ORIGINAL PAPER

The Prevalence of Intraventricular Haemorrhage and Associated Risk Factors in Preterm Neonates in the Neonatal Intensive Care Unit at the University Teaching Hospital, Lusaka, Zambia

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ABSTRACT

Objectives: The study was undertaken with the aims of determining the prevalence and most frequent grade of IVH as well as associated risk factors in preterm neonates with birth weight 1.5kg or less admitted to the neonatal intensive care unit at the UTH in Lusaka, Zambia

Design: This was a cross sectional study where 298 preterm neonates meeting the study's inclusion criteria had cranial ultrasound done in the first three days of life and on the seventh postnatal day. Data on the risk factors was obtained from the neonatal referral form, maternal records and direct interview with the neonate's mother.

Main outcomes and Measures: The main outcomes were the prevalence of IVH and the most frequent grade of IVH. The variable any-IVH generated at the time of analysis was used in determining the prevalence of IVH and also as the dependent variable in multivariate logistic regression. Any-IVH was the highest grade of IVH obtained on either the first 3 days or day 7 on cranial ultrasound.

Results: In this study, the prevalence of intraventricular haemorrhage in preterm infants with birth weight 1.5kg and less was 34.2% in the first seven days of postnatal life. Grade 1 (mild) IVH was the most frequent (54.9%) followed by severe IVH (grade 3 and 4) at 27.5%. The case fatality rate was 85.7% for those with grade 4 in the first three days of life. Grade 2 was the least prevalent at 17.7%.

Risk factors significantly associated with IVH were birth weight [p=0.04, OR= 0.25(0.06-0.98) 95% C.I.] and gestational age [p=0.02, OR= 0.82 (0.69-0.97) 95%C.I.]

Conclusions: The study found a similar or even lower overall prevalence to that reported in studies in Africa and globally, while the frequency of severe IVH was relatively very high with a high case fatality rate (85.7%) in the first seven days of postnatal life in respect of grade 4 IVH.

Risk factors significantly associated with IVH were birth weight and gestational age while the former was also significantly associated with severe IVH as in other studies internationally.

INTRODUCTION

Intraventricular haemorrhage (IVH) is related to bleeding in the capillary network of the germinal matrix of the developing brain. It is classified into four grades anatomically according to findings on cranial ultrasound depending on whether it is restricted to the subependymal area, extends to the lateral ventricles with or without dilatation and brain parenchyma involvement.[1, 2] The grading is useful for counselling of the preterm babies' parents or caregivers about prognosis.[1] IVH occurs mostly in the first three days after birth in preterm neonates born at or before 32 weeks gestation but may also occur beyond the first week. Specific problems that may manifest later in children who had IVH as neonates include cerebral palsy, post-haemorrhagic hydrocephalus, cognitive/intellectual impairment and epilepsy.

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Very low birth weight/extremely low birth weight (VLBW/ELBW = birth weight less than 1.5kg) preterm neonates account for 20% of the total admissions to the neonatal intensive care unit (NICU) at the University Teaching Hospital (UTH) annually with case fatality rates of more than 45% (2007 and 2008 NICU ward statistics). It is these neonates that are at risk for IVH and its long term sequelae.

IVH remains a serious problem and is reported to have an incidence of 50% globally in the VLBW and ELBW infants.[1] In the southern African region, a study in South Africa[3] reported a prevalence of around 53% in VLBW neonates. There were no other known reported studies on prevalence in the sub-region at the time of this study. IVH causes mortality ranging from 27-50% (severe IVH) and about 5% (mild to moderate IVH).[2, 4] Prevalence of IVH and associated risk factors is unknown in the VLBW/ELBW preterm neonates admitted to NICU at UTH as no prevalence studies have been undertaken before. In addition, cranial ultrasound was not routinely done to screen for IVH before this study, in contrast to other NICUs internationally where it is recommended to be done routinely.[5] As such it is a condition that is rarely looked for. Consequently, there has been no description of the commonly prevalent grades of IVH and its contribution to the morbidity and mortality in these neonates at UTH. Recently a study done at a public hospital in Johannesburg, South Africa observed a lack of current, valid statistics from NICUs in developing countries even though large numbers of patients are treated annually. In that study an argument was made on the need to have local data relevant to a developing country to facilitate planning as it is not possible to transpose data from one area to another.[6]

This cross sectional study was therefore undertaken to determine the prevalence of IVH in preterm infants with birth weight 1.5kg and less presenting to the NICU at the UTH. Some of the potentially associated risk factors for its occurrence were also studied with a view to providing locally relevant data on IVH in preterm neonates with birth weight 1.5 kg and less.

METHODS

The study was undertaken at the neonatal intensive care unit (NICU) of the University Teaching Hospital, Lusaka, Zambia from September 15, 2010 to February 21, 2011.

Included in the study were neonates with estimated gestational age (EGA) less than or equal to 32weeks, birth weight 1.5kg and below, post-delivery age less than or equal to seven days on admission and written consent to enrol into the study by the infant's caregiver/parent. Excluded from the study were neonates whose caregivers/parents refused to consent to enrol into the study and those that died before the first cranial ultrasound.

Neonates meeting the inclusion criteria were consecutively enrolled to the study until the sample size of 298 was reached. The sample size was calculated using the formula $\mathbf{N = z^2(p)(1-p)/L^2}$, assuming 50% IVH prevalence in the preterm neonates $\leq$1.5kg birth weight at the 90% confidence level & non-compliance of 10%, Where N = required sample size, z = 1.64 (Z-alpha, population constant), p = assumed population IVH prevalence as above and L was the desired width of confidence interval (0.1). The values for the formula variables were chosen with the knowledge that the NICU at UTH admits between 500 – 600 preterm neonates with birth weight $\leq$1.5kg annually and the study was to be conducted over a period of six months.

Risk factors studied were mode of delivery, sex, prolonged rupture of membranes (PROM - at least 18 hours duration), place of birth, birth weight, estimated gestational age (EGA), presence or absence of respiratory distress syndrome (RDS) due to surfactant deficiency and clinical chorioamnionitis. Birth weight was taken as the weight done on admission to NICU (by a Secca, model 3341321008, electronic scale) or the one on the referral form that accompanies all neonates admitted, for those presenting later than 48 hours. The EGA was taken as the one determined using the mother's last normal menstrual period (LNMP) or that determined by the new expanded Ballard score within 24-48 hours of admission. The latter was taken as the EGA if it was greater by more than two weeks that determined by the LNMP. Diagnosis of RDS on the NICU at UTH, as in other centres, is based on initial clinical symptoms and the clinical course and a chest radiograph consistent with RDS. Clinical chorioamnionitis was defined as presence of at least two of the following: maternal fever ($\geq$38^{0}C), PROM, foetal tachycardia (>160 beats/minute), uterine tenderness with a malodourous infant and no other infection source. Appropriate information on the risk factors was obtained from the maternal antenatal record and by direct inquiry from the mother.

Transfontanelle cranial ultrasound was performed twice: The first within or at 72 hours of life and as soon as possible after enrolment for those presenting to the NICU older than 72 hours. The second was done on the seventh day of postnatal life. The standard saggital and coronal

views were done looking for echodensities (haemorrhage) in the subependymal area, intra- and periventricular as well as other brain parenchymal areas. Using the information so gained the IVH grade was determined as indicated in table 1 below and recorded on the cranial ultrasound reporting form adapted for the study. Axial views, where indicated, were done for ventricular size determination. The cranial ultrasound scanning was performed using the cranial ultrasound machine (Aloka SSD 900) on the ward which uses a 7.5MHz convex probe ideal for neonatal cranial ultrasound by the principal investigator and by two radiographers from the radiology department at UTH. The principal investigator had had prior training in ultrasound image recognition. Ultrasound images were only reported by the principal investigator as no other appropriate reporter was available to the study at the time. Echolucent findings in association with echodensities on cranial ultrasound in the first three days was not reported as findings consistent with IVH but more likely periventricular leukomalacia (PVL). The study was approved by the University of Zambia Biomedical Research Ethics Committee.

Table 1: IVH grading

Grade	Radiological appearance - Site of haemorrhage
1	Subependymal region and/or germinal matrix (less than 10% ventricular extension)
2	Subependymal haemorrhage with extension into the lateral ventricles filling without or with mild ventricular enlargement (10 - 50% ventricular filling)
3	Subependymal haemorrhage with extension into the lateral ventricles with significant ventricular enlargement (more than 50% ventricular filling)
4	Intraparenchymal haemorrhage

Data analysis

Data was analysed using Epi info version 3.5.1. The dependent variable was any-IVH generated at the time of analysis. Any-IVH was the highest grade of IVH obtained on any of the time periods when cranial ultrasound was done. Multivariate logistic regression analysis was used in studying the association between independent and dependent variables at the 95% confidence level comparing those neonates with and without any-IVH. Logistic regression analysis was also performed using severe IVH as the outcome variable with the independent variables.

RESULTS

Figure 1: Showing enrolment and neonates with and without any-IVH

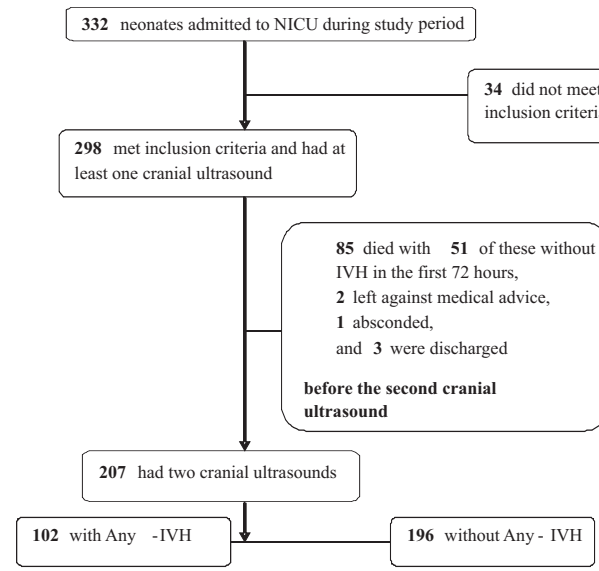

Table 2: Subject demographic and clinical characteristics

Estimated gestational age - Mean(SD)		**29.3 weeks (±1.93)**		
Sex - Male – Number (%)		142 (47.7)		
Female – Number (%)		156 (52.3)		
Birth weight – mean(SD)		1.2kg (±0.22)		
Place of birth – UTH - Number (%)		164 (55)		
Outside UTH -Number (%)		134 (45)		
Any -IVH – Number (%)		**102 (34.2)**		
Any -IVH and IVH by day of Ultrasound		**Any IVH**	**Day 3**	**Day 7**
Grades –Number (%)	1	56 (54.9)	45 (15.2)	42(20.3)
	2	18 (17.7)	15(5.1)	11(5.3)
	3	19 (18.6)	17(5.7)	8(3.9)
	4	9 (8.8)	7(2.4)	3(1.4)
No IVH - Number (%)		196 (65.8)	212 (71.6)	143(69.1)

Any-IVH was present in 102 (34.2%) with grade 1(mild) IVH being the most frequent in just over half the neonates at 56 (54.9%). Severe IVH was at 27.5%. A total of 84 (82.4%) neonates had IVH in the first 3 days and 64 (30.9%) on day 7, with actual breakdown of grades by day of cranial ultrasound shown in table 2 above.

Table 3: Characteristics for the IVH and No IVH groups

		Any-IVH	No IVH	P-Value	Odds Ratio (C.I. at 95%)
Postnatal Age (hours)	Mean(SD)	26.6(±25.1)	24.8(±28.4)	0.61	
Sex	Male Number (%)	48(47.1)	94(48.0)	0.88	0.96(0.60-1.56)
	Female Number (%)	54(52.9)	102(52.0)	0.88	0.96(0.60-1.56)
Place of birth	UTH Number (%)	59(57.8)	105(53.6)	0.48	1.19(0.73-1.93)
	Outside-UTH Number (%)	43(42.2)	91(46.4)	0.48	1.19(0.73-1.93)
Birth weight	**Mean(SD)**	**1.15(±0.24)**	**1.26(±0.21)**	**0.0001**	
Mode of Delivery Number (%)	Vertex	82 (80.4)	154 (78.6)	0.85	
	Breech	10 (9.8)	18 (9.2)	0.85	
	C/S	9 (8.8)	23 (11.7)	0.85	
	Forceps	1 (1)	1 (0.5)	0.85	
RDS	Number (%)	68 (66.7)	113 (57.7)	0.13	1.49(0.89-2.42)
PROM	Number (%)	18 (17.6)	28 (14.3)	0.45	1.29 (0.67-2.46)
Gestational age	**Mean(SD)**	**28.7(±1.99)**	**29.6(±1.81)**	**0.0000**	

There was no case of clinical chorioamnionitis found as defined in this study among the 298 neonates' mothers.RDS was present in the 181(60.7%) while PROM was present in 46 (15.4%). There was a statistically significant difference between neonates with IVH and no IVH in terms of estimated gestational age and birth weight and no significant statistical difference in the rest of the risk factors between those with IVH and no IVH.

Table 4: Multivariate logistic regression for seven risk factors and any-IVH

PARAMETER		Odds Ratio	P-value
Postnatal age		1.00 (1.00-1.02)	0.17
Estimated gestational age		**0.82 (0.69–0.97)**	**0.02**
Place of birth		1.51 (0.88-2.61)	0.13
Mode of delivery	**Caesarean/breech**	0.82 (0.26-2.63)	0.74
	Vertex/breech	1.03 (0.43-2.47)	0.94
	Forceps/breech	2.30 (0.1-42.75)	0.57
Birth weight		**0.25 (0.06-0.98)**	**0.04**
PROM		1.16 (0.59-2.28)	0.68
RDS		1.20 (0.74-2.07)	0.51

The multivariate logistic regression model analysis in table 4 above, showed statistically significant association between EGA and birth weight and any-IVH. Further multivariate logistic regression analysis showed statistically significant association only between birth weight and severe IVH (grades 3 and 4).

Table 5: IVH progression from the first 3 days to day 7

		NUMBER WITH IVH GRADE ON DAY 7 FOR EACH IVH GRADE INTHE FISRT 3 DAYS				
		No IVH	**1**	**2**		**4**
IVH GRADE FIRST 3 DAYS OF LIFE (Number)	**No IVH**	139	16	1	0	0
	1(45)	3	24	4	1	1
	2(15)	0	1	6	2	0
	3(17)	0	0	0	5	1
	4(7)	0	0	0	0	1

Overall, only 12.7% of the patients showed worsening in terms of the IVH grade from the first 72 hours to day 7 of life. Of these, 4 (2%) had actually progressed from either mild or moderate to severe IVH. Those that did not show any changes in the cranial ultrasound findings from the first 72 hours to day7 were 175 (85.4%), with over half of these remaining without IVH.

DISCUSSION

This study investigated the prevalence of IVH in neonates admitted to the NICU at UTH with birth weight less than or equal to 1.5kg and some of the associated risk factors. As the only NICU among public institutions in Zambia, it was imperative to have information on the prevalence of IVH which condition has potential to seriously compromise the quality of life of affected surviving neonates. The overall prevalence was found to be 34.2%, with mild (grade 1) being the most frequent at 54.9% while severe IVH accounted for 27.5%. Similar studies in South Africa[3] and Nigeria[7] though with fewer subject numbers, have shown much lower rates in the frequency of severe IVH but higher overall prevalence of IVH. Over the last two to three decades the rates for severe IVH which has the worst prognosis both in the short and long term has remained almost unchanged globally and in some instances even increased but still much lower than found in this study.[8, 9] In developed countries this may be attributed to the decrease in the death rates of the ELBW/VLBW infants. In resource-limited settings, one may propose that non-availability of means to investigate for appropriate risk factors and intervene appropriately or adopt measures proved to be effective in other settings, may be the reason the rates of severe IVH have remained unchanged. This may also be true for the UTH in Lusaka where this study was conducted.

The findings in terms of timing of the occurrence and progression of IVH were in keeping with what is known about IVH in literature.[2, 10, 11, 12, 13] Of note in this study was that no neonate without IVH in the first 72 hours of life had severe IVH by day 7 among those that had cranial ultrasounds on the two time periods. This would lead one to suggest that the best time for intervention to prevent severe IVH for neonates with birth weight 1.5kg and less in the NICU at UTH would have to be within the first 72 hours of life.

Analysis of some of the associated risk factors showed a statistically significant difference in birth weight and estimated gestational age between neonates with and those without IVH. These would be useful as a guide to which preterm neonates to target in terms of prevention of IVH in the NICU at UTH. Recently an observational study reported a neuroprotective effect of erythropoetin in ELBW infants with IVH[14]. This offers a promising preventative therapeutic option for consideration in future in the treatment of the at-risk infants. Other studies looking at birth weight and gestational age as risk factors for IVH have shown similar findings.[10, 15, 16, 17] Multivariate logistic regression analysis still showed significant association between both estimated gestational age and birth weight and IVH but not mode of delivery, place of birth, postnatal age, surfactant deficiency disease, prolonged rupture of membranes and sex. It is to be noted that recently studies have shown that caesarean section may not actually reduce the incidence of IVH or future neurodevelopmental handicap as was initially thought.[8, 15, 18]

However further multivariate logistic regression for the risk factors and severe IVH showed statistically significant association in birth weight only. It will be important here to mention that in literature some of the above risk factors are reported to be significantly associated with IVH: gender with males being more at risk than females,[19, 20, 21] inter-hospital transfer with those being transferred with increased incidence and severity of IVH than those managed at the hospital or unit where they are delivered,[10, 22] RDS-surfactant deficiency and mode of delivery.[22, 23] Other studies have not shown a significant association in some of these factors like this study as indicated above.[7, 15, 18] The varied findings may be due to the different study designs employed, a lot being retrospective in design.

An interesting finding was absence of clinical chorioamnionitis among any of the mothers of neonates included in the study. This could have been due to the clinical parameters selected for use being less sensitive and less specific for chorioamnionitis (i.e. maternal fever ($\geq 38^0$C), PROM, foetal tachycardia, uterine tenderness with a malodourous infant and no other source of infection). For example, few mothers (about 3) who had fever $\geq 38^0$C and PROM also had other clearly identifiable pathologies to explain the fever i.e. pulmonary tuberculosis, malaria and pneumonia at the same time. Therefore other parameters such as laboratory examination of amniotic fluid and histopathological examination of the placenta and membranes would be of great value in documenting chorioamnionitis. This was not possible under this study.

It is hoped that this study with the findings as discussed above has provided baseline data on the prevalence of IVH and some associated risk factors in the ELBW/VLBW infants in the NICU at UTH. This has potential to further improve the care of these neonates in term of appropriate counselling of the parent/caregiver about the possible future neurological sequelae if an infant is found to have IVH. Further studies to look into modifiable risk factors for severe IVH are needed in view of the finding of a relatively high frequency of severe IVH at 27.5%.

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