INCIDENCE AND RISK FACTORS FOR DEVELOPMENT OF PERIVENTRICULAR-INTRAVENTRICULAR HAEMORRHAGE IN THE VERY PRETERM BABIES ADMITTED TO THE NEW BORN UNIT AT KENYATTA NATIONAL HOSPITAL

Principal Investigator: Dr. Bernice N. Mukuria

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Department of Paediatrics and Child Health,

University of Nairobi,

P.O. Box 30197-00100,

Nairobi.

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Thank you, and may God bless you.

DECLARATION

This dissertation is my original work and has not been presented for the award of a degree in any other university.

Signed: ..... Date: .....

Dr. Bernice N. Mukuria,
H58/81401/2015
Resident – Department of Paediatrics & Child Health,
University of Nairobi.

This dissertation has been presented with our full approval as supervisors.

Signed: ..... Date: .....

Prof. Rachel N. Musoke (MB. Ch.B, M.Med (Paed); Diploma in Neonatology (UK)),
Associate Professor – Department of Paediatrics & Child Health,
University of Nairobi.

Signed: ..... Date: .....

Dr. Brian Maugo (MB. Ch.B, M.Med (Paed)),
Lecturer – Department of Paediatrics & Child Health,
University of Nairobi.

Signed: ..... Date: .....

Dr. Jasper Muruka (MB. Ch. B, M.Med (Radiology)),
Consultant Radiologist,
Kenyatta National Hospital.

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LIST OF ABBREVIATIONS

BBB	Blood-brain barrier
CBF	Cerebral blood flow
CPAP	Continuous positive airway pressure
cUS	Cranial ultrasound
DIC	Disseminated intravascular coagulation
ELBW	Extreme low birth weight
GM-IVH	Germinal matrix-intraventricular haemorrhage
HIE	Hypoxic-ischaemic injury
IPPV	Intermittent positive pressure ventilation
IVH	Intraventricular haemorrhage
KNH	Kenyatta National Hospital
NBU	New born unit
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PI	Principal Investigator
PV-IVH	Periventricular-intraventricular haemorrhage
RDS	Respiratory distress syndrome
TFU	Trans-fontanelle ultrasound
UoN	University of Nairobi
VLBW	Very low birth weight

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CASE DEFINITIONS

PV-IVH was defined as bleeding within the capillary network of the germinal matrix of the developing brain, classified anatomically into four grades according to severity (*Papile, et al)*

Very preterm: these are neonates who are born at a gestational age of ≤32weeks

*Outcome of interest***:** PV-IVH (any grade) seen on cranial ultrasonography.

ABSTRACT

Background

Germinal matrix-intraventricular haemorrhage (GM-IVH) is bleeding into the brain's ventricular system that originates from the capillary network of the primitive germinal matrix, which normally regresses before term. Also known as periventricular-intraventricular haemorrhage (PV-IVH), it involves the periventricular motor tracts, and is associated with both short and long-term complications including seizures, developmental delay and cerebral palsy. It is also associated with a higher mortality rate. PV-IVH has been shown to be inversely related to gestational age and birth weight, and is thus mostly observed among babies born before 32 weeks gestational age, who generally lie within the very low birth weight (VLBW) and/or extremely low birth weight (ELBW) categories. Clinical presentation varies, with most infants remaining asymptomatic. Others may demonstrate a sudden deterioration in clinical state, following which a diagnosis of PV-IVH may be suspected. Diagnosis, therefore, is mostly made on surveillance cranial ultrasonography, and this is the recommendation globally.

Objectives

The objective of this study was to determine the incidence, and describe any associated risk factors for intraventricular haemorrhage in the very preterm babies within the first 7 days of life.

Participants and Methods

This was a cohort study where two cranial sonography scans were carried out initially within 72 hours of life, and then at day 7 among neonates born at ≤ 32 weeks gestational age.

Results and Conclusion

A total of 195 neonates were recruited, and 144 (73.8%) of these survived to day 7 of life, with a male to female ratio of approximately 1:1. Median gestational age was 31 weeks (IQR 29 – 32), and the median birth weight was 1440g. Overall prevalence of PV-IVH was 8% (95% CI 4 to 12%), with majority (60%) being grade I haemorrhage, and the remainder 40% being grade II haemorrhage. Multivariate analysis revealed significant risk factors for PV-IVH as being severe RDS ($p = 0.005$), male gender ($p = 0.035$) and being small for gestational age ($p = 0.001$)

INTRODUCTION

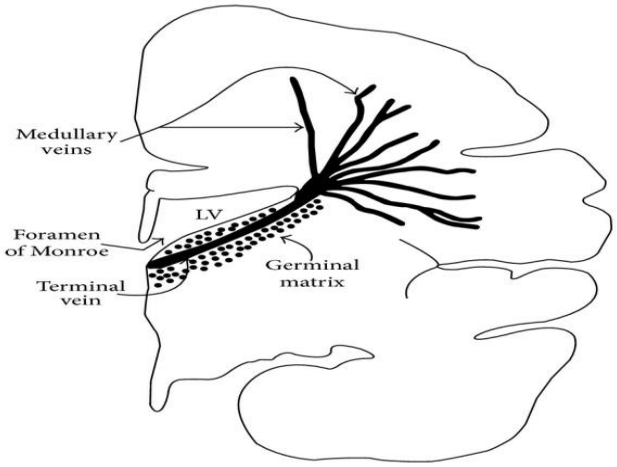
Definitions

Germinal matrix-intraventricular haemorrhage (GM-IVH) is a major complication of prematurity, and is defined as bleeding into the brain ventricular system, originating from the capillary network of the primitive germinal matrix [1]. The germinal matrix is a richly vascularised collection of neuronal-glial precursor cells in the developing brain[1]. Also termed periventricular-intraventricular haemorrhage (PV-IVH), germinal matrix-intraventricular haemorrhage involves the periventricular white matter (motor tracts) and may extend into the ventricular system. In more severe forms, IVH involves the cerebral parenchyma. PV-IVH is associated with both short and long-term complications including cerebral palsy, developmental delay and seizures. Infants who develop PV-IVH have been shown to have a higher mortality rate. [3] For purposes of this publication, the terms GM-IVH and PV-IVH have been used interchangeably.

The germinal matrix is located ventrolateral to the lateral ventricle – on the head of the caudate nucleus and beneath the ventricular ependyma[2] – and normally regresses by term. During foetal development, however, it is the site of both neuronal and glial cell proliferation. Neuroblasts divide and migrate into the cerebral parenchyma, with completion of neuronal proliferation by approximately 20 weeks of gestation. The germinal matrix continues to support the division of glioblasts and differentiation of glial elements up to approximately 32 weeks of gestation. At this time, regression of the germinal matrix is nearly complete.[1] [2]

The germinal matrix cells are highly metabolically active and thus rich in mitochondria. [2] This makes them highly sensitive to low oxygen states. The matrix receives its blood supply from a primitive and inherently fragile mesh-like capillary network [1],[2]. Arterial supply to the plexus is through the Heubner artery and the lateral striate arteries, both of which are within the distribution of the anterior and middle cerebral arteries. Venous drainage is via the terminal vein, which empties into the internal cerebral vein, which in turn drains into the vein of Galen[1]. This fragile capillary network is the primary site at which haemorrhage as seen in GM-IVH occurs (Fig. 1).

Figure 1: Germinal Matrix - the predilection site for intraventricular haemorrhage in preterm infants.[38]



Key: LV - Lateral Ventricle.

Anatomical Classification of Germinal Matrix/Intraventricular Haemorrhage

PV-IVH is traditionally classified into four grades of severity, based on radiological appearance. There are two main grading systems, as defined by Papile[3], et al, and/or Volpe[4]. Both systems rely on the detection of blood in the sub-ependymal germinal matrix, and the ventricles.

Classification according to Papile et al is as follows: Grade I haemorrhage is restricted to the sub-ependymal region and/or germinal matrix. Grade II haemorrhage is sub-ependymal haemorrhage, with extension into the lateral ventricles with no ventricular enlargement. Grade III haemorrhage is as the previous, with associated ventriculomegaly (hydrocephalus). Grade IV haemorrhage – the most severe form – is haemorrhage into the brain parenchyma.[1],[2],[3] (Fig. 3 and 4)

Figure 2: Grade I haemorrhage (A) and Grade II haemorrhage (B)[1]

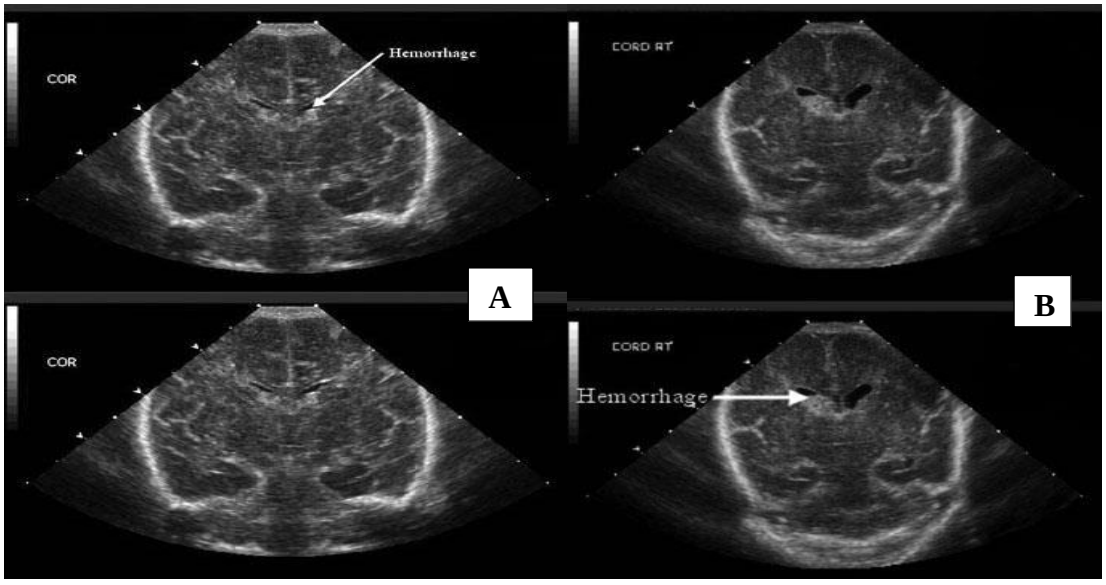
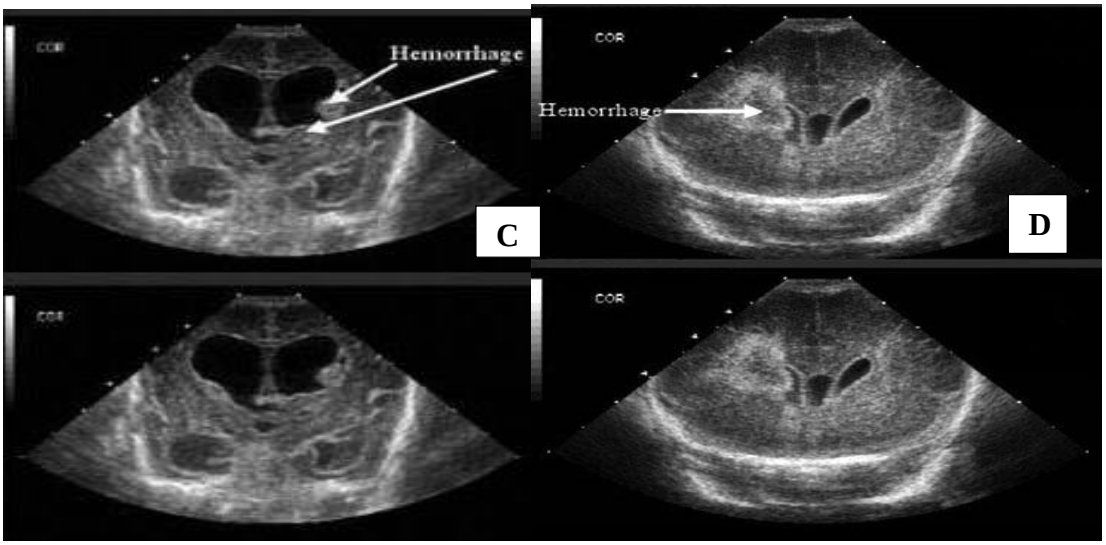


Figure 3: Grade III haemorrhage (C) and Grade IV haemorrhage (D)[1]



Volpe's classification is as follows: Grade 1 refers to germinal matrix haemorrhage without intraventricular haemorrhage, or with IVH occupying <10% of the ventricular area on parasagittal view. Grade 2 is IVH occupying 10 – 50% of the ventricular area on parasagittal view. Grade 3 is IVH occupying >50% of the ventricular area on parasagittal view. Periventricular venous haemorrhagic infarction is noted separately as a consequence rather than a continuum of IVH and is occasionally termed 'Grade 4'.[4],[5]

Severity of haemorrhage with regard to grading has a direct correlation with prognosis. Infants who develop grade 1 and/or grade 2 haemorrhage are at risk of developmental disability. Those who develop grade 3 and/or grade 4 haemorrhages are at increased risk of

post haemorrhagic hydrocephalus, cerebral palsy, cognitive/intellectual impairment as well as epilepsy. Higher grades of IVH are also associated with a higher mortality rate. Grading PV-IVH is therefore a useful tool for the counselling of parents and/or caregivers on prognosis and sequelae.

Risk Factors and Pathogenesis of PV-IVH

Periventricular-intraventricular haemorrhage has been shown to be inversely related to gestational age, and birth weight. Advanced maternal age [39] and the use of more than two doses of antenatal steroids [40] have been associated with lower incidence of PV-IVH. Maternal infection, primiparity and pre-eclampsia however, have been associated with occurrence of periventricular-intraventricular haemorrhage [40]. Perinatal factors associated with PV-IVH include spontaneous vertex delivery, premature rupture of membranes (PROM), ante-partum haemorrhage and presence of meconium stained amniotic fluid. Neonatal factors such as gender, presence of respiratory distress syndrome, asphyxia, hypothermia or sepsis have been shown to be associated with PV-IVH. [2],[6] Other associated factors include pneumothorax, hypoxia, hypercapnoea, seizures, thrombocytopenia and/or haemostatic failure, and presence of a patent *ductus arteriosus*.[1],[2],[6],[7] These risk factors appear to induce periventricular-intraventricular haemorrhage primarily through hypoxia with resultant disturbance in cerebral blood flow. Thrombocytopenia appears to contribute to haemorrhage by causing haemostatic failure.[2]

There are three major pathogenic mechanisms in the neonate that are thought to lead to intraventricular haemorrhage: disturbance in cerebral blood flow (CBF), the inherent fragility of germinal matrix vasculature and platelet/coagulation disturbances.[2] These, alongside neonatal risk factors for IVH, are summarised in Table 1.

Table 1: Neonatal Factors in Pathogenesis of PV-IVH

Major Mechanism	Presumed Mechanism	Risk Factors
1. Disturbance in CBF	Fluctuation in CBF	Hypoxia Hypercapnoea Severe acidosis Ventilator asynchrony Severe RDS Presence of a PDA Frequent airway suctioning Rapid bicarbonate infusion
	High cerebral venous pressure	Pneumothorax High ventilator pressure Prolonged labour and vaginal delivery
	Abnormal blood pressure	Hypotension/hypertension Sepsis Dehydration
	Pressure-passive circulation	Extreme prematurity ELBW Clinical instability, as from severe respiratory compromise and/or sepsis
2. Inherent fragility of germinal matrix vasculature	Worsened by inflammatory injury to blood-brain barrier	Sepsis HIE
3. Platelet and coagulation disturbances	Haemostatic failure	Thrombocytopenia DIC

Diagnosis and Management of PV-IVH

Clinical presentation of PV-IVH varies widely, and is dependent on the size of the bleed. Most infants remain asymptomatic, or may demonstrate subtle signs such as a small drop in haematocrit that can easily go unnoticed. Haemorrhage is subsequently found on surveillance cranial ultrasonography. Some infants may present with a sudden, unexplained drop in haematocrit level; and physical findings related to anaemia (such as pallor and/or poor perfusion) may be demonstrable. Other infants may present with overt signs such as sudden

and significant clinical deterioration, usually associated with anaemia, metabolic acidosis, hyperglycaemia or hypoglycaemia, respiratory acidosis, apnoea, hypotonia and stupor. Progression can be rapid and may result in shock and death. Between these extremes of presentation, infants may demonstrate varying degrees of neurological and systemic signs such as poor perfusion, pallor/ashen colour, irregularities of respiratory pattern, and altered mental status.

PV-IVH is diagnosed primarily through the use of brain imaging studies, with cranial (trans-fontanelle) ultrasonography being the imaging modality of choice.[1],[8] Computed tomography and magnetic resonance imaging have been used as supplementary tools in the imaging of IVH.[8],[9] Ultrasonography is however preferred due to its portability, which allows for imaging to be performed with minimal disturbance of the infant. Ultrasonography scanning is associated with a sensitivity of close to 100%, and a specificity of 91%, and can identify IVH of >5mm. Smaller haemorrhages are more difficult to detect, though using the posterior fontanelle as an additional acoustic window can help enhance reliability of the diagnosis.[10] Ultrasonography, however, is associated with a higher rate of inter-observer disagreement, which is not the case with either CT or MRI scanning. CT and MRI scanning can be performed with greater specificity compared to ultrasonography. These modalities however would require for the infant to be moved, as well as necessitate sedation. For these reasons, ultrasonography is preferred.

Because PV-IVH can occur without clinical signs, screening and serial examinations are necessary for the diagnosis.[1] Current recommended schedules for routine screening of the very preterm neonate include an initial trans-fontanelle ultrasound (TFU) within 72 hours of life, with a second TFU on day 5 to 7 of life.[11],[12] Subsequent ultrasounds are carried out on a weekly basis. Frequency of ultrasound scanning is determined on a case-by-case basis after the initial routine scans have been performed.[11],[13] Though studies point toward a general decline in incidence of PV-IVH, it remains a major problem of modern neonatal intensive care units globally.[2]

LITERATURE REVIEW

PV-IVH continues to be a major problem of preterm, premature infants in modern neonatal intensive care units worldwide.[2] The incidence of PV-IVH in the very low birth weight (VLBW) infants (<1500g) in the United States declined from around 40-50% in the early 1980s to about 7-20% in the late 1980s up to date. Though there were undoubtable changes in neonatal care in this period, no planned intervention occurred;[2] no reason for this decline was given. In extremely low birth weight (ELBW) infants (<1000g), PV-IVH occurs in about 45%.[2] Most studies surrounding GM-IVH have been about preterm infants with the more severe forms of haemorrhage (Grade III and IV), likely because these are much easier to detect with cranial ultrasound, and also are associated with more adverse outcomes thus more likely to generate interest.[14]

A study carried out by Papile, et al [3] in New Mexico (USA) followed VLBW infants from birth to age 6 months, so as to assess evolution of intraventricular haemorrhage. The investigators employed serial CT scanning of the brain coupled with autopsy findings to diagnose and characterise periventricular-intraventricular haemorrhage. Using a total sample size of 46, Papile et al were able to determine an inverse relation between gestational age and birth weight, as well as a direct correlation between severe asphyxia and the development of intraventricular haemorrhage.[3] The study concluded that the bulk of PV-IVH is clinically silent, and often times greatly under reported. Subsequent studies in the US have placed the overall incidence of PV-IVH at 20-40%, with some studies reporting an incidence of up to 50% [1]. With the advances in neonatal care and practice, however, current prevalence rates in the US – a high resource setting – remains at 20-30% at majority of centres.[2]

Basanayake, et al [11] conducted a prospective study on babies born before 37 weeks' gestation which aimed to describe incidence and risk factors for development of PV-IVH in premature babies. A total of 126 babies were studied, and the diagnosis and characterisation of PV-IVH was made through the use of previously defined ultrasound findings. Overall incidence of PV-IVH was found to be 9.5%, However, a greater incidence was demonstrated in babies with a lower gestational age at time of birth, with an incidence of 24.5% reported for babies born at <32weeks gestation. When controlled for birth weight, an incidence of 43% was reported for ELBW infants, and one of 22% for VLBW babies. Incidence of PV-IVH was found to be greater in babies requiring CPAP (8%) and/or IPPV (92%). A lower incidence was noted in babies whose mothers had received antenatal steroids.

A prospective, cross-sectional study carried out by Adegoke et al [12] in a resource constrained facility in Nigeria reported an overall PV-IVH prevalence of 24.1%, with majority of cases (76.2%) being characterised as either Grade I and Grade II haemorrhage following cranial (trans-fontanelle) ultrasound. Scanning was performed only once, between 60 hours and 7 days of life. Study participants all had birth weights below 1500g, and majority were born before 32weeks gestation. Prevalence of IVH was greatest (80%) in babies born before 28 weeks of gestation, and least (12.1%) in babies born after 32 weeks of gestation. No association was found between development of IVH, and such factors as gender, maternal age and/or level of education. Positive association was made between IVH and need for oxygen therapy (including duration of oxygen therapy), severe birth asphyxia, and lack of antenatal steroid use.

A Zambian cross-sectional study by Mulindwa et al [15] was undertaken with the overall aim to determine prevalence and most frequent grade of IVH as well as associated risk factors in preterm babies admitted to the NICU at the University Teaching Hospital in Lusaka. Babies admitted to the study were all born at 1500g or less. Diagnosis and characterisation of IVH was by cranial ultrasound performed within the first three days of life, and subsequently on the seventh postnatal day. About 300 neonates were studied over a 5-month period. Gestational age was estimated using the mother's last normal menstrual period and/or using the new expanded Ballard score within 24-48hours of admission. Overall prevalence of IVH was reported to be 34.2%, with majority cases being described as Grade I (54.9%). Haemorrhage was mostly observed within the first 72 hours of life (82.4%).

Sandler et al [16] conducted a prospective study aimed at determining the prevalence of PV-IVH among VLBW infants at Baragwanath Hospital (South Africa). A total of 282 infants were studied over a 4-and-a-half-month period. Cranial ultrasound was performed in one third of non-ventilated patients, and all ventilated patients on days 3, 7 and 14. Overall prevalence of PV-IVH was found to be 53% for VLBW infants, and 52% for infants born before 35 weeks gestational age. Majority cases had either grade I or grade II PV-IVH, and only 12% had grade III to grade IV haemorrhage. Prevalence and severity was seen to be directly related to both decreasing birth weight and decreasing gestational age. Need for active resuscitation at birth and mechanical ventilation were noted to be predictors of development of PV-IVH.

Swai et al [6] in a prospective study carried out in Tanzania's Muhimbili National Hospital reported an incidence of IVH of 61.8% overall, with majority being Grade I and II haemorrhage. Serial cranial ultrasound scans were performed at or before 72 hours of life, then after 2 weeks and after 4 weeks. Throughout this interval, majority cases of IVH remained Grade I and Grade II. Majority IVH (81.3%) occurred within the first three days of life. Infants who were diagnosed with grade four IVH at initial scanning died before 2 weeks of life. Those who were diagnosed with grade III IVH at initial scan progressed to grade IV haemorrhage by 2 weeks of life, and died by 4 weeks postnatal age. This study was thus able to demonstrate the higher mortality rate associated with the higher grades of IVH.

Within the same study was a nested case control study to address various perinatal factors associated with the development of IVH. This was able to demonstrate a positive correlation with such factors as need for oxygen therapy, hypothermia, RDS, and birth asphyxia. IVH was seen more in infants delivered via spontaneous vertex delivery, compared to those born via caesarean section. Neonates who developed IVH had a lower mean haemoglobin compared to neonates without haemorrhage. This however was thought to be an outcome rather than a predictor of IVH. As has been shown in previous studies, incidence of IVH was higher in infants born with VLBW, and/or before 32 weeks gestational age. Increased incidence was also noted in the ELBW infants.

A cohort study by Bashir et al [17] sought to find out the incidence of intraventricular haemorrhage among the LBW (birth weight ≤1750g) population in the new born unit at Kenyatta National Hospital using real time cranial ultrasonography.[17] A total of 140 LBW infants were included in the study. Gestational age range among the participants was between 27 and 36 weeks, and the birth weight ranged between 650g and 1750g. Scans were performed on days 1, 3 and 7. Incidence of IVH was found to be approximately 33%, and majority (80.4%) haemorrhage was diagnosed within 72 hours of life. Diagnosis of IVH was made both on ultrasonography and on autopsy. 45.7% diagnoses were made on autopsy alone, while 54.3% were made on ultrasound alone. All four grades of intraventricular haemorrhage were demonstrated, and grade III being the most frequently observed with 50% incidence. Grade I haemorrhage was least commonly seen (10.9%) which is not in keeping with literature, where grade I and grade II are seen most commonly. However, no reason was given for this. The study demonstrated the inverse relationship between incidence of IVH and birth weight, as well as gestational age. Mortality rate with IVH was shown to be 56.5%, as has been demonstrated before by Papile, et al. [3] The study also showed that most

haemorrhage indeed does occur within the first 3 days of life, as demonstrated by Volpe, et al.[18] Notably, this particular study was carried out at a time when level 3 nursing care was not available at the NBU within KNH.

Table 2: Summary of Reviewed Literature

Author; Year	Study Title	Methodology; Key Findings
Papile L, Burstein J [3].; 1978	**Incidence and Evolution of Sub-ependymal and Intraventricular Haemorrhage**	**Prospective study.** Overall IVH incidence 43%; case fatality rate of infants with IVH – 55%.
Bashir A [17]; 1991	**The Incidence of Intracranial Haemorrhage in LBW infants at the New Born Unit in Kenyatta National Hospital**	**Cohort Study;** 32.9% incidence of IVH
Sandler D, Cooper P, Bolton K[16]; 1994	**Periventricular-Intraventricular Haemorrhage in Low Birth Weight Infants at Baragwanath Hospital**	**Prospective study; 53% prevalence of IVH**
Swai P, Manji K, Kwesigabo G [6]; 2005	**Periventricular leukomalacia/intraventricular haemorrhage among VLBW infants at Muhimbili National Hospital, Dar-es-Salaam, Tanzania**	**Prospective study with nested case control;** 32.5% prevalence of IVH
Basanayake S, Weerasekere M [11]; 2012	**Incidence of PVH/IVH among premature infants in a tertiary care hospital in Sri Lanka**	**Prospective, descriptive study; Overall IVH incidence 9.5%**
Mulindwa M, Sinyangwe S, Chomba E [15]; 2012	**Prevalence of IVH and associated risk factors in preterm neonates in the NICU at the University Teaching Hospital in Lusaka, Zambia**	**Cross sectional study;** 34.2% prevalence of IVH
Adegoke S, Olugbemiga A [12]; 2014	**Intraventricular Haemorrhage in the new born weighing <1500g**	**Prospective, cross sectional study.** 24.1% incidence of IVH

STUDY JUSTIFICATION

This study evaluated the contribution of periventricular-intraventricular haemorrhage to preterm morbidity and mortality in the context of improved new born care, as the most recent data on the same is from a similar study carried out 27 years ago.

Study Utility

Early screening for PV-IVH allows early diagnosis, as well as gives way for informed counselling by the clinician of parents and caregivers on the clinical course and outcomes – both short term and long term – expected in infants diagnosed with IVH of any grade.

An early diagnosis of IVH also allows for formulation of conclusive follow up plans in lieu of expected complications.

RESEARCH HYPOTHESIS

With the changes in new born care over the last three decades, including availability of NICU care as well as availability of nurses trained in neonatal critical care, it was hypothesised that the incidence of periventricular-intraventricular haemorrhage would have reduced since the last study of the same.

Research Question

What is the incidence, and what are the risk factors associated with the development of periventricular-intraventricular haemorrhage in the very preterm baby admitted to the New Born Unit at Kenyatta National Hospital?

STUDY OBJECTIVES

Primary Objective

To determine the incidence of periventricular-intraventricular haemorrhage in preterm neonates with a gestational age of ≤32 weeks admitted to the new born unit at Kenyatta National Hospital.

Secondary Objective

To describe the risk factors associated with the development of periventricular-intraventricular haemorrhage within the first 7 days of life among the study population.

METHODOLOGY

Study Design

This was a cohort study.

Study Area

Patients were recruited from within the new born unit at Kenyatta National Hospital (KNH). KNH is the largest and oldest public, tertiary referral hospital in Kenya, with a total bed capacity of 2000. The hospital is located immediately west of the Upper Hill business hub in the capital city Nairobi. The NBU is housed on the first floor of the hospital and it sees a total of about 400 admissions monthly. Of these, about 70% are preterm babies, and among these, about two thirds are admitted with birth weights of ≤1500g. Within the NBU are smaller rooms into which infants are admitted according to their various weight categories or depending on need for ICU care. These are the NICU, Neonatal High Dependency Unit (NHDU), B1 and B2 (housing very preterm infants), B3 (housing LBW/late preterm infants, up to ~2000g), Isolation room, and kangaroo mother care (KMC) rooms.

At capacity, these nurseries can hold up to 40 infants each. Within these nurseries are facilities for oxygen supplementation (via CPAP, non-rebreather masks or nasal prongs). The NICU has a bed capacity of 6 and at full functionality can facilitate the mechanical ventilation of up to 6 infants. CPAP is also available and is mainly provided in the NICU setting. Very preterm infants may be admitted to the NICU for mechanical ventilation or to receive CPAP depending on availability of either of the two. Each nursery within the NBU is allocated 2 specialist nurses trained in neonatal care. Nurses stationed in the NICU are also trained in neonatal critical care.

Study participants were recruited from within nurseries B1, B2 and the NICU.

Study Population

Included in the study were 195 preterm neonates born at ≤32 weeks and admitted to the new born unit at Kenyatta National Hospital at birth or within 72 hours of life.

Inclusion Criteria

Included in the study were preterm infants with a gestational age of ≤32weeks admitted to the unit within 72 hours of life, and for whom documented (written) informed consent from mothers or primary caregivers was obtained.

Exclusion Criteria

Neonates with gross central nervous system malformations, those admitted after 72 hours of life and those for whom informed consent was denied were not included in the study.

Sample Size and Sampling Methods

The sample size was calculated using a simple formula for sample size determination in incidence studies (*Daniel, 1999)* [20], thus:

$$n = \frac{Z^2 P(1-P)}{d^2} = \frac{1.96^2 \times 0.2\ (1-0.2)}{0.06^2} \approx \mathbf{195}$$

Where:

- n = sample size
- Z = normal standard deviation taken with a 95% confidence interval, set at 1.96
- P = expected prevalence of PV-IVH in study population, estimated at 24%
- d = study precision, taken at 6%

Study Tools

All the data collected was entered into a customised data collection form (appendix VIII) for ease of analysis.

Study Variables

These included such exposures as need for mechanical ventilation, maternal use of antenatal steroids, patient age, gender, birth weight etc. as outlined above under the discussion on risk factors. These were then related to the main outcome – PV-IVH – and analysed appropriately.

Study Outcomes

The main study outcome was the observation of any grade of PV-IVH following cranial (trans-fontanelle) ultrasonography.

Study Period

November 2017 to February 2018.

DATA COLLECTION

Patient Recruitment Procedure

Preterm babies were recruited by consecutive sampling from the NBU at Kenyatta National Hospital, until the target sample size was achieved. This was done by the principal investigator. Neonates meeting the eligibility criteria were identified through perusal of the NBU 'Admission Book', as well as through perusing files of those already admitted to the unit and undergoing management either in the NICU or in Nurseries B1 and B2. Some were recruited at admission to the new born unit. Following this, the investigator approached parents/primary caregivers and obtained written, voluntary and informed consent. Consenting took place either during the admission process for those presenting at the unit for the first time, and in between feeding time for those already admitted to the unit.

A pre-designed consent form (appendix III-VI) was administered to the parents/primary caregivers of eligible patients, to document the informed consent. This consent form had a concise description of the study, detailing the study procedure as well as the benefits and risks of participating in the study. A discussion between the principal investigator and the parent/primary caregiver took place to ensure that the caregiver fully understood all information provided within the consent form. At this point, all queries regarding contents of the consent form were addressed by the principal investigator. Obtained consent was completely voluntary, and free of coercion.

Once consent was given, data collection commenced among the selected participants. All relevant data was obtained from both the patients and their parents/primary caregivers. Mothers were interviewed as much as was possible to ascertain such historical aspects as maternal age and gravidity, presence or absence of preterm/premature rupture of membranes, presence or absence of maternal comorbidities (hypertension, diabetes mellitus, HIV), mode of delivery, and use of antenatal steroids.

Patients' inpatient files were perused and data on patients' gestational age, birth weight, head circumference and results of laboratory investigations relevant to this study obtained. PDA was only recorded as being present in those patients who had an echocardiogram performed by the hospital paediatric cardiologist confirming diagnosis. Records of working diagnoses and management that the patients were undertaking at the time of data collection were also kept.

For all patients admitted to the NBU, birth weight was measured using a SECA 354 weighing scale, with the baby laying on the weighing scale while unclothed, after resetting the scale. Weight was measured to the nearest 0.05g, as per the weighing scale setting, and documented appropriately. Following this, the principal investigator undertook an assessment of gestational age using the new Ballard score [21], after which a cranial ultrasound was performed. In the event that gestation as recorded using last normal menstrual period versus that determined by clinical assessment (new Ballard score) had a disparity of 2 or more weeks, gestational age was taken as that obtained through clinical assessment. For all participants, cranial ultrasonography was performed initially within 72 hours of life, and then at 7 days of life using a portable ultrasound machine (Siemens® 'ACUSON P500 Ultrasound System, FROSK Edition'.)

Sonography was done via the anterior fontanelle, in the coronal and sagittal planes using a 5-7MHz (megahertz) curvilinear transducer. Anterior, mid and posterior coronal plane images were obtained by swiping the ultrasound probe in a fronto-occipital and then an occipito-frontal direction. Mid sagittal and bilateral (right and left) parasagittal plane images were obtained by swiping the probe right to left, then left to right at the midline. All ultrasounds were carried out using these standard techniques, and any observed haemorrhage was recorded in the described planes.

The cranial ultrasounds were done by the principal investigator, after undergoing training on the same under the supervision of a qualified radiologist. Training was undertaken over a 2-week period before the study commenced; initial ultrasounds were performed under supervision of a qualified radiologist. All images obtained were saved on a flash drive and presented to a blind panel of at least three radiologists (all with at least 3 years post-qualification experience) for verification and validation of findings. Confirmed diagnosis was then entered into the predesigned data collection tool (appendix VIII)

DATA MANAGEMENT AND ANALYSIS

Data was entered into customised Microsoft Access® database and analysed using STATA® software. Descriptive univariate analysis was used to summarise the sample characteristics. Both maternal and new born demographic characteristics measured using continuous variables such as gestational age and birth weight were summarised using a measure of central tendency (either mean or median) and a measure of variation (either SD or range) depending on whether the data showed a normal or skewed distribution. For categorical variables including presence or absence of specific maternal or neonatal conditions, frequencies were reported along with percentages. The dependent variable was calculated by counting all neonates with radiological evidence of PV-IVH, using this as a numerator in calculating incidence of the same.

To determine factors associated with PV-IVH and categorical variables, bivariate cross tabulation for each factor versus PV-IVH incidence was conducted and the Chi square test for independence performed. Bivariable associations between numerical variables and PV-IVH was analysed using the student t test. Statistical significance was determined using a p value of 0.06. Multivariable logistic regression analysis was then conducted with PV-IVH incidence as the dependent variable and all the covariates showing significant associations in the bivariate analysis as independent variables. Findings were then summarised using tables and charts.

ETHICAL CONSIDERATIONS

1. Permission to collect and analyse data for this study was sought from the Kenyatta National Hospital/University of Nairobi Ethics, Research and Standards Committee, through submission of a copy of the proposal to pursue this research as well as all study tools used for purposes of this research. Written approval to continue with the study was filed in November 2017 (Ref: KNH-ERC/A/345).
2. There were no modifications to the study protocol affecting the patient's volition to take part in the study, the intent of the study, and/or patient safety.
3. The purpose of the study was carefully explained to the parents or primary caregivers of the patients under study with a view of obtaining informed, written consent prior to recruiting any child to the study.
4. No experimental investigations or products were employed in this study. Cranial ultrasound scans were performed on each participant. These were non-invasive and pose no acute or long-term risks to the participants.
5. Participants accrued the added benefit of routine screening for PV-IVH, as is the standard of care internationally. They were also educated on the condition, and they received early counselling and preparation for adverse effects of the same.
6. Strict confidentiality was observed throughout the entire study period, held in trust by participating investigators, research staff and the study institutions. The study participants were assigned study identification numbers and no personal identification data was recorded.
7. No information concerning the individual study findings will be released to any unauthorized third party without prior written approval of the study institution and/or the Ethics, Research and Standards Committee.

RESULTS

Sample Characteristics

Infant characteristics

The study recruited a total of 195 neonates born at ≤32 weeks and admitted to the NBU at KNH within 72 hours of birth. The mean age at the time of recruitment was 2 days (SD ± 0.8), with 72 (37%) neonates recruited on the day of delivery (Table 3). There were 99 (51%) males giving a male to female ratio of approximately 1:1. Out of the 195 neonates, there were 126 (65%) VLBW babies and 26 (13%) ELBW babies. The median gestation ages (IQR) were 31 weeks (29-32) and 32 weeks (29-32) based on the Ballard score and gestation by estimated date of delivery (EDD), respectively.

Of the 195 recruited neonates, 51 (26.2%) died before reaching day 7 of life. They however were not followed to autopsy. Therefore, a total of 144 neonates were followed up to day 7 of life and received 2 cranial ultrasounds within this period.

Table 3: Characteristics of VLBW or Preterm Neonates Admitted to KNH NBU

	Frequency (%)
Age on admission	
Day 1	72 (37)
Day 2	54 (28)
Day 3	69 (35)
Gender	
Male	99 (51)
Female	96 (49)
Birth weight	
ELBW (≤1000 g)	26 (13)
VLBW (≤1500g)	169 (87)
Median gestation age	
Ballard score*	31 (IQR 29 to 32)

Maternal Characteristics

The mean age of mothers was 29.9 years (SD ±5.8) with a range between 20 and 44 years. Of these mothers 73 (37%) were aged 25 to 29 years (Table 4). Ninety-three (48%) of records contained details on the number of antenatal clinic visits and 31 (16%) indicated that an obstetric ultrasound was done while 124 (64%) indicated no obstetric ultrasound was performed. Hypertension and gestational diabetes occurred in 58 (30%) and 3 (2%) of mothers, respectively. There were 17 (9%) HIV positive mothers. Antenatal steroids were administered in 7 (4%) of the mothers.

Table 4: Characteristics of mothers with VLBW or Preterm Neonates Admitted to NBU, KNH

	Frequency (%)
Maternal age	
20-24 years	30 (15.4)
25-29 years	73 (37.4)
30-34 years	56 (28.7)
≥35 years	36 (18.5)
Antenatal Steroids Given	7 (4)
Hypertension	58 (30)
VDRL Positive	7 (4)
HIV Positive	17 (9)
Gestational Diabetes	3 (2)

Incidence of Periventricular-Intraventricular Haemorrhage in Neonates

The overall incidence of periventricular-intraventricular haemorrhage within the first 7 days of life was 8% (95% CI 4 to 12%). The incidence of periventricular-intraventricular haemorrhage of any grade was 4% (95% CI 1 to 7%) within 72 hours, and 5% (2 to 9%) at day 7 follow up. There was no significant difference in incidence of PV-IVH within 72 hours versus at day 7 follow up (McNemar Chi-square P value = 0.248).

Figure 4: Overall Incidence of PV-IVH

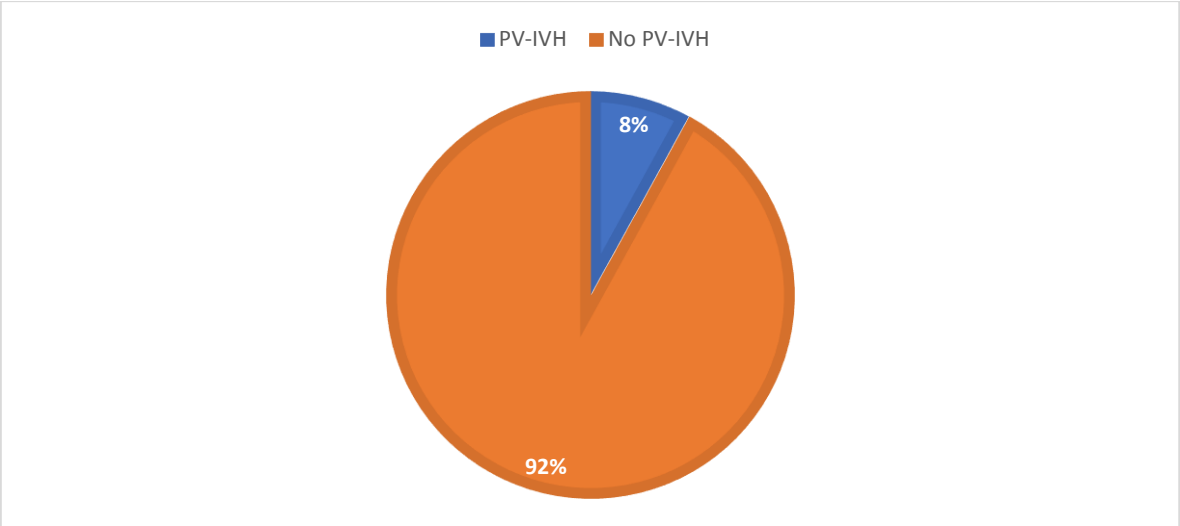
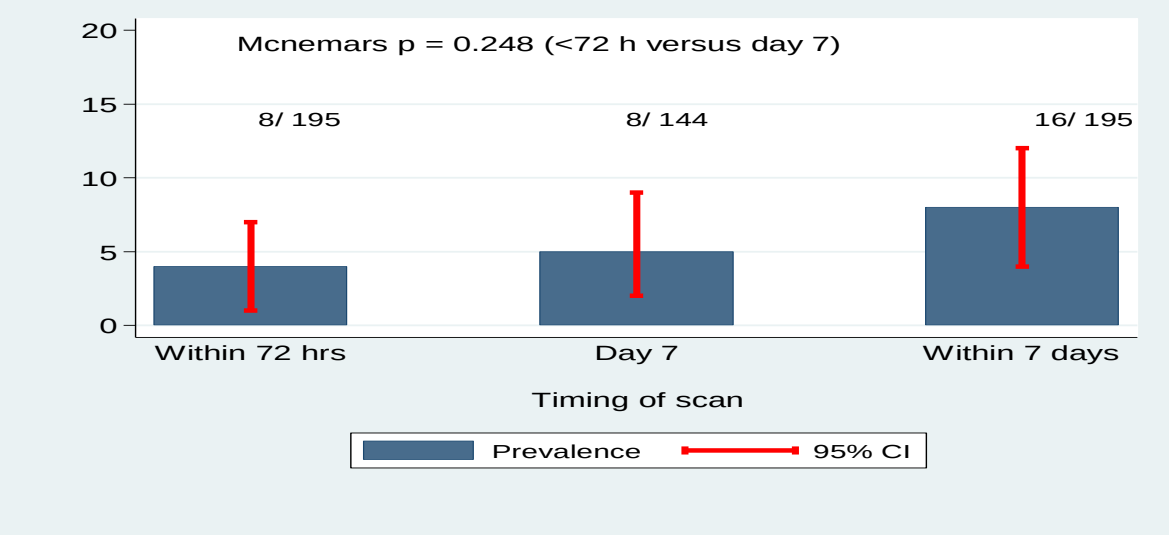


Figure 5: Incidence of PV-IVH at/or within 72 hours, on day 7 and within 7 days



Overall, grade I haemorrhage was seen in 60% while grade II was seen in 40%. Severe forms of PV-IVH were not observed on ultrasound.

Factors Associated with the Development of PV-IVH

The infant factors associated with the development of periventricular-intraventricular haemorrhage within the first 7 days of life were male gender (p = 0.043) and being small for gestational age (p = 0.041), Table 5. Three-quarters of all neonates with PV-IVH were male.

Of the twenty neonates who were small for gestational age, 25% were found to have PV-IVH (p=0.041). There was no significant association between PV-IVH and the remaining infant factors: mode of delivery (p = 0.949), resuscitation at birth (p = 0.108) and presence of PDA (p = 0.06).

Table 5: Infant Factors Associated with PV-IVH

	PV-IVH		
	Yes (n=16)	**No (n=179)**	**P value**
	n (%)	**n (%)**	
Gender			
Male	12(75)	87(49)	0.043*
Female	4(25)	92(51)	
Birth Weight			
≤1000g	0(0)	26(15)	0.102
1000 – 1499g	8(50)	92(51)	0.915
≥1500 g	8(50)	61(34)	0.202
Size for Gestational Age			
Small	4(25)	16(9)	0.041*
Appropriate	12(75)	156(87)	0.178
Large	0(0)	7(4)	0.420
Median gestation (Ballard) *	31 (IQR 32-32)	32 (IQR 29-32)	0.032*
Mode of delivery			
SVD	8(50)	88(49)	0.949
CS	8(50)	91(51)	
Resuscitated at birth			
Yes	12(75)	97(54)	0.108
No	4(25)	82(46)	
Presence of PDA			
Yes	0(0)	33(18)	0.06
No	16(100)	146(82)	

Among the maternal factors, HIV status (p = 0.016) showed significant associations with PV-IVH, table 6. Antenatal steroid administration (p = 0.420), gestational diabetes (p = 0.602), hypertension (p = 0.191) and VDRL (p = 0.420) were not significantly associated with PV-IVH.

Table 6: Maternal Factors Associated with the Development of PV-IVH

	PV-IVH		
	Yes	**No**	**P value**
	n (%)	**n (%)**	
Use of antenatal steroids			
Yes	0(0)	7(4)	0.420
No	16(100)	172(96)	
Hypertensive			
Yes	8(50)	50(28)	0.191
No	8(50)	99(55)	
VDRL			
Yes	0(0)	7(4)	0.420
No	16(100)	172(96)	
HIV			
Yes	4(25)	13(7)	0.016*
No	12(75)	166(93)	
Gestational diabetes			
Yes	0(0)	3(2)	0.602
No	16(100)	176(98)	

Other Factors

There was no evidence of an association between presence of PDA (p = 0.06) or sepsis (p=0.698) and development of PV-IVH. The mean haemoglobin among neonates with PV-IVH was 12g/dl (SD 0.5) compared to 15g/dl (SD 2) in those without PV-IVH (p<0.001), table 7.

Table 7: PDA, Sepsis and Haemoglobin Levels in Neonates with and/or without PV-IVH

	PV-IVH		
	Yes	**No**	**P value**
	n (%)	**n (%)**	
PDA Present			
Yes	0(0)	33(18)	0.06
No	16(100)	146(82)	
Sepsis			
Yes	4(25)	53(30)	0.698
No	12(75)	126(70)	
Mean Infant Haemoglobin (SD)	12 (±0.5)	15 (±2)	<0.001

Severe RDS occurred in 8 (50%) of the neonates with PV-IVH and 32 (18%) of those without (p = 0.005), table 8. Oxygen and continuous positive airway pressure were also more frequently administered in the neonates with PV-IVH (100% and 50%, respectively) as opposed to those without PV-IVH (75% and 15%, respectively), Table 8.

Table 8: Management of RDS in Neonates with and without PV-IVH

	PV-IVH		
	Yes	**No**	**P value**
	n (%)	**n (%)**	
Severe RDS	8(50)	32(18)	0.005*
Oxygen administered	16(100)	114(64)	0.01
Continuous Positive Airway Pressure	8(50)	26(15)	0.001*
Endotracheal tube in situ	0(0)	7(4)	0.407

Multivariate Logistic Regression

A multivariate logistic regression model of PV-IVH as the dependent variable was carried out considering gender, small for gestational age (SGA) status and HIV status. This showed that both gender (p = 0.035) and SGA (p = 0.001) were significantly associated with PV-IVH but HIV status was not (p = 0.072). The odds of PV-IVH among female neonates was 79% lower than in males (OR = 0.12, 95% CI 0.05-0.9), while neonates who were small for gestational age had 13.5 times greater odds of PV-IVH compared to neonates with appropriate or large size for gestational age (OR = 13.5, 95% CI 2.72-67).

Table 9: Multivariate Logistic Regression of Independent Predictors of PV-IVH

	Odds Ratio	95% CI		P value
Male	1.0			
Female	0.21	0.05	0.90	0.035*
Appropriate/ large for gestational age	1.0			
Small for gestational age	13.50	2.72	67.00	0.001*
HIV positive	1.0			
HIV negative	0.29	0.08	1.11	0.072

Attrition

An attrition rate of 26% was observed, which resulted in a 1% loss in precision. The desired precision was 6% but the actual precision after attrition was 7%. A precision of 7% around an incidence of 24%[12] is adequate.

DISCUSSION

Overall incidence of periventricular-intraventricular haemorrhage at any point during the first week of life was found to be 8%, which falls within the range of 7-20% seen in developing nations. [2] This value is significantly lower than that recorded from previous regional studies that found rates of between 24% and 53% [6], [11], [12], [16], and a previous Kenyan study that observed an incidence of 33%. [17] The difference in incidence across the studies, specifically, between this and the older Kenyan study may be attributed to the fact that different populations were studied, and this study did not include follow up to autopsy. There has also been an improvement, overall, in the standard of new born care available at the KNH New Born Unit, and the current study involved minimal manipulation of the study participants (they did not have to be moved to and from the radiology department as was thecase in the previous study), which may have prevented occurrence of or worsening of intraventricular haemorrhage. Frequent handling of preterm babies in the neonatal intensive care setting has been thought to be associated with development of intraventricular haemorrhage. [22]

Incidence of intraventricular haemorrhage of any grade was found to be 4% within 72 hours, and 5% on day 7 follow up. There was no observed difference in likelihood of developing PV-IVH between the first 72 hours, compared to day 7 follow up. This is not in keeping with literature that showed majority haemorrhage taking place within the first 72 hours of life. [6], [15], [16] No specific factor was identified that may explain this finding.

Fifty-one neonates (26.2%) died before a second cranial ultrasound could be performed, giving a survival rate of 73.8% among the study population up to the postnatal age of one week. Clinically, those who died had been on management for severe neonatal sepsis or severe respiratory distress. Seeing as respiratory distress was found to be a significant risk factor for PV-IVH, it is possible that a diagnosis of the same among these was missed, and would possibly have been confirmed had these neonates been followed up to autopsy.

Only grade I (60%) and grade II (40%) haemorrhages were observed in this study. A possible reason for this may be that there was minimal manipulation of these babies throughout the study period, as all scans were performed bedside. Majority of observed PV-IVH was grade I and this is in keeping with previous studies. None of those with grade I PV-IVH progressed to higher grades of PV-IVH by day 7 follow up. All the babies who developed PV-IVH were those categorised as VLBW. None of the recruited ELBW babies developed PV-IVH. There

was thus no significant correlation made between birth weight and development of PV-IVH. All the babies recruited for this study were born between 29 and 32 weeks gestational age. There was no significant difference with regard to PV-IVH development among the entire group given the slight difference in gestational age. As late preterm babies were excluded from this study, a correlation between gestational age and development of PV-IVH was not analysed.

Among the maternal factors analysed, none was found to have a significant correlation with PV-IVH development. Of note, however, was that there was inadequate documentation of maternal factors including antenatal steroid use, comorbidities, and antenatal history. Though initial analysis revealed a potential association of maternal HIV status with PV-IVH, a multivariate regression analysis was able eliminate this as a confounder but the numbers were small. There was inadequate data to analyse antenatal steroid use as a potential protective factor for PV-IVH.

The main factors found to be significant in the causation of PV-IVH from this study were severe respiratory distress syndrome, male gender and small size for gestational age. RDS is a known neonatal factor contributing to PV-IVH development through causing fluctuations in cerebral blood flow. [1], [2], [6], [7] Male gender has previously been reported as an independent risk factor for PV-IVH and has also been found to be related to poor neurological outcome.[23] Preterm babies who are also born SGA have been observed to have an increased risk of IVH compared to those born at appropriate size for gestational age. [24] Occurrence of PV-IVH in the SGA baby has been thought to result from prenatal or intrapartum events superimposed upon decreased supportive tissue in the infant's germinal matrix. PDA and sepsis were not found to be significant risk factors for PV-IVH. Infants with PV-IVH in this study had a lower mean haemoglobin level compared to those without, and this was thought to be more as a result of haemorrhage rather than a contributory factor to the same.

Though there were low numbers observed to have an outcome of PV-IVH, the study has highlighted the importance of prioritised cranial ultrasound screening of the very preterm babies, particularly those with the significant associations described above.

Study Strengths

1. The cranial ultrasounds were performed by the principal investigator, and this ensured standardization of data collection, as there was minimal dependence on others for the same.
2. The scans were carried out within the nursery, at bedside, and this allowed for minimal disturbance of the infant with movement.

Study Limitations

1. Sonography is largely a subjective imaging modality as findings and interpretations of the same are investigator dependent. This limitation was minimised by having the PI doing all the scans and interpretation included at least 3 radiologists with a minimum of 3 years post qualification experience verifying and validating results from obtained images. Cranial ultrasound scans were repeated when needed, based on advice from the consultant radiologists.
2. Relatively high mortality rate among study participants, coupled with lack of follow up to autopsy meant that some cases of PV-IVH may have been missed.
3. A more conclusive analysis of risk factors could not be performed, owing to the low numbers of intraventricular haemorrhage observed.
4. Most of the antenatal and obstetric history was filled from clinic records, which are subject to clerical errors including those of omission.

Recommendations

1. A further prevalence study may be done in follow up to this, possibly including follow up over a longer period of time (at least one month). Noting the high mortality rate as well, it may be worthwhile to include follow up to autopsy in any future study.
2. Preterm babies with severe respiratory distress or those born SGA should be prioritized for cranial ultrasound scanning.

CONCLUSION

1. Overall, the prevalence of periventricular-intraventricular haemorrhage among very preterm babies born at or before 32 weeks gestational age in Kenyatta National Hospital was found to be 8%.
2. Factors found to be significant for PV-IVH were presence of severe respiratory distress syndrome, male gender and being small for gestational age.

DISSEMINATION PLAN OF STUDY FINDINGS

1. The overall study findings will be presented to the academic staff of the Department of Paediatrics and Child Health of the University of Nairobi, in partial fulfilment of the requirements for the award of a Master of Medicine degree in Paediatrics and Child Health.
2. These findings will also be made available to the staff running the new born unit, in a hope to inform policy and practice therein.

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APPENDICES

Appendix I: Proposed Study Timeline

AGENDA	ACTIVITY	TIME PERIOD
1	Proposal development	March – July 2017
2	Proposal submission for ethical approval	Aug 2017
3	Pre-testing	November 2017
4	Data collection	November 2017– February 2018
5	Data analysis	March - May 2018
6	Manuscript writing	July 2018
7	Manuscript submission for publication	August 2018
8	Final thesis submission and defence	October 2018

Appendix II: Study Budget

AGENDA	ACTIVITY	UNIT	UNIT COST (KES)	TOTAL COST (KES)
Proposal Development	Printing draft copies	5	200	1000
	Printing and binding final proposal copies	5	600	3000
Data Collection	Stationery	400	15	6000
	Ultrasound machine	1	-	-
Data analysis	Statistician	1	20000	20000
Manuscript write-up and publishing	Printing drafts	5	1000	5000
	Printing final copies	5	1000	5000
	Final thesis printing and binding	5	2000	10000
	Publication	1	10000	10000
Contingency funds				40000
Total Cost				100000

Appendix III: Consent Information Form

PV-IVH STUDY PARENT/PRIMARY CAREGIVER CONSENT INFORMATION FORM

Study Title: Prevalence and Risk Factors of Periventricular-Intraventricular Haemorrhage in the Very Preterm Baby in the New Born Unit at Kenyatta National Hospital

Principal Investigator: Dr. Bernice N. Mukuria (Resident, Paediatrics)

Supervisors: Prof. Rachel Musoke (Consultant Neonatologist)

Dr. Brian Maugo (Consultant Paediatrician)

Dr. Jasper Muruka (Consultant Radiologist)

Investigator's Statement:

Hello! This is to humbly request the participation of you and your child in a research study which is to take place in the course of your child's admission to the new born unit. The purpose of this document is to provide you with the necessary information that you need in order to decide whether or not you would like to participate. This process is called **informed consent**. Kindly read the consent information carefully, and feel free to ask any questions that may arise.

Introduction:

Periventricular-intraventricular haemorrhage (PV-IVH) is a significant cause of illness and death in the preterm baby. It involves bleeding within the brain and may occur with little or no symptoms. Occasionally, however, it may be diagnosed following sudden deterioration of clinical status in a previously stable baby. Because it may occur without any symptoms, routine screening through brain ultrasound is necessary, and is the accepted standard of care internationally. When severe, bleeding can lead to long term complications including cerebral palsy, seizures, and developmental delay. Non-severe bleeding may resolve without complications.

Study Procedures & Costs:

As part of this study, I wish to perform brain ultrasounds on your child. The first ultrasound will be by the age of 3 days, and the second will be when your child is 7 days old. All this

will be while your child is admitted to the new born unit at the hospital. All the scans will be interpreted by qualified radiologists and will be performed at no additional cost to you.

Benefits of Participation:

The results of the study will be availed to you and your doctor and will be part of the treatment plan for your child.

You and your child will have the added benefit of a concise diagnosis being made in good time.

Findings from this study will be used to inform policy and thus improve practice in the new born unit at Kenyatta National Hospital.

Risks:

There will be no risks imposed on you or your child during the course of this study. There will be no invasive procedures carried out as part of the study.

Voluntariness:

You and your child's participation in the study will be fully voluntary, and you are free to withdraw participation at any point.

Refusal to participate in the study is allowed and is within your rights. This will in no way compromise the care of your child while they are admitted to the new born unit

Confidentiality/Dissemination Plan:

All information obtained regarding your child, yourself and/or your family will be held in strict confidentiality. Specific information regarding you, your child and/or your family will not be released to a third party without your written permission. Overall findings from the entire study will be shared, with no specific reference to individual children and/or their families, with the department of paediatrics and child health as well as the staff of the new born unit. No personal information will be shared to any third party.

Do you have any questions?

Appendix IV: Consent Certificate

Serial Number: _____

I _____have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I am a parent/guardian to _____ and hereby voluntarily consent to our participation in this research.

Parent/Guardian signature: _____ Date: _____

Principal Investigator's signature: _____ Date: _____

Witness' signature: _____ Date: _____

Who to Contact for Questions, Clarifications and Arising Issues:

Should you have any question regarding the study, including results with respect to your child, kindly contact either of the listed persons. Further, should you want to learn more about your rights as a research participant, kindly contact the KNH Ethics, Research and Standards Committee.

Name: Dr. Bernice N. Mukuria (Principal Investigator)
Mobile number: 0733 429 274
Email: bernice_mukuria@hotmail.com

Name: Prof. Rachel N. Musoke
Mobile number: 0721 307 160
Email: rachel.musoke@uonbi.ac.ke

Name: Dr. Brian Maugo
Mobile number: 0727 150 531
Email: brianmaugo@gmail.com

Name: Dr. Jasper Muruka
Mobile number: 0722 642 661
Email: jaspermuruka@gmail.com

Kenyatta National Hospital/University of Nairobi Ethics & Research Committee
College of Health Sciences
P. O. Box 19676-00202, Nairobi
Tel.: (+254 20) 2726300-9, Ext. 44355
Email: uonknh_erc@uonbi.ac.ke

Appendix V: Consent Form (Kiswahili)

UTAFITI JUU YA PV-IVH / FOMU YA RUHUSA (YA KUJAZWA NA MZAZI)

Nambari ya Kitambulisho cha Mgonjwa: _____

Tarehe: _____

Kichwa cha Utafiti: Prevalence and Risk Factors of Periventricular-Intraventricular Haemorrhage in the Very Preterm Baby in the New born Unit at Kenyatta National Hospital

Mtafiti Mkuu: Dk. Bernice N. Mukuria (Mkazi, Matibabu)

Wasimamizi: Profesa Rachel Musoke (Mshauri wa Neonatologist)

Dk. Brian Maugo (Mtaalamu wa Daktari wa watoto)

Dk. Jasper Muruka (Radiologist Mshauri)

Taarifa ya Mpelelezi:

Hujambo! Hii ni kwa unyenyekevu kuomba ushiriki wenu na mtoto wako katika utafiti ambao utafanyika wakati wa kuingia kwa mtoto wako kwenye wodi ya watoto wachanga KNH. Madhumuni ya waraka huu ni kukupa habari muhimu unayohitaji ili uamue kama ungependa kushiriki. Utaratibu huu unaitwa kibali cha idhini. Tafadhali soma habari ya ridhaa kwa uangalifu, na usikie huru kuuliza maswali yoyote ambayo yanaweza kutokea.

Utangulizi:

Periventricular-intraventricular haemorrhage (PV-IVH) ni sababu kubwa ya ugonjwa na kifo katika mtoto wa awali. Inahusisha kutokwa na damu ndani ya ubongo, na inaweza kutokea kwa dalili kidogo. Mara kwa mara, hata hivyo, inaweza kupatikana baada ya kuzorota kwa ghafla kwa hali ya kliniki katika mtoto aliyekuwa tayari imara. Kwa sababu inaweza kutokea bila dalili yoyote, uchunguzi wa kawaida kupitia ultrasound ya ubongo pamoja na mitihani kadhaa ni muhimu, na ni kiwango cha kukubalika cha huduma duniani kote. Wakati mkali, kutokwa na damu kunaweza kusababisha matatizo ya muda mrefu ikiwa ni pamoja na kupooza kwa ubongo, kifafa, na kuchelewa kwa maendeleo. Makundi yasiyo ya kali ya kutokwa damu yanaweza kutatua bila matatizo.

Faida za Ushiriki:

Matokeo ya utafiti utafanywa kwako na daktari wako.

Wewe na mtoto wako mtakuwa na manufaa ya ziada ya uchunguzi mkali unaofanywa kwa wakati mzuri.

Matokeo kutoka kwa utafiti huu yatatumika kuwajulisha sera na hivyo kuboresha mazoezi katika kitengo kichanga katika Hospitali ya Taifa ya Kenyatta.

Hatari:

Hakutakuwa na hatari zilizowekwa kwako au mtoto wako wakati wa utafiti huu. Hakutakuwa na taratibu za uvamizi zinazofanyika kama sehemu ya utafiti.

Hiari:

Wewe na ushiriki wako katika utafiti huu utakuwa kikamilifu kwa hiari, na uko huru kujiondoa ushiriki wakati wowote.

Kukataa kushiriki katika utafiti huu hakutakabiliana na huduma ya mtoto wako wakati anapougua kwenye kitengo cha watoto

Usiri:

Taarifa zote zinazopatikana kuhusu mtoto wako, na familia yako utafanyika kwa siri kali. Maelezo maalum kuhusu wewe, mtoto wako na / au familia yako haitatolewa kwa mtu wa tatu bila idhini yako iliyoandikwa. Hata hivyo, matokeo ya jumla kutoka kwa utafiti wote yatajadiliwa, bila kumbukumbu maalum kwa watoto binafsi na / au familia zao.

Je, una swali lolote?

Appendix VI: Consent Certificate (Kiswahili)

Namba ya Serial: _____

Mimi _____nimesoma habari hii iliyotangulia, au imesomezwa. Nimekuwa na fursa ya kuuliza maswali kuhusu hilo na maswali yoyote niliyoyauliza yamejibiwa kwa kuridhika kwangu. Mimi ni mzazi / mlezi kwa _____ na hapa ninakubali kwa hiari kushiriki katika utafiti huu.

Saini ya Mzazi / Mlezi: _____ Tarehe: _____

Saini ya Mpelelezi Mkuu: _____ Tarehe: _____

Wa Kuwasiliana nao kwa Maswali, Ufafanuzi, na Matatizo Yanayotokea: Wakati utakapokuwa na swali lolote kuhusu utafiti, ikiwa ni pamoja na matokeo kwa kuheshimiana na mtoto wako, wasiliana kwa yeyote aliyetajwa. Zaidi, ungelipenda kujifunza zaidi kuhusu haki zako kama mshiriki wa utafiti, wasiliana kwa uangalifu na Kamati ya Maadili, Utafiti na Viwango vya KNH.

Jina: Dr. Bernice N. Mukuria (Mtafiti Mkuu)
Nambari ya simu: 0733 429 274
Barua pepe: bernice_mukuria@hotmail.com

Jina: Prof. Rachel N. Musoke
Nambari ya simu: 0721 307 160
Barua pepe: rachel.musoke@uonbi.ac.ke

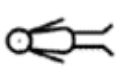
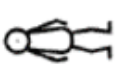
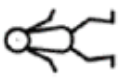
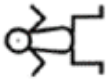
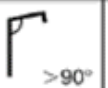
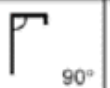
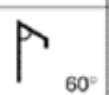
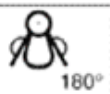
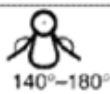
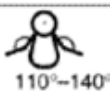
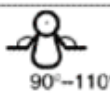
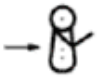
Jina: Dr. Brian Maugo
Nambari ya simu: 0727 150 531
Barua pepe: brianmaugo@gmail.com

Jina: Dr. Jasper Muruka
Nambari ya simu: 0722 642 661
Barua pepe: jaspermuruka@gmail.com

Kenyatta National Hospital/University of Nairobi Ethics & Research Committee
College of Health Sciences
P. O. Box 19676-00202, Nairobi
Tel.: (+254 20) 2726300-9, Ext. 44355
Email: uonknh_erc@uonbi.ac.ke

Appendix VII: New Ballard Score Sheet

Neuromuscular Maturity

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

Physical Maturity

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 anterior ⅔	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled 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	Clitoris prominent, small labia minora	Clitoris prominent, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

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

Appendix VIII: Data Collection Tool

Study Title: Prevalence and risk factors for the development of periventricular-intraventricular haemorrhage in the very preterm neonate admitted to the new born unit at Kenyatta National Hospital

Instructions:

Thank you for agreeing to be a part of this study!

This form is to be filled as part of the study referenced above, through interviews with the mothers/caregivers, perusal of inpatient files, and performance of cranial ultrasound.

Kindly fill in **all** the blank spaces.

Any additional information is to be filled in the remarks section at the end of this document.

Any details that can be used to identify patients or their parents/caregivers explicitly/specifically shall not be entered into this form.

PARTICIPANT IDENTIFICATION NUMBER (PIN)			
DATE (dd/mm/yy)			
SECTION I: INFANT DETAILS			
DATE OF BIRTH (dd/mm/yy)		**DATE OF ADMISSION (dd/mm/yy)**	
AGE (days)		**GENDER**	**[ ] Male** **[ ] Female**
BIRTH WEIGHT (g)		**CURRENT WEIGHT (g)**	
GESTATIONAL AGE BY DATES (weeks)			
ESTIMATED GESTATIONAL AGE (Ballard Score)			
SIZE FOR GESTATIONAL AGE		**Small [ ] Appropriate [ ] Large [ ]**	
MODE OF DELIVERY		**SVD [ ] C/S [ ] BREECH [ ] VACUUM [ ]**	
RESUSCITATION AT BIRTH		**YES [ ] NO [ ]**	

PRESENCE OF PDA		**YES [ ] NO [ ]**	
SECTION II: MOTHER'S DETAILS			
AGE (years)			
NUMBER OF ANC VISITS		**OBSTETRIC U/S DONE?**	**YES [ ]** **NO [ ]**
LMP (dd/mm/yy)		**USE OF ANTENATAL STEROIDS**	**YES [ ] NO [ ]**
EDD (dd/mm/yy)			
Haemoglobin (g/dL)		**HYPERTENSION**	**YES [ ] NO [ ]**
VDRL	**POSITIVE [ ] NEGATIVE [ ] NOT DONE [ ]**		
HIV	**POSITIVE [ ] NEGATIVE [ ] NOT DONE [ ]**		
GESTATIONAL DIABETES		**YES [ ] NO [ ]**	
SECTION III: IMAGING			
AGE AT 1ST US SCAN (days)		**1 [ ] 2 [ ] 3 [ ]**	
HEAD CIRCUMFERENCE (cm)			
WORKING DIAGNOSIS			
ADDITIONAL DIAGNOSES			
IVH SEEN?	**YES [ ] NO [ ]**	**If yes, what grade?**	**1 [ ] 2 [ ] 3 [ ] 4 [ ]**
Treatment			
2nd US SCAN – DAY 7			
HEAD CIRCUMFERENCE (cm)			

WORKING DIAGNOSIS			
ADDITIONAL DIAGNOSES			
IVH SEEN?	**YES [ ] NO [ ]**	**If yes, what grade?**	**1 [ ] 2 [ ] 3 [ ] 4 [ ]**
Treatment			
SECTION IV: CLINICAL INFORMATION			
ON OXYGEN? **If yes, duration?** **(days)**	**YES [ ] NO [ ]**	**PDA PRESENT?**	**YES [ ] NO [ ]**
ON CPAP? **If yes, duration?** **(days)**	**YES [ ] NO [ ]**	**SEPSIS?**	**YES [ ] NO [ ]**
ETT IN SITU? **If yes, duration?** **(days)**	**YES [ ] NO [ ]**	**SEVERE RDS?**	**YES [ ] NO [ ]**
Mean Haemoglobin (g/dL)			
Remarks			

Appendix IX: Radiology – Quality Assurance Protocol

KENYATTA NATIONAL HOSPITAL PROCEDURE FOR ULTRASOUND (Source – Radiology Department, Kenyatta National Hospital)

1. **Scope**

The procedure is carried out on patients who require diagnostic ultrasound examination using ultrasound machine, covers scans of cranium, abdomen, blood vessels, endo-cavitary, neck, breast, scrotum, musculoskeletal, any other soft tissues and intervention procedures.

2. Purpose

To perform highly quality sonographic examination on the requested examination for diagnostic purpose.

3. Terms & Definitions

3.1 Ultrasound – is a non-ionising radiation imaging procedure using high frequency sound waves.

4. Responsibilities

The radiologist/sonographer on behalf of the head of department shall ensure that the ultrasonography procedures are carried out as stipulated and the reports shall be of high diagnostic quality.

5. Method

5.1 Medical Records personnel shall:

5.1.2 Receive the ultrasound request from the patient

5.1.3 Give the patient appointment date based on the patient clinic date or urgency or take the request to the sonographer/radiologist for emergency counter signature and booking.

5.1.4 Give the patient appropriate preparation needed for the ultrasound examination requested (full bladder for pelvic scan and starving for abdominal scan)

5.1.5 Inform the patient about the cost of the examination

5.1.6 The medical officer shall charge on the patient's charge sheet in the patient's file for in patients (ward patients)

5.2 On the day of appointment the patient shall:

5.2.1 Go to the cashier's office to pay for the examination requested

5.2.2 Go to the records desk for registration

5.2.3 Wait in designated ultrasound room/waiting area according to the requested ultrasound examination

5.3 The radiographer shall:

5.3.1 Prepare the room, machine and the accessories needed for scanning

5.3.2 Provide gown for the patient to change when necessary depending on the examination

5.3.3 Instruct the patient on what to do and confirm the patients' preparedness

5.3.4 Explain the procedure to the patient

5.3.5 Scan the patient and consult the radiologists for an opinion on difficult cases

5.3.6 Write the reports after the examination and take it to the secretary for typing in urgent cases or give to the medical officer to receive or take it for typing. In the absence of typist, a carbon copy report written.

5.3.7 Release the patient with instruction on how and where to collect the report depending on the urgency or whether the patient is from clinic or ward patient, accordingly.

5.4 The radiologist shall:

5.4.1 Confirm the patient and the examination requested

5.4.2 Change the patient if necessary depending on the examination

5.4.3 Explain the procedure to the patient

5.4.4 Do intervention procedures

5.4.5 Do all Doppler procedures

5.4.6 Assist the sonographer on difficult cases

5.4.7 Write the reports and take for typing or write on carbon copy in absence of a typist

5.5 The radiology nurse shall:

5.5.1 Book the patient for intervention procedure

5.5.2 Explain to the patient the preparation instructions and the cost of the examination

5.5.3 On the examination day, the nurse prepares a trolley for the intervention procedure

5.5.4 Assists the radiologist during procedure

5.5.5 Takes nursing care of the patient during and after the procedure

5.6 The secretary shall:

5.6.1 Type the draft hand-written report

5.6.2 Take the report for proof reading and signing to the person who wrote the report for emergency cases or takes it to the medical record officer

5.6.3 The proof-read report is then taken to the medical record officer for dispatch to the appropriate clinic, ward or requesting doctor

5.7 The medical records shall:

5.7.1 Dispatch the report to the patient or keep in safe custody at the records department

5.7.2 Coordinate the dispatch of reports for delivery to outpatient or out station

5.7.3 Ensure accurate recording and dispatch of the reports delivery from radiology department

6. References

R. C. RUMARE

Appendix X: Ethical Approval Letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/345

8th November, 2017

Dr. Bernice N. Mukuria
Reg. No. H58/81401/2015
Department of Paediatrics and Child Health
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mukuria,

REVISED RESEARCH PROPOSAL – PREVALENCE AND RISK FACTORS FOR DEVELOPMENT OF PERIVENTRICULAR-INTRAVENTRICULAR HAEMORRHAGE IN THE VERY PRETERM BABY ADMITTED TO THE NEW BORN UNIT AT KENYATTA NATIONAL HOSPITAL (P452/08/2017)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above proposal. The approval period is from 8th November 2017- 7th November 2018.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
d) Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

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