IVH: I_____, II_____, III _____, IV_____, PHH_____

Repeat cranial sonar: yes_____no_____

Date of 5th cranial ultrasound_____ head circumference_____

IVH: yes_____, no_____ Age of diagnosis of IVH: _____

Grade of IVH: I_____, II_____, III _____, IV_____, PHH_____

CT Scan: yes_____, no_____. MRI Scan: Yes_____, no_____.

Findings:

_____
_____
_____
_____

Management of IVH:

Medical: acetazolamide_____, Lasix_____

Serial taps: yes_____, no_____.

Complications

Seizures:yes____, no____, Antiepileptic drugs:phenobarbitone/keppra/dormicum/phenytoin/lidocaine

Maintenance treatment:_____, _____

Post Hemorrhagic hydrocephalus:yes_____, no_____.

VPS_____, VSG_____, ETV_____, other _____

Date of insertion of shunts: _____/_____/_____

Outcome

Date of outcome: _____/_____/_____. HC at discharge/death:_____cm

Discharge_____, Death_____.

Appendix: c

Cranial sonar Indications

· Preterm infants, especially if weighing <1500g
· Birth asphyxia with stage II-III HIE- early sonar to exclude oedema or periventricular echodensities (PVEs), haemorrhage or structural abnormalities; later sonar for cystic changes
· Seizures- to exclude similar findings as in birth asphyxia and IVH
· Macrocephaly or microcephaly- to exclude hydrocephalus or structural abnormalities
· Dysmorphic infants with involvement of CNS or midline defects like hypotelorismto exclude structural abnormalities
· Suspected congenital infections, namely cytomegalovirus and toxoplasmosis- to exclude intracerebral calcifications

Screening cranial ultrasound in preterm infants

Routine ultrasound must be done in all infants weighing <1500g
Head ultrasound schedule for preterm infants:

1. First ultrasound: Within the first 7 days of life
    a. Will identify >90% of cases of IVH;
    b. Identify increased periventricular echodensities
2. Second ultrasound: At 10-14 days of life
    a. Will identify progression of PVEs,
    b. Periventricular cysts may become apparent.
    c. May identify early development of post haemorrhagic hydrocephalus
3. Last ultrasound at 28 days and beyond or before discharge
    a. Periventricular cysts may become apparent
    b. Post haemorrhagic hydrocephalus will be apparent by this time

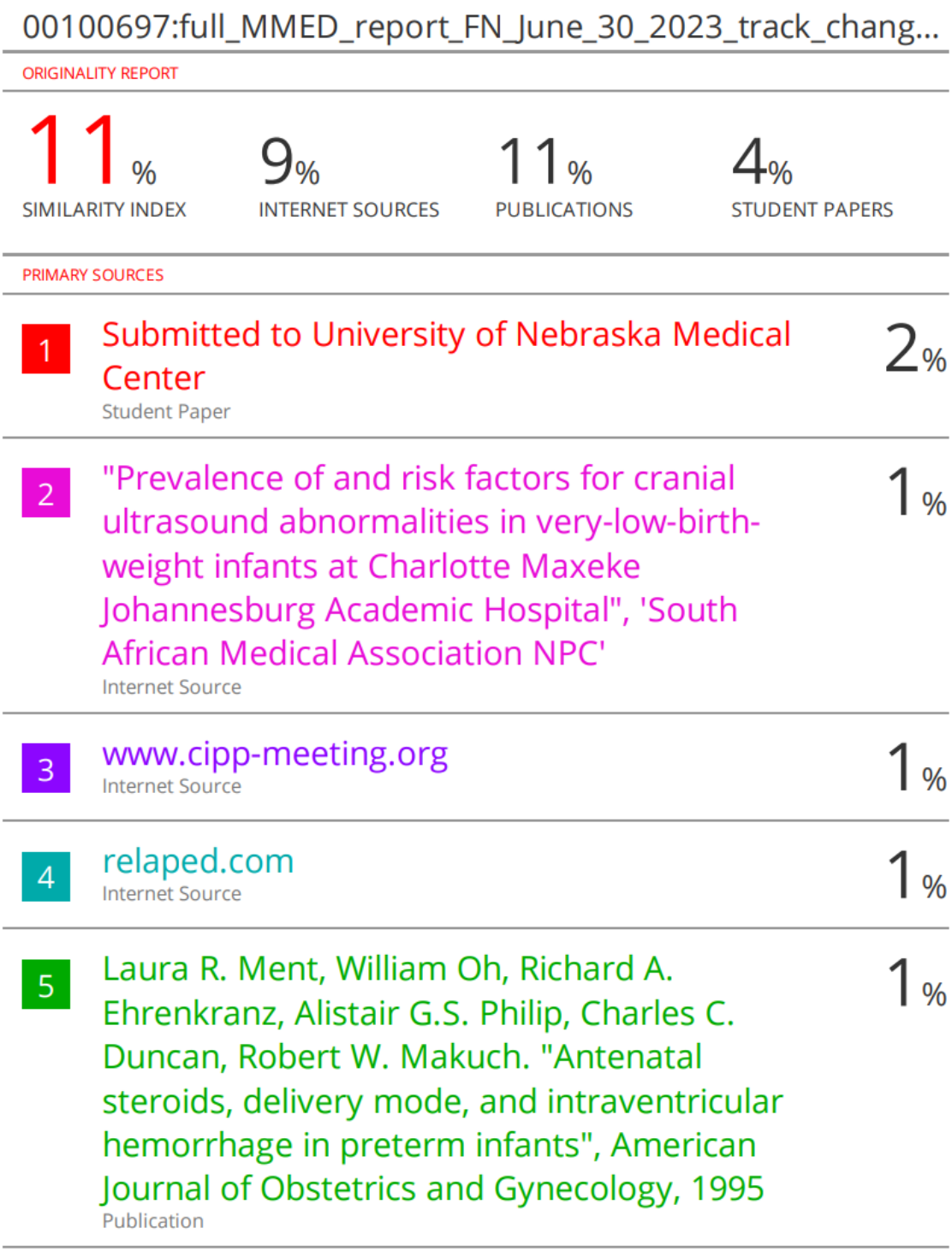
Grading of IVH

· Grade I Germinal matrix haemorrhage
· Grade II Blood within ventricular system without distension
· Grade III Blood within ventricular system with distension
· Grade IV/ III+IPE IVH + Intraparenchymal bleed (echodensity)

Reference

1. Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In Volpe JJ. Neurology of the newborn, 4th Edition p428;2000
2. Van Wezel-Meijler G, Steggerd SJ, Leijser M. Cranial ultrasonography in neonates: role and limitations. Semin Perinatol 2010;34:28-38

Appendix D: Turn- it- in report



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Publication

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Appendix E: Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr K Mabasa

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190739

NAME: (Principal Investigator)	Dr K Mabasa
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Rahima Moosa Mother and Child Hospital
PROJECT TITLE:	Prevalence and risk factors of intraventricular haemorrhage in very low birth weight infants at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	2019/07/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs N Firdose and N Nandi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/10/25

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore reports and re-certification will be due early in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES