

## CHAPTER ONE

### 1.1 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.<sup>1, 2</sup> The grading is useful for counselling of the preterm babies' parents or caregivers about prognosis. <sup>1</sup>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.

Very low birth weight/extremely low birth weight (VLBW/ELBW) preterm neonates account for 20% of the total admissions to the neonatal intensive care unit (NICU) at the University Teaching Hospital (UTH) annually (2007 and 2008 NICU ward statistics) with case fatality rates of more than 45%. 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.<sup>1</sup> In the southern African region, a study in South Africa<sup>3</sup> 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).<sup>2, 4</sup>

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.

## **1.2 STATEMENT OF THE PROBLEM**

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. 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.

Follow up of the VLBW/ELBW infants on the neonatology unit at the UTH is done until they attain a weight of 2.5kg and then are discharged. Therefore, any neurological deficit following IVH will only be noted before or at the time the infant attains this weight while that manifesting later may be missed.

Cranial ultrasound was not routinely done to screen for IVH in the at-risk VLBW/ELBW infants<sup>1, 2</sup> in the NICU at UTH before this study, in contrast to other NICUs internationally where it is recommended to be done routinely.<sup>42</sup>The cranial ultrasound is not done routinely because most of the doctors looking after these neonates on a day to day basis are not trained on it. The radiology department at UTH does not have a Sonographer specifically assigned to carry out these routine cranial ultrasounds as well due to staffing challenges. This was revealed by a check on the NICU before this study was undertaken.

## **1.3 STUDY JUSTIFICATION**

Data from developed countries, where most studies on the subject have been done, cannot be readily extrapolated due to resource limitations, different antenatal maternal disease patterns and poor socioeconomic conditions in Zambia generally and UTH specifically.

This study therefore was undertaken to show the prevalence and severity of, as well as risk factors associated with IVH in preterm neonates with birth weight 1.5kg and below admitted to the NICU at the UTH. This information might influence future management of these infants especially in NICU and follow up upon discharge from the NICU. Findings of the study may also potentially form a basis for future research work on the subject matter.

## **1.4 LITERATURE REVIEW**

The site where intraventricular haemorrhage (IVH) originates is the subependymal germinal matrix, which is an area of embryonic neurones and glial cells for the developing brain. “During foetal development this is a site of neuronal proliferation as neuroblasts divide and migrate into the cerebral parenchyma. By approximately 20 weeks' gestation, neuronal proliferation is completed; however glial cell proliferation is still on-going. The germinal matrix supports glioblasts division and glial elements differentiation until approximately 32 weeks' gestation at which time regression is almost complete.”<sup>1</sup>

### **1.4.1 Pathophysiology**

Particular features of the germinal matrix that render it susceptible to bleeding include the following: Metabolically active and mitochondria-rich cells, supplied by a primitive rete-like capillary network which in turn is fed by the anterior and middle cerebral arteries, a lack of tight junctions between endothelial cells and also lack of a strong basement membrane. Being mitochondria-rich the area is quite sensitive to ischaemia. Another important factor to be considered in the pathophysiology of IVH is the fact that premature neonates have low and narrower cerebral auto-regulation capacity to that of term neonates. Loss of cerebral auto-regulation and abrupt alterations in blood flow and pressure are thought to be responsible for the occurrence of intraventricular haemorrhage although it is said occasionally to occur spontaneously in neonatal infants with less than 1kg birth weight.<sup>1, 4</sup> Loss of cerebral auto-regulation leads to a pressure-passive cerebral blood flow pattern leaving systemic pressure as the determinant of cerebral blood flow. Therefore changes in the blood flow pattern in the presence of this pressure-passive setup leads to haemorrhage.

Multiple events can rapidly alter cerebral blood flow and pressure potentially overwhelming the auto-regulatory mechanisms of the premature neonate. These include a number of risk factors that have been proposed for the development of IVH by this mechanism and also by other yet unexplained mechanisms: chorioamnionitis or intrauterine infection,<sup>5-8</sup> respiratory distress syndrome,<sup>5-8</sup> inter-hospital transfer of the preterm neonate,<sup>9-11</sup> breech presentation,<sup>12</sup> gender,<sup>11-13</sup> premature rupture of

membranes,<sup>6, 7</sup> mode of delivery,<sup>7, 12-15</sup> prolonged labour,<sup>10,16</sup> postnatal resuscitation and intubation,<sup>10, 11,16</sup> early onset sepsis,<sup>17, 18</sup> maternal smoking,<sup>19</sup> low birth weight and gestational age,<sup>6, 11, 12, 16, 20-23</sup> repeated endotracheal suctioning<sup>10, 16</sup> metabolic acidosis and rapid bicarbonate infusion<sup>10, 13</sup> high frequency ventilation,<sup>24</sup> thrombocytopenia,<sup>5</sup> reduced clotting factor levels (specifically factor VII),<sup>25</sup> fertility treatment<sup>26</sup> and high sodium intake.<sup>27</sup>

### 1.4.2 Clinical aspects

80-90% of IVH occurs between birth and the third day of life with 50% on the first day while 20-40% will progress in the first week of life. This forms the basis for screening programmes on seventh day of postnatal life for IVH in preterm neonates. Delayed bleeding, though rare, may occur after the first week of life and accounts for 10-15%<sup>1, 2, 28</sup>

IVH has four grades based on radiological appearance. This grading is useful for prognostic reasons and for counselling parents and caregivers:-

**Table 1** IVH grading<sup>1</sup>

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

These grades can further be classified as mild (grade 1), moderate (grade 2), and severe (grades 3 and 4). Ventricular enlargement is defined as mild (0.5–1cm), moderate (1.0–1.5cm) or severe (>1.5cm).<sup>1, 2</sup>

IVH remains a significant cause of morbidity & mortality in premature neonates accounting for 60%-70 % (0.5kg-0.75kg) and 10%-20 % (1kg-1.5kg)<sup>2</sup> in the USA and around 50% globally in countries with similar resources<sup>1</sup>. A study in Brazil, South America found an incidence of IVH of 53.8% in neonates less than 1kg with

70% being the frequency for mild IVH<sup>29</sup> while another study also in Brazil found an incidence of periventricular-intraventricular haemorrhage of 42.3% with 63.8% moderate, 27.7% mild and 8.3% severe IVH.<sup>30</sup>

Few studies have been done or published in Sub-Saharan Africa on prevalence of IVH in preterm neonates and the associated risk factors. A study done in South Africa at Baragwanath hospital found a prevalence of about 53% for infants weighing less than 1.5kg. In that study 12% had severe IVH<sup>3</sup>. A study at the central hospital in Yaoundé, Cameroun, found a prevalence of 58.3% in infants born between 28-31weeks gestation and 34.8% between 32-34 weeks gestation<sup>31</sup> while one done at a Nigerian university hospital found mild IVH at 22% and 7.5% moderate to severe IVH.<sup>32</sup>

Sequelae following intraventricular haemorrhage relate to post-haemorrhagic hydrocephalus and cerebral parenchyma damage. The last of these is most critical and careful assessment of periventricular parenchyma in the infant with IVH during the acute period of illness may be of value in predicting outcome. Further sequelae are from the shunting procedure in cases of the post haemorrhagic hydrocephalus that results.

Specific problems that may manifest later in these children include cerebral palsy, post-haemorrhagic hydrocephalus, cognitive/intellectual impairment and epilepsy. These are said to occur in higher rates in preterm infants with all IVH grades when compared to children without IVH.<sup>33, 34, 35, 36</sup>

## **CHAPTER TWO**

### **2.1 MAIN OBJECTIVE**

To determine the prevalence of intraventricular haemorrhage and some associated risk factors in preterm neonates with birth weight 1.5kg and below admitted to the NICU at the UTH

### **2.2 SPECIFIC OBJECTIVES**

- I. To determine the proportion of infants with birth weight 1.5kg and below who present with IVH in the first seven postnatal days.
- II. To determine the most frequent grade of IVH occurring in preterm neonates with birth weight 1.5kg and below.

## **CHAPTER THREE**

### **METHODS**

#### **3.1 Study design**

This was a cross sectional study undertaken to look at the prevalence and the most frequent grade of IVH and some associated risk factors in preterm neonates with birth weight 1.5kg and below admitted to the neonatal intensive care unit (NICU) at the University Teaching Hospital, Lusaka, Zambia from September 15, 2010 to February 21, 2011.

#### **3.2 Study site**

The study was conducted at the NICU at UTH, Lusaka, Zambia. The NICU mostly admits neonates, both preterm and term, delivered at UTH and the surrounding outlying areas of Lusaka and Central provinces within a radius of about 50-100 kilometres from the Lusaka urban Central Business District. VLBW (birth weight 1.5kg or less) and ELBW (birth weight 1kg or less) neonates are admitted and treated following NICU protocols. They are discharged from the NICU when a weight of 1.4kg is reached, are free of any medical complication requiring admission and are feeding well. They are then reviewed weekly on the ward until a weight of 1.7kg after which follow-up is in the Out-patient clinic until a weight of 2.5kg is reached. During the period of the study cranial ultrasound was done routinely on all ELBW/VLBW admitted to the unit as part of care.

#### **3.3 Sample profile**

##### **3.3.1 Subject inclusion criteria**

Included in the study were neonates with:

- I. Estimated gestational age (EGA) less than or equal to 32 weeks
- II. Birth weight 1.5kg and below
- III. Post-delivery age less than or equal to seven days on admission to NICU
- IV. Written consent to enrol into the study by the infant's caregiver/parent.

### **3.3.2 Subject exclusion criteria**

Excluded from the study were neonates whose:

- I. caregivers/parents refused consent to enrol into the study
- II. age was more than 7 days postnatally
- III. EGA was more than 32 weeks
- IV. birth weight was more than 1.5kg and
- V. Death before the first cranial ultrasound

### **3.4 Sample size and sampling technique**

Neonates meeting the criteria were consecutively enrolled to the study with the help of two research assistants (nurses) until the sample size of 298 was reached. The sample size was calculated using the formula  $N = z^2(p)(1-p)/L^2$ , assuming 50% IVH prevalence in the preterm neonates  $\leq 1.5\text{kg}$  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 and  $L$  = 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  $\leq 1.5\text{kg}$  annually and the study was to be conducted over a period of six months.

### **3.5 Data collection**

On admission to the NICU or shortly thereafter, but usually between 07:30 hours in the morning and 18:00 hours in the evening of every day of the week during the study period, VLBW/ELBW were assessed for inclusion into the study. Particular attention was paid to the birth weight which was taken as the one done on the ward on admission for those neonates admitted within 48 hours of birth or the one on the referral form that accompanies all neonates admitted to the ward, for those presenting later than 48 hours. In the latter case if no birth weight was indicated on the form, weight done on admission was taken as birth weight. A Secca, model 3341321008, electronic scale was used for weighing neonates on the ward. The EGA was taken as the one determined using the mother's LNMP but or that determined by the new

expanded Ballard score (Appendix D). The latter was taken as the EGA if it was greater by more than two weeks that determined by the LNMP. The Ballard score was done by either the admitting medical officer or the principal investigator within 24-48 hours of admission. If the Ballard score gave an interval such as 32 – 34 weeks, then the lower value, that is 32 weeks, was taken as the EGA.

Presence or absence of RDS due to surfactant deficiency as diagnosed clinically by the admitting medical officer according to local protocol was noted. Because there is no laboratory test to diagnose RDS, the diagnosis on the NICU at UTH, as in other centres, is based on initial clinical symptoms (signs within the first four hours of birth) and the clinical course (over the next thirty-six to seventy-two hours) and a chest radiograph consistent with RDS. Response to surfactant treatment is not yet part of the definition due to non-availability of surfactant in the unit at UTH. Clinical chorioamnionitis was defined as presence of at least two of the following: maternal fever ( $\geq 38^{\circ}\text{C}$ ), PROM (of duration 18 hours or more), foetal tachycardia ( $>160$  beats/min), uterine tenderness with a malodourous infant and no other infection source. Other risk factors and information on the neonate and the maternal antenatal and intrapartum periods was obtained from the maternal antenatal record and by direct inquiry from the mother. These were appropriately recorded on the study questionnaire, (see appendix A).

Informed consent was obtained from the mother/caregiver of the neonate using the form included in this report (appendix C) after it was read and explained to the mother/caregiver. The form was available in English and two local languages, Bemba and Nyanja.

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 ultrasounds were usually done during the day between 06:00 hours in the morning and 18:00 hours in the evening. 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. Axial views, where

indicated, were done for ventricular size determination. Findings were appropriately recorded on the cranial ultrasound reporting form attached as appendix B. 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<sup>37</sup> by the principal investigator and initially by two radiographers from the radiology department at UTH for the first month of the study. The principal investigator had had prior training in ultrasound image recognition, abdominal, obstetrical and gynaecological ultrasound. The training was conducted at UTH by Fontys University of applied sciences (Netherlands) in conjunction with the Zambian Ministry of Health. The training consisted of both theory and hands-on practical. The cranial ultrasound images were printed out and attached to both the patient file and the data collection tools for the particular study subject labelled with the study number. The study numbers were serial numbers from 1 to 298. 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).

### **3.6 Data analysis**

Data was analysed using Epi info version 3.5.1. The independent variables studied in addition to birth weight and gestational age were maternal clinical chorioamnionitis, surfactant deficiency disease, mode of delivery, sex, prolonged rupture of membranes and place of birth. 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 (first 3 days or day 7). 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.

### **3.7 Ethical considerations**

Ethical clearance was sought and granted from the University of Zambia Biomedical Research Ethics Committee for the study. All information collected from the neonate's parent/caregiver was treated with the utmost confidentiality. Case records were kept in lockable drawers on the ward. The study procedure and objectives were communicated to the neonate's parent/caregiver in the language they best understood (see appendix C). Findings of the cranial ultrasound and the possible immediate and long term implications appropriate for the findings were communicated to the parent/caregiver as soon as they were available. The results were also recorded on the neonate's file and promptly made available to the attending doctors for appropriate management in the immediate period. The management if IVH is present is supportive (e.g. blood transfusion if anaemia occurred). Repeat cranial ultrasounds to determine ventricular size and/or daily occipito-frontal circumference were done so as to detect post-haemorrhagic hydrocephalus. The parent/caregiver to the neonate did not incur any additional costs as a result of the study.

## CHAPTER FOUR

### 4.1 RESULTS

A total number of 332 preterm infants with birth weight 1.5kg and below were admitted to the NICU at UTH between September 2010 and February 2011. 298 of these met the inclusion criteria and so were recruited into the study and analysis. All 298 patients had at least one cranial ultrasound done. 207 (69.5%) patients had two cranial ultrasounds done. 85 patients (28.5%) died with 51 (60%) of these without IVH in the first 72 hours, 2(0.7%) left against medical advice, 1(0.3%) absconded and 3(1%) were discharged before the second cranial ultrasound could be done, representing a fallout rate of 30.5%.

**Table 2-** Subject demographic and clinical characteristics

<b>Estimated gestational age-Mean(SD)</b>		<b>29.3 weeks (<math>\pm 1.93</math>)</b>		
<b>Sex - Male – Number (%)</b>		142 (47.7)		
Female – Number (%)		156 (52.3)		
<b>Birth weight – mean(SD)</b>		1.2kg ( $\pm 0.22$ )		
<b>Place of birth – UTH- Number (%)</b>		164 (55)		
Outside UTH-Number (%)		134 (45)		
<b>Any-IVH – Number (%)</b>		<b>102 (34.2)</b>		
<b>Any-IVH and IVH by day of Ultrasound</b>		<b>Any IVH</b>	<b>Day 3</b>	<b>Day 7</b>
<b>Grades –Number(%)</b>	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)
<b>No IVH- Number (%)</b>		196 (65.8)	212 (71.6)	143(69.1)

**Table 3-** Characteristics for the IVH and No IVH groups

		Any-IVH	No IVH	P-Value	Odds Ratio (C.I. at 95%)
<b>Postnatal Age (hours)</b>	Mean(SD)	26.6(±25.1)	24.8(±28.4)	0.61	
<b>Sex</b>	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)
<b>Place of birth</b>	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)
<b>Birth weight</b>	<b>Mean(SD)</b>	<b>1.15(±0.24)</b>	<b>1.26(±0.21)</b>	<b>0.0001</b>	
<b>Mode of Delivery</b>	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	
<b>RDS</b>	Number (%)	68 (66.7)	113 (57.7)	0.13	1.49(0.89-2.42)
<b>PROM</b>	Number (%)	18 (17.6)	28 (14.3)	0.45	1.29 (0.67-2.46)
<b>Gestational age</b>	<b>Mean(SD)</b>	<b>28.7(±1.99)</b>	<b>29.6(±1.81)</b>	<b>0.0000</b>	

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%). IVH regardless of the day (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.

From table 3 above there was 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 model for 7 risk factors and any-IVH

PARAMETER		Odds Ratio	P-value
Postnatal age		1.00 (1.00-1.02)	0.17
Estimated gestational age		<b>0.82 (0.69–0.97)</b>	<b>0.02</b>
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		<b>0.25 (0.06-0.98)</b>	<b>0.04</b>
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. No significant association between any-IVH and any one of sex, postnatal age, mode of delivery, place of birth, RDS and PROM was observed.

Further multivariate logistic regression analysis for the risk factors and severe (grades 3 and 4) IVH showed statistically significant association only between birth weight and severe IVH (see table 5 below).

**Table 5 –** multivariate logistic regression model for severe (grades 3 and 4) IVH

PARAMETER		Odds Ratio	P-value
Postnatal age		1.01 (0.99-1.03)	0.17
Sex		1.40 (0.57-3.42)	0.46
Estimated gestational age		0.78 (0.59-1.04)	0.09
Place of birth		1.49 (0.55-4.00)	0.43
Mode of delivery	Caesarean/breech	10.5 (0.93-119.09)	0.06
	Vertex/breech	2.66 (0.31-23.22)	0.38
	Forceps/breech	104.15 (2.68-4040.63)	0.01
Birth weight		<b>0.01 (0.00-0.14)</b>	<b>0.0004</b>
PROM		1.86 (0.65-5.36)	0.25
RDS		1.09 (0.40-2.95)	0.87

**Table 6** IVH progression from the first 3 days to day 7

		NUMBER WITH IVH GRADE ON DAY 7 FOR EACH IVH GRADE IN THE FIRST 3 DAYS				
		No IVH	1	2	3	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

The above table shows the progression of IVH from the first three days to the seventh day of postnatal life. The analysis included only those neonates that had cranial ultrasounds in the first three days of life and then on day 7. The numbers in the columns of the various IVH grades on day 7 are in comparison with each row of the number with IVH grade in the first three days of life. Of neonates with mild IVH, 4 (2%) showed resolution in the ultrasound findings i.e. three complete with no echodensities/echolucent images noted and in one features of a lesser grade of IVH noted by day 7 of postnatal life. Of those who had cranial ultrasound within 72 hours and then the repeat ultrasound on day 7, no change in sonographic findings for 175 (85.4%) of neonates across all grades of IVH was observed while worsening i.e. echodensities suggestive of new or higher grade of IVH, was noted in 26 (12.7%).

Except for the one shown above, all the other six neonates (85.7%) with IVH grade 4 within the first 72 hours of life died before day 7 ultrasound. Not shown is that 57 neonates who had cranial ultrasound and no IVH within the first 72 hours did not have cranial ultrasound on day 7 for the reasons already given in the first paragraph of this chapter. These were therefore not included in the analysis table 6 above.

## CHAPTER FIVE

### 5.1 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<sup>3</sup> and Nigeria<sup>32</sup> 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.<sup>38, 39</sup> 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.

For neonates with IVH, 84 (82.4%) had it in the first three days of life. 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. However, 175 (85.4%) did not show any changes in the cranial ultrasound findings from the first 72 hours to day7, with over half of these remaining without IVH(table 6). The foregoing findings were in keeping with what is known about timing of the occurrence and progression of IVH.<sup>2, 28, 40, 41, 42</sup> Of note in this study is 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 for 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. In making this suggestion we took into account the fact that only 51 (17.1%) of the neonates without IVH in the first 72 hours of life died before the second ultrasound on day 7 and no autopsies were performed on these as part of the study to see if they had IVH.

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 erythropoietin in ELBW infants with IVH<sup>43</sup>. This offers a promising preventative therapeutic option for consideration in future in the treatment of the high-risk infants identified as above (birth weight less 1.2kg and gestation less than 29 weeks) at the UTH NICU. Other studies looking at birth weight and gestational age as risk factors for IVH have shown similar findings.<sup>28, 29, 44, 45, 46</sup> Multivariate logistic regression model 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.<sup>38, 44, 47</sup>

However further multivariate logistic regression for the risk factors and severe IVH showed statistically significant association in birth weight only. Only two neonates (twins) of the 298 were delivered by forceps and one of these had severe IVH. This number delivered by forceps was too small for any meaningful analysis. 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,<sup>48, 49, 50</sup> 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,<sup>9, 28</sup> RDS-surfactant deficiency and mode of delivery.<sup>9, 51</sup> Other studies have not shown a significant association in some of these factors like this study as indicated above.<sup>32, 44, 47</sup> The varied findings may be due to the different study designs employed.

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 ( $\geq 38^{\circ}\text{C}$ ), PROM, foetal tachycardia, uterine tenderness with a malodourous infant and no other source of infection). For example, few mothers (about 3) who had fever  $\geq 38^{\circ}\text{C}$  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.

In a recently published study looking at determinants of survival in VLBW neonates in a public sector hospital in Johannesburg an argument was made on the need for locally generated data to guide policy decisions and improve care of these infants: “There is therefore a lack of current, valid statistics from such units (neonatal units from developing countries), even though large numbers of patients are treated annually. It is essential to have this information to guide forward planning for therapeutic interventions, budgeting and staffing, with the aim of improving outcome. Local data relevant to a developing country is essential to facilitate this planning; it is not possible to transpose data from one area to another.”<sup>52</sup> 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.

## **CHAPTER SIX**

### **6.1 CONCLUSION**

The prevalence of intraventricular haemorrhage in preterm neonates with birth weight less than or equal to 1.5kg in this study was 34.2% in the first seven days of postnatal life. The most frequent grade was grade 1 (mild) IVH which accounted for 54.9% of all IVH while severe IVH (grade 3 and 4) was at 27.5%. Though the study found a similar or even lower overall prevalence to that reported in studies in Africa and globally, 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.

### **6.2 LIMITATIONS**

In this study cranial ultrasound on the neonates was not performed beyond the first week of postnatal life as part of screening for delayed haemorrhage as is recommended in other units<sup>42</sup>. It was also performed only by the principal investigator beyond the first month of the study after the Sonographer assigned to the study left thereafter for unforeseen reasons and was not replaced. Future studies at the UTH NICU can incorporate screening beyond the first week and more than one reporter for the ultrasound findings.

The study did not include other risk factors that are common reasons for admission to the NICU at UTH such as neonatal sepsis and asphyxia. Blood pressure and patent ductus arteriosus were also not included. The unit has serious challenges of confirming actual septicaemia as well as measuring blood pressure and this, it was anticipated, would have been a challenge in studying these important modifiable risk factors. Futures studies are needed to include these and probably investigate further the finding of a relatively high frequency of severe IVH.

Lastly, autopsies were not performed on those neonates who died before the second cranial ultrasound could be done to establish the cause of death, if they had no IVH on ultrasound in the first three days of life. This was not part of the study design.

However it would be important for future studies to incorporate this especially to capture those neonates with IVH occurrence beyond the first three days and dying as a result.

### **6.3 RECOMMENDATIONS**

Routine Cranial ultrasound should be done on all preterm neonates with birth weight 1.5kg or less admitted to the NICU at UTH. This will allow 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.

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**APPENDIX B**

**CRANIAL ULTRASOUND REPORTING FORM**

Date.....

Study number.....

CRANIAL ULTRASOUND RESULTS	Left		Right	
	Yes	No	Yes	No
<b>ECHODENSISTY SITE</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Echodensity present</b>				
If yes, mark all that apply	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>A. Subependymal</b>				
<b>B. Intraventricular</b>				
If yes,	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) <10% filled				
ii) 10-50% filled				
iii) >50% filled				
<b>C. Intracerebral</b>				
If yes, Mark all that apply	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i) Frontal				
ii) Temporal				
iii) Parietal				
iv) Occipital				
v) Thalamus				
vi) Posterior fossa				
<b>D. Other</b> (Enter below)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

(Adapted from the cranial ultrasound central reader form in the article by Susan R. Hintz et al, **Interobserver reliability and accuracy of cranial ultrasound interpretation in premature infants.** *Journal of paediatrics*, 2007; 150(6):592 – 596

## **APPENDIX C**

### **CONSENT FORM**

#### **Invitation**

You are invited to participate in this study that is looking at intraventricular bleeding and some associated risk factors in preterm neonatal infants of gestational age less than 33 weeks and postnatal age one week or less.

#### **Nature and purpose of the study**

This study is being conducted because preterm infants of gestational and postnatal age indicated above are prone to having intraventricular bleeding as a result of circumstances at the time of delivery and during admission to neonatal intensive care units in the period immediately following their delivery. Intraventricular bleeding further puts them at risk of lifelong neurodevelopmental disability. Identification of the risk factors that significantly lead to the occurrence of this bleeding will help with minimisation of the same and hence the occurrence of the bleeding itself and consequently improve the outlook on future quality of life of the baby.

#### **Procedures of the study**

If you accept to participate in the study, information on your antenatal period and the delivery as well as on your baby will be collected. Thereafter, head ultrasound scan will be performed on your baby and then you will be informed of the findings.

#### **Possible risks and discomfort**

Your baby will not be exposed to any known risks by enrolling into the study. Ultrasound scanning as is used in the hospital on patients is not known to be dangerous or harmful to any part of the human body. Your baby will be looked after on the ward by the attending doctors like any other preterm baby admitted to the ward.

#### **Possible benefits**

Findings on the scan will be used appropriately in the management of your baby by the attending doctors.

#### **Confidentiality**

All information collected in this study is strictly confidential and data or information that will be collected and reported will not include your names.

## **Consent**

Your participation in this study is strictly voluntary. You and the baby will not suffer any consequences if you decide not to participate in the study and you may also withdraw from the study at any time and for any reason without any consequences to your baby or yourself.

Thank you for considering your baby's and your participation in this study. If you have any concerns, clarifications or questions please do not hesitate to contact Dr Mulindwa or the University of Zambia Biomedical Research Ethics committee on the following addresses;

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I.....hereby confirm that I have sufficiently been explained to about the nature, conduct, possible benefits and risks of this clinical study. I have also received and/or read and understood the above written information about the study and am aware that my personal details and that of my baby will be anonymously processed into the research report. I have understood that I may voluntarily, at any point, withdraw my participation and that of my baby without suffering any consequences. I have been given sufficient time to ask questions and seek clarifications and of my own free will agree to myself and my baby's participation in the study.

Participant's signature or thumb print

Date...../...../.....

Person obtaining informed consent

Date...../...../.....

## **IPEPALA LYA KUSUMINISHANYAPO (CONSENT FORM)**

### **Ubwite**

Mukwai mwaitwa, imwe no mwana wenu, kuku kwatamo lubali mu isambililo ili. Lilelolesha pa bwafya bwakusuuma umulopa ku bongo elyo na mafya yamo ayalenga ici ukucitika mu tunya utufyalwa 1.5kg nokubwela panshi elyo ne nshiku ishefumo imilungu amakumi ya tatu na itatu nokubwelela panshi elyo kabili inshiku ukufikafye pali cine lubali ukufuma kuku fyalwa.

### **Umusango we sambililo elyo no mulandu lilecitilwa**

Ili sambililo lilecitwa pamulandu wakutila utunya utufyalwa pa nshita isoselwe pakubala tulakwata ubwafya bwakusuuma umulopa ku bongo. Ici cicitika pa mulandu wa ficitika pa nshita ya kufyalwa na pa nshita ya kutekwa kuno cipatala ca tunya utwa mweshi umo. Ukusuuma umulopa ku bongobongo kulonaula bongobongo. Ici cileta amafya yambi mu mweo wa mwana kuntanshi. Isambililo ili lile esha ukufwailisha ifintu fimo ifisangwa mu tunya utu kwata ubwafya bwa kusuuma kwa mulopa ku bongo. Ici kuti ca yafwilisha kuku cefyako nangula ukufumyapo ifi fintu kuntanshi no kwafwilisha aba abaana.

Nga mwasumina uku kwatamo ulubali mwi sambililo ili, twalafwayako ukwishiba ifintu fimo pa nshita mwali nefumo lya mwana elyo na pa nshita ya kupapa. Ama pepala yalya ya bomfiwa ilyo muli nefumo kucipimo nayo kuti twafwaya ukumonapo fimo ifya kwafwilisha kwisambililo line. Pa numa, umwana wenu akapimwa pa mutwe na mashini intu tubomfya ukumona mukati ka bongo nga cakuti muli ubwafya bwa kusuuma umulopa. Ici cikacitwa imiku ibili munshiku cine lubali elyo fyonse ifikasangwa tuka mulondolwela.

Ukukwato lubali mwisambililo ili takwakalenge ubwafya nangula ubusanso ubuli bonse ku mwana. Mashini tu bomfya ukupiminako ku mutwe ta yaishibwa ukuleta ubusanso ubuli bonse ku baana. Ilyo umwana wenu ali kuno cipatala akulaundapwafye bwino kuli ba shing'anga nga baana bonse abatekwa kuno.

Fyonse ifyasangwa panuma ya kupimwa fikabomfiwa muku ndapa umwana ilyo ali muno cipatala.

Tukasunga inkama ya fyonse fintu tulemwipusha elyo na fyonse tukalemba pamulandu we sambililo line li tamwakabe amashina yenu no mwana.

Ukusumina ukukwato lubali mwi sambililo ili techakupatikisha iyo, caku ipelafye mwebene nga mwasumina panuma ya masihiwi yantu twamulondolwela. Nga mwakana ukukwatamo lubali temulandu iyo. Kabili ngamwasumina ukukwatamo lubali kuti mwafumamo pa nshita iili yonse ukwabulo mulandu uuli onse

Twamutasha pa nshita intu mwapela elyo napakukwato lubali mwisambililo ili.

Nga kuli amepusho yambi mwinga kwata panshita iili yonse kuti mwaipusha ba Dr Mulindwa nangu abakumupando wa kabungwe kaba University of Zambia Biomedical Research Ethics committee, ngefi:

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Ine,.....ndesuma nokushininkisha ukuti nabanondolwela mukulinga umubela kabili nokucitwa kwesambililo ili nafyonse ifingafwilishako umwana wanda ilyo ali no lubali mwi sambililo ili. Ni mpokelela/nokubelenga fyonse pe sambililo line li nefyo ishina lyandi ne lya mwana wandi talyakalumbulwe nangula pamo mukulemba kwe sambililo line. Kabili ni ng'umfwa no kwishiba ukuti inshita iili yonse kuti nafumamo mwisambililo line no mwana wanda ukwabula ubwafya nangu bumo. Ni mpelwa nenshita iya linga ukwipusha amepusho yonse. Elyo kanshi kukufwaya kwandi ne mwine naipela no mwana wandi ukukwato lubali mwisambililo ili.

Ishina nangu icikakatilo ca bale kwatamo ulubali mwi sambililo

.....Ubushiku...../...../.....

Inte pakusuminishanya

.....Ubushiku...../...../.....

## **CHIBVOMEKEZO (CONSENT FORM)**

Muitanindwa kuzatengako mbali mumaphunziro omwe aona pa za umoyo za ana akanda amene amatulusa magadzi mumidzipe za mumutu yao ndi zina zache zoopyeza ku ana awa osakhwanisa mwezi yobadwilamo. Ana obadwa ndi mwezi yokwana insano ndi umodi ndi sabata imodzi ndipo ubwerera pansu ku ana akhanda amatsiku okhwanila sabata imodzi.

### **Cholinga chamaphunziro**

Cholinga cha mamphunziro awa ndi kuti ana amagesi omwe amabadwa ndi mwezi yosankwanila bwino amapezeka uchosa magazi mumizipe za mumutu yao kupyolela mdzochitika dzomwe zimacitika pa nthawi yobeleva ndiponso pa nthawi yomwe amakhala mucipatala ca malaiti. Mbvuto iyi yochosa magadzi mumizipe ya mu mutu ya ana awa. ndikahale ndi choonadi pa mabvuto a umoyo wa ana anu omwe amapezeka ana awa imayikisa ana mumabvuto yoti samakula bwino ai ndipo amakhala ndi zilema zosiyana siyana. Udziba chomwe chilengesa kuti ana awa adzichotsa magadzi chidzathandidzira kucepesta bvuto iyi ndiponso umoyo wa ana awa udzakhala wabwino.

### **Mundandanda wamaphunziro**

Ngati mudzabvomeredza kuti mwana wanu atengeko mbali mumaphunziro aya tidzafuntsako mafunso kuti ndizibe zonse zomwe zichitika pomwe munali ndi pathupi ndi po beleka mwana uyu. Pambuyo pache tidzamukopa chikope cha mu mutu pa ma tsiku atatu ndi asanu ndi awiri kuyambira tsiku yomwe mwana adabadwiramo. Zomwe zidzathuluka mu mamphunziro awa tidzamudziwitsani.

### **Ziopyezo ndi zoipa**

Mwana wanu sazagundiwako pa mabvuto aliyontse kamba kohala pa maphunziro aya ayi. Chipatala chino chimatenga zikope za mutu ya ana ndiponso sitinapedzeko mbvuto iliyonse.

### **Angakale malipilo**

Chikope cha mu mutu chomwe tizamtenga mwana wana chidzathandidzira kuti ma dotolo adziwe mo mutsamalira mwana wanu ndipo umoyo wache udzapita patsongolo.

### **Chisinsi**

Zomwe zidzatulukamo mumaphunziro aya azidzakhala zachisinsi koma ndiza uzako adotolo anzanga kuti pa modzi tinghathe odziwa motsungira ana awa. Dzina lanu kapena la mwana wanu sidzapedzekako pa pepala.

### **Cibvomekezo**

Aya maphunziro ndi yozipereka kodzifunira. Ngati mwasankha kusatengako mbali, inu ndiponso mwana wanu adzatsamalilidwa ngathi ana ena. Muli omasuka kuleka

maphunziro panthawi ili yonse ndi kusankha kwanu sikudzakhuza chisamalilo chili chonse chimene mungathe kutenga kuchipatala m'tsogolo.

Zikomo kwambiri pobvomedza mwana wanu kuti atengako mbali mumaphunziro aya. Ngati muli ndimafunsto khalani omasuka kuti timumatsulileni pomwe simunabvetsetse. Omwe mungafuntse mungathe kufunsa a Dr. Mulindwa Makasa Justin Kapena a ku University of Zambia Research and Ethics Committee:

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Ine .....ndasimikidza kuti andifotokozerwa mwasatane satane zamaphunziro aya. Andifotokozerwa Ziopyezo ndi zoipa ndiponso ndimalipilo amaphunziro aya. Ndalandiratsa ndipo ndawerenga chi pepala cha chibvomekezo ndipo ndabvetsetsa mokwanira. Ndidziba kuti zochitika mumaphunziro aya zizakhala zachitsintsi. Ndidziwa kuti ndiri omasuka kuleka maphunziro panthawi iliyontse ndipo mwana sazakhala ndi bvuto iliyonse. Ndinakhala ndimpata ofunsa mafuntso yonse yazochitika mumaphunziro aya. Ndavomera kozipereka kuti mwana wanga atengeko mbali mumaphunziro aya.

Ndalandira chikope cha pepala yosainidwa/yosindikizda chala.

..... /..... /.....  
Otengako mbali sainani/ sindikidzani chala. Tsiku

..... /..... /.....  
Dzina la anchito a maphunziro sainani Tsiku

## APPENDIX D

### THE NEW EXPANDED BALLARD SCORE

#### Physical Maturity

	Physical maturity -1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: -1 <40 mm: -2	<50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola-no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (-1), tightly (-2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

(Source: Behrman R. E, Kliegman R. M., Jenson H. B. **Nelson textbook of paediatrics**, 17<sup>th</sup> edition, Philadelphia, WB Saunders, 2004, pp552)

## Neuromuscular maturity

	-1	0	1	2	3	4	5
Posture							
Square window (wrist)	 $<90^\circ$	 $90^\circ$	 $60^\circ$	 $45^\circ$	 $30^\circ$	 $0^\circ$	
Arm recoil		 $180^\circ$	 $140-180^\circ$	 $110-140^\circ$	 $90-110^\circ$	 $<90^\circ$	
Popliteal angle	 $180^\circ$	 $160^\circ$	 $140^\circ$	 $120^\circ$	 $100^\circ$	 $90^\circ$	 $<90^\circ$
Scarf sign							
Heel to ear							

(Source: Behrman R. E, Kliegman R. M., Jenson H. B. **Nelson textbook of paediatrics**, 17<sup>th</sup> edition, Philadelphia, WB Saunders, 2004, pp552)

### Maturity rating

Score	Weeks
- 10	20
- 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

(Source: Behrman R. E, Kliegman R. M., Jenson H. B. **Nelson textbook of paediatrics**, 17<sup>th</sup> edition, Philadelphia, WB Saunders, 2004, pp552)