# INTRAVENTRICULAR HAEMORRHAGE: PREVALENCE AND RISK FACTORS IN BABIES BORN WITH GESTATIONAL AGE LESS THAN 32 WEEKS IN MALAYSIAN NATIONAL NEONATAL REGISTRY

**(2008 – 2011)**

**ASMA ABOLGASIM ELMAHDI IBRAHIM**

**UNIVERSITI SAINS MALAYSIA**

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**By**

**ASMA ABOLGASIM ELMAHDI IBRAHIM**

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## ABBREVIATIONS

| | |
|---|---|
| 3D US | 3-dimension ultrasound |
| ADH | Antidiuretic hormone |
| AGA | Appropriate gestational age |
| APC | Activated Protein C |
| BPD | Bronchopulmonary dysplasia |
| CA | Chorioamnionitis |
| CBF | Cerebral blood flow |
| CBV | Cerebral blood volume |
| CMV | Conventional Mandatory Ventilation |
| CP | Cerebral palsy |
| CRC | Clinical Research Centre |
| CSF | Cerebral spinal fluid |
| CUS | Cranial ultrasound |
| EC | East Coast Malaysia |
| ELBW | Extremely Low Birth Weight |
| EM | East Malays |
| EOS | Early onset sepsis |
| GA | Gestational age |
| GDM | Gestational diabetes mellitus |
| GIT | Gastrointestinal tract |
| HFOV | High frequency oscillatory ventilation |
| IVH | Intraventricular haemorrhage |
| LBW | Low birth weight |
| LGA | Large gestational age |
| LOS | Late onset sepsis |
| MNNR | Malaysia National Neonatal Registry |

| | |
|---|---|
| MRI | Magnetic Resonance Imaging |
| nCPAP | Nasal Continuous Positive Airway Pressure |
| NEC | Necrotizing enterocolitis |
| NICUs | Neonatal Intensive Care Units |
| PDA | Patent ductus arteriosus |
| PEEP | Positive end-expiratory pressure |
| PROM | Premature rupture of the membranes |
| PVL | Periventricular leukomalacia |
| RDS | Respiratory distress syndrome |
| ROP | Retinopathy of prematurity |
| SGA | Small gestational age |
| SPSS | Statistical Package for Social Sciences |
| VLBW | Very low birth weight |
| WC | West Coast Malaysia |
| WHO | World Health Organization |

PENDARAHAN INTRAVENTICULAR: KADAR KELAZIMAN DAN FAKTOR RISIKO DI KALANGAN BAYI YANG DILAHIRKAN PADA USIA KANDUNGAN KURANG DARI 32 MINGGU DI DALAM MALAYSIAN NEONATAL REGISTRY (2008 -2011)


## ABSTRAK

**Pengenalan**

Pendarahan dalam ventrikel otak adalah merupakan salah satu penyebab utama kecacatan neurologi di kalangan bayi pramatang dan menyumbang kepada kematian dan kesan jangkapanjang. Tujuan utama kajian ini adalah untuk menentukan kadar kelaziman dan faktor-faktor yang berkaitan dengan masalah pendarahan dalaman ventrikel di kalangan bayi yang dimasukkan ke unit rawatan rapi neonatal yang didaftarkan di Pendaftar Neonatal Kebangsaan di Malaysia (Malaysian Neonatal Registry) dari 2008 – 2011.

**Objektif:**

**Objektif umum:**

Untuk menentukan kadar kelaziman masalah pendarahan dalaman ventrikel otak dan faktor-faktor berkaitan di kalangan bayi pramatang di Malaysia.

**Objektif spesifik:**

Untuk menentukan kadar perubahan pada pemeriksaan ultrasonografi kranium dari tahun 2008 hingga 2011.

Untuk menentukan kadar kelaziman secara keseluruhan masalah pendarahan dalaman ventrikel otak di hospital-hospital yang berdaftar dengan Pendaftar Neonatal Kebangsaan di Malaysia dari tahun 2008 hingga 2011.

Untuk membandingkan kadar masalah pendarahan dalam ventrikel di antara hospital yang berdaftar dengan Pendaftar Neonatal Kebangsaan daripada tahun 2008 hingga 2011.

Untuk menentukan faktor-faktor risiko berkaitan yang menyebabkan pendarahan dalaman ventrikel otak di kalangan bayi pramatang yang lahir pada usia kandungan kurang daripada 32 minggu yang dimasukkan ke unit rawatan rapi neonatal di Malaysia daripada 2008 hingga 2011.

**Kaedah Kajian:**

Kaedah yang digunakan adalah kajian lintang. Data daripada 36 buah hospital di Malaysia yang berdaftar dengan Pendaftar Neonatal Kebangsaan dari tahun 2008 hingga 2011 telah dianalisis menggunakan pengkalan data elektronik. Kriteria kemasukan ke dalam kajian adalah bayi yang lahir pada umur kandungan kurang daripada 32 minggu dan berat semasa lahir adalah kurang 1500 gram. Pranatal, cara kelahiran dan perkara yang berlaku semasa neonatal dianalisis. Ultrasonografi kranium adalah cara yang digunakan untuk memastikan diagnosa pendarahan dalam ventrikel. Data telah dimasukkan dan dianalisis menggunakan perisian SPSS versi 22.0. Data mengikut kategori telah diterjemah dalam bentuk frekuensi, peratusan dan pembandingan telah dilakukan menggunakan *chi-square test*. Tahap signifikan yang digunakan adalah nilai $p<0.05$. Analisi deskriptif telah digunakan untuk menentukan kadar kelaziman pendarahan dalam ventrikel di kalangan bayi pra-

matang. Analisis regrasi mudah dan berganda telah digunakan untuk menentukan faktor-faktor penyumbang kepada masalah ini.

**Hasil Dapatan Kajian:**

Jumlah bayi yang telah menyertai kajian adalah 10927 dan kadar kelaziman masalah pendarahan dalaman ventrikel otak secara keseluruhan bagi bayi yang telah menjalani pemeriksaan ultrasonografi kranium adalah 39.5%. Secara keseluruhan, 85.4% bayi yang terlibat telah menjalani pemeriksaan ultrasonografi kranium ini. Peratusan mengikut tahap keseriusan perdarahan adalah Tahap I sebanyak 13.7%, Tahap II adalah 12%, Tahap III adalah 8.7% dan Tahap IV adalah 4.9%. Tahap yang serius (Tahap III dan IV) adalah tinggi di kalangan bayi yang lahir pada umur kandung antara 22 hingga 25 minggu (32.7%) dan berat semasa lahir di antara 500 hingga 750 gram (29.7%).

Kadar kelaziman mengikut lokaliti hospital pula adalah 40% di hospital-hospital yang terletak di Malaysia Timur, 38% di Pantai Barat Semenanjung Malaysia dan 36% di Pantai Timur Semenanjung Malaysia, dengan nilai $p>0.05$.

Analisis regrasi berganda menunjukkan umur kandungan yang kurang matang, kurang berat masa kelahiran, ventilasi secara konvensional, HFOV, pneumothorax, PDA, NEC dan infeksi merupakan pembolehubah tidak bersandar yang signifikan yang berhubungkait dengan masalah pendarahan dalaman ventrikel.

**Kesimpulan:**

Kadar kelaziman pendarahan dalaman ventrikel di kalangan bayi pra-matang yang terlibat dengan kajian ini adalah 39.5%. Umur kandungan yang kurang matang,

kurang berat semasa lahir, ventilasi secara kovensional, HFOV, pneumothorax, PDA, NEC, nCPAP, ibu berpenyakit kencing manis dan infeksi boleh dikira sebagai faktor utama penyebab kepada masalah ini berlaku.

INTRAVENTRICULAR HAEMORRHAGE: PREVALENCE AND RISK FACTORS IN BABIES BORN WITH GESTATIONAL AGE LESS THAN 32 WEEKS IN MALAYSIAN NATIONAL NEONATAL REGISTRY (2008 – 2011)

# (2008 – 2011)

## ABSTRACT


### Introduction

Intraventricular haemorrhage (IVH) is a major cause of neurological disabilities in prematures babies, an important cause of mortality and long-term morbidity. This study aimed to determine the prevalence and factors associated with IVH among Malaysian neonates admitted to neonatal intensive care units (NICUs) which participated in Malaysian National Neonatal Registry (MNNR) from 2008-2011.

### Objective

**General objective:**

To determine the prevalence of IVH and associated risk factors among premature babies in Malaysia.

**Specific objective:**

To determine the overall prevalence of IVH in hospitals participated in the MNNR from 2008-2011.

To compare the prevalence of IVH between the hospitals participated in the MNNR from 2008-2011.

To determine the associated risk factors of IVH among preterm infants < 32 weeks admitted to Malaysian NICUs from 2008-2011

To determine the changes in cranial ultrasound (CUS) performed from 2008-2011.

**Methods:**

This was a cross sectional study. Data from 36 Malaysian hospitals participated in MNNR 2008-2011 electronic database was analysed. The inclusion criteria included neonates with gestational age (GA) < 32 weeks and birth weight (BW) ≤ 1500 grams. Prenatal, delivery characteristic and neonatal events were analysed. Cranial ultrasonography (CUS) was the modality to diagnose IVH. Data entry and analysis conducted using SPSS for window version 22.0. Categorical data were expressed in frequency, percentage, and comparison made using the chi-square test. The level of significance used was $p < 0.05$. Descriptive analysis was done to determine the prevalence of IVH among premature babies. Simple and multiple logistic regression analysis were used to determine the associated factors of IVH.

**Results:**

The total babies recruited were 10927 and the prevalence of IVH (overall) in babies whom CUS performed was about 39.5%. Overall, CUS was performed in 85.4% babies. Grade I IVH was 13.7%, Grade II was 12%, Grade III was 8.7% and

Grade IV was 4.9%. The prevalence of severe IVH (grade III & IV) was highest in the smallest groups i.e. the GA group 22 - 25 weeks (32.7%) and BW group 500 – 750gram (29.7%). Prevalence of IVH in East Malaysia hospitals was 40%, West Coast hospitals were 38% and East Coast hospitals was 36 %, $p > 0.05$.

Multiple logistic regression analysis showed that lower GA, lower BW, conventional ventilation, HFOV, pneumothorax, PDA, NEC and infection were significant independent variables associated with IVH

**Conclusion:**

The prevalence IVH among the studied premature babies was 39.5%. Lower GA, BW, conventional ventilation, HFOV, pneumothorax, PDA, NEC, n CPAP, lack of antenatal steroid, maternal diabetic and infection were considered the main associated risk factor with IVH.

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the study

Intraventricular haemorrhage (IVH) is an important cause of mortality and long-term morbidity in preterm babies (Bassan, 2009). The global incidence of IVH has declined from 50% - 80% (1980) to 10% - 40% (2010s) (Lee *et al.*, 2010b) . The incidence of IVH varied among different nations (Behrman and Butler, 2007). Because of the persistently relatively high incidence of IVH and the significant financial and societal burden of this disease, many postnatal medical prevention strategies have been explored (McCrea and Ment, 2008). The prevalence of IVH has decreased gradually in developed countries during the last decade when comparing with developing countries. There are very a few studies from developing countries.

Antenatal steroids have been proven to be beneficial in preventing complications related to premature delivery. As the use of antenatal corticosteroids increases from 24% to 87% (Stoll *et al.*, 2015), the morbidity and mortality rates in premature babies decreases. Large randomized studies have revealed a 50% reduction in the incidence of Respiratory distress syndrome (RDS) following administration of antenatal corticosteroids, in addition to other complications such as severe IVH and necrotizing enterocolitis (NEC) (Roberts, 2010).

Prematurity is the most important clinical problem in obstetrics and neonatal medicine (Blencowe *et al.*, 2013b). The costs of managing these premature babies are very high – not only during the initial neonatal treatment but also after discharge

from the neonatal unit and the financial burden on the family tends to be large (Dalili *et al.*, 2014) . Neonates born too early, especially those with very low gestational age (GA) are at risk to develop IVH, which is often complicated with cerebral palsy, mental retardation and disability (Allen, 2008).

Cranial ultrasound (CUS) is an excellent instrument to detect the most common brain abnormalities in preterm and full-term neonates, to study the evolution of lesions and to follow brain maturation (van Wezel-Meijler *et al.*, 2010a). With the availability of portable ultrasound machine in many NICUs, it is technically much easier to image the neonatal brain repeatedly even in the most sickest premature neonates. (Leijser *et al.*, 2006).

A thorough literature search did not yield large studies in Malaysia determining the incidence and importance of individual risk factors for IVH in preterm babies. That is why this study was undertaken with the objectives to assess the incidence of and the importance of individual risk factors for IVH in Malaysian tertiary hospitals.

## 1.2 Prematurity

Preterm birth is an important perinatal health problem in the world. In 2010, expected 14·9 million babies (uncertainty variety 12·3–18·1 million) babies were born too early, representing a preterm birth rate of 11.1%. The percentage of preterm deliveries varies depending on the geographical location (Blencowe *et al.*, 2013a). The developing countries in Sub-Saharan Africa and South Asia account for half the world's births, more than 60% of the world's preterm births. Over 80% of the children's mortality (1.1 million deaths) are due to preterm birth complications (Lawn *et al.*, 2013). The cause of the highest number of the deaths within the first 7 days after birth is not congenital malformations, but preterm birth (Beck *et al.*, 2010). Most important improvements in perinatal management, including antenatal corticosteroids, early surfactant usage, and high technology for pre- and postnatal care and monitoring, can improve the survival rates of very preterm babies (Israel, 2011).

Preterm birth is defined by the WHO as delivery before 37 completed weeks or 259 days of gestation. Based on gestational age (GA), prematurity is further divided into the following sub-groups: Extremely preterm - GA < 28weeks; very preterm: GA 28 to 32 weeks; moderate to late preterm - GA 32 to 37 weeks (Tucker and McGuire, 2009) .

There is also another classification for premature babies, according to birth weight (BW). The extremely low birth weight (ELBW) are babies born with BW $\leq$ 1000g, infants born with a weight between 1000 and 1500 g are termed very low birth

weight (VLBW), and those with birth weight between 1500 g and 2500 g are classified as low birth weight (LBW) (Tucker and McGuire, 2009) (WHO, 2011).

Preterm birth is still not understood, and the aetiology is multi-factorial. Contributing risk factors related to preterm delivery include medical conditions of short interval between pregnancies, previous preterm birth, occupation and educational level, low socioeconomic status , infertility treatments and genetic influences (Goldenberg *et al.*, 2008; Muglia and Katz, 2010; Raisanen *et al.*, 2013).

Preterm birth is really a global problem. In the lower-income countries, 12% of babies are born early compared with 9% in higher-income countries. In general poorer societies are at higher risk (Organization, 2015). Around 9.6% (12.9 million) births globally are preterm, the prevalence of preterm and low BW (LBW) births in the United States is estimated at 8.2% per year (Soleimani *et al.*, 2014). In some European countries, the prevalence of preterm delivery continue to plateau or decreased between 1996 and 2008 (Zeitlin et al. 2013). The United States had a higher infant mortality rate when compared with Europe (Mac Dorman & Mathews, 2010). In addition to dissimilarity in mortality rates between countries, there are also disparities between races. In a study done by Blencowe in 2009, it was shown that the preterm birth rates were 11% in white Americans and 18 % in black Americans. Women younger than 17 years or older than 40 years had more prematurity than other age groups (Blencowe et al. 2012).

In Malaysia, a study in Hospital Kuala Lumpur in 1991, revealed the prevalence of LBW was 13.5% but these babies contributed to 74.8% of all deaths (Tahir *et al.*, 1991). Another study in Hospital Seremban, in 2008 found a prevalence

of LBW infants as13.96%. Recent data analysis by Department of Statistics Malaysia, Putrajaya in 2011 showed a prevalence of LBW in the Malaysian population of 11% (Sutan *et al.*, 2014).

In the last decades, the survival rate of premature babies has increased markedly, despite the growing number of live born VLBW infants. Unfortunately, the incidence of neuro-developmental complications remained high among these premature survivors. The most common brain damage among premature infants includes IVH which was the main topic of this study, post-haemorrhagic hydrocephalus (PHH), and periventricular leukomalacia (PVL) (Volpe, 2001).

Almost all major organ systems are immature in preterm babies. There are many respiratory complications associated with prematurity such as respiratory distress syndrome (RDS) (Stoll et al. 2010) and bronchopulmonary dysplasia (BPD) (Bhandari & McGrath-Morrow 2013). Gastrointestinal immaturity is also a common problem of prematurity, leading to mild feeding intolerance to the most severe complications such as NEC in about 5% to 10% (Schulzke et al. 2007). Patent ductus arteriosus (PDA), is the most common complications of the heart (Hamrick & Hansmann 2010). Sepsis is another very common problem of preterm infants (Saigal and Doyle, 2008).

## 1.3 Intraventricular haemorrhage

Intraventricular haemorrhage (IVH) is the main common variety of neonatal intracranial haemorrhages. It starts as bleeding originating from the germinal matrix and spreads from there under the ependymal lining of the lateral ventricles (grade I). When the ependymal layer gives way, the blood enters the ventricle (grade II) and if severe it may cause dilatation of the ventricle (grade III). The most severe IVH is characterized by blood breaking through the ventricle wall into the parenchyma of the brain, intraparenchymal bleeding or grade IV. This grading of IVH is based on the Papile classification system (Papile, 1978). The presence of severe IVH (grade III or IV) had strong association with motor impairment (Futagi, 2006).The grading and causality of IVH is discussed further below.

IVH is an important cause of morbidity and mortality in VLBW and ELBW infants and a main cause of neurological impairment and severe cognitive deficit in low BW infants. Even though technology and quality of care in NICUs around the world have progressed tremendously, it is still an important cause of morbidity. There are two main reasons first, the incidence is directly associated with the degree of prematurity and second, the percentage of premature infants surviving has increased steadily (Kim *et al.*, 2014). In other words, neuroprotection for premature infants remains a main concern because many VLBW and ELBW babies, who would have died decades, previously tend to survive now. Specific treatments for IVH remain limited (Allen, 2013). The causes of IVH are multifactorial and are primarily related to intrinsic weakness of the germinal matrix vasculature and due to instability of cerebral blood flow. Even though the different grades of IVH have been referred

to in the text above while discussing the progression of an IVH, the classification is given in a more schematic way, below:

- Grade I: germinal matrix haemorrhage.
- Grade II: IVH without distension of the ventricular system.
- Grade III: blood heavy and distending the ventricular system.
- Grade IV: parenchymal involvement of haemorrhage (Papile *et al.*, 1978)

There had been a decline in the incidence of IVH since the 1980s, the rate ranging between 50% and 80% during that time. In the early 2000s the incidence had reduced to 10% to 15%. The survival rate of extremely preterm babies has increased, but IVH remains a main problem in newborn (Volpe, 2001).

Lee in 2010 reported that the incidence ranged from 15% to 40%, and that the variation was big among different countries (Lee et al. in 2010). Identifying the most important risk factors and knowing the underlying causes of IVH have potential to allow the development of better strategies for prevention of many neurodevelopment complications of preterm babies. Prenatal risk factors such as low GA, low BW, vaginal delivery, low Apgar score, intrauterine infection, and metabolic acidosis, early onset sepsis have been proposed to be associated with the pathogenesis of IVH (Lee et al. in 2010). Other suggested risk factors for IVH include temperature instability (hypothermia and hyperthermia), apnoea, feeding problems, bradycardia, hypoglycaemia and hyperglycaemia (Walker, 2013). Laboratory findings such as leucocytosis, leukopenia, thrombocytopenia and elevated C- reactive protein, (even if there is negative blood culture) have been proposed as risk factors (Osborn *et al.*,

2003; Vural *et al.*, 2007). Another study also identified other risk factors e.g. prolonged resuscitation, hypotension and the presence of clinical features as respiratory distress syndrome, seizures, pneumothorax, decreased urine output, and NEC (Cloherty *et al.*, 2008). Some risk factors for IVH are related to maternal illness e.g. maternal diabetes mellitus (gestational and presentational diabetes mellitus), preeclampsia, premature rupture of the membranes (PROM), and oligohydramnios (Tioseco *et al.*, 2006).

The most common way for diagnosis of IVH is cranial ultrasound (CUS) that is used routinely in premature babies for screening IVH, (Ment *et al.*, 2002). CUS has been used to diagnose IVH since the late70s. Although MRI is increasingly being used, CUS is the most readily presented and commonly used neuro-imaging technique in the Neonatal intensive care unit (NICU) (Brouwer *et al.*, 2014). Serial CUS appears highly effective in diagnosing the brain insult in preterm babies, even though it may miss cerebellar abnormalities. MRI does recognize these lesions, but its practicality is limited (Brouwer *et al.*, 2014). It has been reported that 90% of IVHs occur within the first 3 days after birth. Lumbar puncture is another diagnostic procedure that can be used to detect IVH (Volpe, 2001).

Fifty percent to seventy five percent (50% to 75%) of preterm survivors with severe IVH have been reported to progress to hydrocephalus, cerebral palsy, and mental retardation. A quarter of the nondisabled survivors developed psychiatric problems with executive function (Indredavik *et al.*, 2010). In the neonatal age 5 – 10 % of preterm babies with severe grades of IVH mostly manifested with seizures and post haemorrhagic hydrocephalus and high mortality (McCrea and Ment, 2008).IVH is often associated with periventricular leukomalacia (PVL)(Ballabh, 2010).

## 1.4 Malaysian National Neonatal Registry (MNNR)

### 1.4.1 Structure

The MNNR consist of an Advisory Board, the Steering Committee members and administrative staff. The Advisory Board, consisting of senior neonatologists and some members of the Steering Committee, supervises and observes the direction of the registry. The Steering Committee consists of a nine members involving neonatologists and a geneticist of participating hospitals and from the Universities. This committee serves to manage, complete and monitor the functions of MNNR and it meets as a minimum, three times a year.

### 1.4.2 History

At a National Paediatrician's meeting in October 2001, it was decided that a registry should be started with the aim to study the outcome of sick babies who were admitted to NICU to Malaysia Hospitals. It is known that a data collection system at national level can help individual NICUs to identify their own strengths and weaknesses in direct comparison with similar units delivering similar care. This is likely to reduce mortality and morbidity of infants.

A first study was done from 1st October to 31st December 2002, in about 14 centres with cooperation of the Clinical Research Centre (CRC), Ministry of Health of Malaysia. In October 2003, a report of this study was published. It was established that the NNR was practically possible and it was suggested that it could be beneficial for the clinical management and policy development. MNNR proper then began in January 1, 2004, and the first reports for the years 2004 and 2005 were published (http://www.acrm.org.my/mnnr/).

### 1.4.3 Registration criteria

MNNR is a critical review of selected infants transferred to the neonatal intensive care unit (NICU). This includes:

A. All new born admitted to a NICU **who**

1. had a gestation of < 32 weeks Up to 31 weeks of +6 days)

2. had a birth weight of 1500 grams and less.

3. Who was ventilated

4. With a major congenital abnormality

5. With a hypoxic ischemic encephalopathy

B. All new born babies (<28days) deaths who died in the NICU, labour room, operating theatre and other wards. Inborn and out born babies will be included except out born babies who expire before arrival. Exclusion from study babies who are at a corrected gestation of > 44/52 (http://www.acrm.org.my/mnnr/).

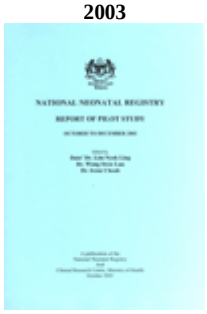
### 1.4.4 The Malaysian Neonatal Registry aims to:

- Determine the frequency and distribution of sick new born in Malaysia.
- Study the mortality and morbidities of newborn who admitted to the NICU.

- Estimate the mortality rates of perinatal, neonatal, and stillbirth inborn babies.
- Match and register the outcomes between different centres.
- Improve the indicators of standard care in numerous areas.
- Study consequences of VLBW babies.
- Encourage and simplifying research on the neonatal serious disorders and their management (http://www.acrm.org.my/mnnr)

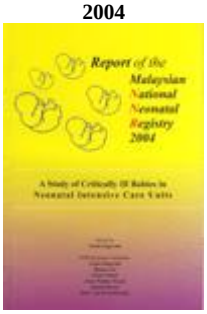
1) There is some report published to the MNNR in the Figure: 0.1

**2003**




Report of Pilot Study - October to December 2002

**2004**




Report of the Malaysian National Neonatal Registry 2004

**2005**


Report of the Malaysian National Neonatal Registry 2005

**2006**


Report of the Malaysian National Neonatal Registry 2006

**2007**


Report of the Malaysian National Neonatal Registry 2007

**2008**

Report of the Malaysian National Neonatal Registry 2008

Figure 0.1: Reports published to the Malaysia national neonatal registry

Source :( **http://www.acrm.org.my/mnnr**) Approval from the Steering committee of the MNNR (Appendix B)

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Prevalence of intraventricular haemorrhage

In recent years, the incidence of IVH, range from 15% - 40 %,according to different centre despite many efforts to reduce the incidence (Lee *et al.*, 2010b). Data from multicentre surveys and neonatal networks presented that the incidence of IVH reduced to 25 % and 10 % in some European countries (Stichtenoth *et al.*, 2012).

Study was done in Germany 2001 to 2005 reported the prevalence of IVH was 40% all grades in premature babies who were (BW <1500 g or birth before 32 weeks (Vogtmann *et al.*, 2012). Dr. Stonestreet from Department of Paediatrics, Women & Infants' Hospital of Rhode Island, USA reported in 2006 the incidence of all types of IVH was 36% with severe types (Grades III and IV) 14 % for premature babies with BWT <1000 g (Stonestreet, 2009).

A study done in Mofid Hospital NICU Tehran, Iran by Sajjadian, in 2010 reported an overall incidence of IVH of 64.4%, grade I was 40%, and grade II was11%, III 25.7% and VI was 2.8% (Sajjadian *et al.*, 2010). Rong, 2012 reported the overall incidence of IVH was 3.9 % for all preterm babies in Wuhan, China. The incidence of IVH increased with decreasing GA. For GA of 35–37 weeks, it was 1.93 % and for GA < 30 weeks, it was up to 36.0 % (Rong *et al.*, 2012).

Mohamed reported in this study at the United States from 1998 to 2004, included more than 1000 hospitals, the overall prevalence of IVH was 14.7% and the overall mortality was 24.5% and 46% of the babies (<1000 g) at birth with IVH (Mohamed and Aly, 2010).

A study done at NICU of Seoul National University Children's Hospital between June 2003 and December 2007, the incidence of IVH overall was 27.8%. Among all babies and 79.7% had grade I , 6.9% had grade II, 4.8% had grade III, and 8.6% had grade IV(Lee *et al.*, 2010b). Another study by Stoll this study were collected the extremely low GA (22–28 weeks) and very low BW (401–1500 g) between January 1, 2003, and December 31, 2007 ,they showed the incidence of IVH declining from 2003 to 2007( 22.1% to 10.5%). The IVH grading were grade I was 10% grade II was 6, grade III was 7 % and grade IV was 9 (Stoll, Hansen et al. 2010).

## 2.2 Pathogenesis of intraventricular hemorrhage

### 2.2.1 Germinal matrix vasculature fragility

The germinal matrix (GM) is a richly vascularized, transient layer adjacent the ventricles. It produces neurons and glial cells, and is exists in the foetal brain between 8 and 36 weeks of gestation. It weakens at 25 weeks (Raets *et al.*, 2013). GM vasculature is selectively susceptible to haemorrhage in premature babies during the first 48 hour of life. This recognized to be related to a rapid angiogenesis of this brain area, resulting in development of nascent vessels that result in a paucity of pericytes and immaturity of extracellular matrix (Billiards *et al.*, 2006). Sonographically, germinal matrix haemorrhages show as sub ventricular echodensities changing into pseudocysts (Horsch *et al.*, 2010).

Premature infants predominantly bleed into the germinal matrix and not into the cortical layer. This may there is an intrinsic weakness in the germinal matrix vasculature compared to other parts of brain. Immaturity or weakness of the blood brain barrier (endothelial tight junctions, basement membrane, pericytes and astrocyte end-feet) can cause fragility of germinal matrix vasculature (Ballabh, 2010).

### 2.2.2 Disturbances in the cerebral blood flow

The term ‘cerebral haemodynamic’ includes cerebral blood flow (CBF), cerebral blood flow velocity, and cerebral blood volume (CBV). The prevention of disturbances in CBF and CBV is essential to prevent IVH. However, constant monitoring of CBF and CBV is still unreachable for clinical use. General information about the regulation of CBF and CBV is significant. Although the knowledge about

these factors is still inadequate, especially concerning auto-regulation and the exact role of CBV (Liem and Greisen, 2010). Fluctuating CBF velocity during the first days after birth strongly correlates with the incidence of IVH. Elimination of this fluctuation in the CBF by intravenous Pancuronium infusion significantly reduced the incidence of IVH (Guzzetta *et al.*, 1986). In premature babies with respiratory distress syndrome (RDS) IVH may be due to fluctuation in the CBF. Nevertheless, most of the neonatal units nowadays use synchronized ventilator modes, which reduce infants "fighting" the ventilator and this may reduce fluctuations in the CBF velocity (Rennie *et al.*, 1987). Besides this, routine use of neuromuscular blocking agents in ventilated babies is not recommended because of long-term neurological adverse effects. A Doppler technique can be used to measure CBF velocity in mechanically ventilated premature babies, with RDS (Ballabh, 2010). Some studies indicated that high CBF is associated with IVH whereas others described that low CBF is associated with increased risk of IVH (Tsuji *et al.*, 2000).

Other clinical conditions as patent ducts arteriosus, hypercarbia, hypotension, and restlessness also contribute to the instability in cerebral blood flow and therefore the development of IVH (Ballabh, 2010). There are factors that can lead to IVH by increasing the CBF, such as a rapid sodium bicarbonate infusion, which creates a high osmotic load and a potential increase in arterial $CO_2$, may cause cerebral vasodilatation altering cerebral hemodynamic (Ballabh, 2010). In the preterm, the resting blood pressure has lower limits of auto regulatory volume than in term infants and numerous reports in sick preterm infants have shown diminished auto regulation (Wong *et al.*, 2012). Instability of the cerebral blood flow can make rupture the vasculature.

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### 2.2.3 Platelet and coagulation disorders

The relationship between IVH and coagulation in the newborn has been an issue of debate. The role of low platelets in the aetiology of IVH is uncertain. In the absence of specific clinical situations known to lower platelets, Coen 2013 suggested that platelet concentrations fall because platelets are consumed when the vessels of the GMH rupture (Coen, 2013). Severe coagulation deficiency has long been considered a major contributing factor in the occurrence of IVH in premature babies and severe grades of IVH has also been shown to happen together with severe derangement of coagulation in extremely low BW infants (Kuperman *et al.*, 2011). It is generally considered advisable to keep the platelets above 100x $10^9$/L for the ELBW during the first week of life .The current usual therapy for newborns includes administration of vitamin K at the first day of life, in order to reduce the risk of haemorrhagic disease of the new born. On the other hand, IVH of preterm is still a major therapeutic challenge (Kuperman, 2013).

### 2.2.4 Genetic factors and intraventricular haemorrhage

Genetic studies of IVH have mainly focused on gene complexes in inflammation and infection (Hallman, 2012). Genetic factors presentation may be independent risk factors of the same level as other known risk factors (Ramenghi *et al.*, 2011). Mutations in coagulation, thrombophilia, and inflammation-related genes might contribute to the development of IVH (Szpecht *et al.*, 2015). Premature babies who are carriers of the prothrombotic mutations are at increased risk for development of IVH. Un similar study by Göpel supposed the factor V Leiden and prothrombin G20210A gene mutations have a protective role against IVH that related to the improved coagulation attributable to the factor V Leiden and prothrombin G20210A (Göpel *et al.*, 2001).Other different study done by Härtel et al establish no association between the prevalence of IVH in premature babies with BWT < 1500 who were carrier of these mutations (Härtel *et al.*, 2006).

## 2.3 Risk factors

Some risk factors are associated with the development of IVH, including neonatal and maternal factors. Neonatal factors were explain with pathogenesis of IVH in Table 2.1

Table 2.1: Neonatal risk factors in the pathogenesis of intraventricular hemorrhage

| Major Pathogenic Mechanism | Putative Mechanisms | Risk Factors | Preventive Measures |
|---|---|---|---|
| **Disturbance in CBF** | Fluctuation in CBF | • Suctioning and handling | • No routine suctioning |
| | | • Hypercarbia, hypoxia, acidosis | • Optimize ventilation |
| | | • Asynchrony between infants and ventilator breathe | • Synchronized ventilation by the use of assist control |
| | | | • Synchronized<br>• mandatory ventilation<br>Modes |
| | | • Severe RDS | |
| | | • Patent ductus arteriosis | • Indomethacin /ibuprofen |
| | | • Rapid infusion of NaHCO3 | • Slow infusion over extended period |
| | High cerebral venous pressure | • Pneumothorax, high ventilator pressure | • Gentle ventilation |

| | | | |
|---|---|---|---|
| | | • Prolonged labour | • Individualized approach as appropriate |
| | Abnormal blood pressure | • Hypotension | • As appropriate for the infant |
| | | • Hypertension | |
| | | • Sepsis | |
| | | • Dehydration | |
| | Pressure passive circulation | • Extreme prematurity and low birth weight (<1000 g) | • As appropriate for infant the infant |
| | | • Clinically unstable resulting from Respiratory compromise, sepsis, or other reasons | |
| **Inherent fragility of germinal matrix Vasculature** | Might be worsened by an inflammatory injury to the BBB | • Hypoxic ischemic insult | • Prenatal GCs stabilize<br>• the microvasculature by increasing: |
| | | • Sepsis | • 1. Pericyte coverage<br>• 2. GFAP expression in Astrocytes<br>• 3. Fibronectin in basal lamina |
| **Platelet and coagulation disturbances** | Haemostatic failure | • Thrombocytopenia<br>• Disseminated Intravascular Coagulopathy | Replacement of blood Products |

Source Ballabh, Praveen. "Pathogenesis and prevention of intraventricular haemorrhage." Clinic perinatology 41.1 (2014):

(Ballabh, 2014)

### 2.3.1 Neonatal factors

#### 2.3.1.1 Low gestational age and low birth weight in neonate

Most mortality and morbidity affects “very preterm” infants who those born before 32 weeks gestation and especially “extremely preterm” infants who are born before 28 weeks of gestation. Over the past 20-30 years, advances in perinatal care have improved outcomes for infants (MacKay *et al.*, 2010). A predictable 15 million babies delivered preterm every year. Approximately 1 million babies die each year because of complications of preterm birth. Many survivors spend a lifetime with disability, including learning disabilities and visual and hearing problems (WHO Preterm birth).

Several studies have shown that low GA and low BW affect the risk of high grade IVH. Therefore, prevention of prematurity is likely the best way to prevent IVH. A program for prevention of prematurity must focus on early identification of women at risk, education about the causes of prematurity, early diagnosis and in utero transfer to a perinatal centre specializing of high-risk deliveries (Khodapanahandeh *et al.*, 2008).

Lee determined that the perinatal risk factors as a low BW and low GA are absolute major risk factors for IVH(Lee *et al.*, 2010b). Low GA and asphyxia, as reflected by the Apgar scores, had an adverse effect on the incidence of severe IVH grades (Weintraub *et al.*, 2001). Same results were obtained by Gleiβner the risk of IVH was mostly connected to low GA (Gleiβner *et al.*, 2000).

#### 2.3.1.2 The Apgar score

The Apgar score is a screening examination worldwide used rapidly evaluates the health of newborn at one minute and five minutes after birth. The 1-minute Apgar score measures how the newborn accepted the birthing progression. The 5-minute Apgar score assesses how fit the newborn is adapting to the environment. Virginia Apgar, M.D. (1909-1974) introduced the Apgar score in 1952 (Apgar Score ADAM American Accreditation HealthCare Commission 2012). Each of five simply recognizable characteristics, respiration, heart rate, colour, reflex electability and muscle tone measured and assigned a value of 0 to 2. Reliability of the Apgar in predicting outcomes of term babies has been a subject of controversy, at least for term babies. A continued scoring at 10 and 20 minutes in babies with poor Apgar scores seemed more reliable predictors of poor outcome than the early scores. Additional research is essential to recognize the threshold at which the Apgar score may best predict adverse outcomes (Malin *et al.*, 2013).

Many studies have documented the strong association between low Apgar score and risk of IVH in preterm babies. (Lee *et al.*, 2010a). A study done at Haifa, by Riskin (Riskin *et al.*, 2008) showed that a low Apgar score at 1 min was significantly associated with IVH (OR 1.72 (1.33-2.21). Another study conducted in premature babies of GA< 32 weeks in a NICU in Isfahan, Iran from 2003-2005 showed that low Apgar scores at 1 min (p =0.0014) & low Apgar scores at 5 min (p =0.005), had a strong association with the development of IVH (Badiee, 2007). Another study was done in Iran showed an association between low Apgar score at 5 min and IVH (OR: 1.58; 95% CI: 1.5-6.32) (Khodapanahandeh *et al.*, 2007). Lehner documented by multivariate analyses in a study at the University of Vienna hospital a

significant association between a 5-min Apgar score lower than seven (P=0.037) and severe IVH(Lehner *et al.*, 2001). Study done by Vogtmann in Germany which showed that a low 1-minute Apgar score was closely related to IVH (Vogtmann *et al.*, 2012). A large number of other studies in different parts of the world showed similar finding (Shankaran *et al.*, 2014) (Synnes *et al.*, 2001) (Osborn *et al.*, 2003) (Weintraub *et al.*, 2001).

#### 2.3.1.3 Respiratory distress syndrome

Respiratory distress syndrome (RDS) is an important cause of short- and long-term morbidity, and mortality worldwide. RDS was earlier identified as hyaline membrane disease in premature babies (van der Ham *et al.*, 2012). In healthy newborns, the alveoli are small, air-exchanging sacs of the lungs layered by surfactant, which is soap-like material formed in the lungs when the foetus matures in preparation for birth. If premature babies have not yet formed enough surfactant, they are not capable to open their lungs to breathe fully. The risk of RDS increases with increasing prematurity (Reiss *et al.*, 2003). A sixty percent chance of developing RDS was documented in babies who were born before 29 weeks of gestation (Vogtmann *et al.*, 2012). Surfactant treatment for RDS became available in the 1990s. A series of surfactant studies showed conclusively a reduction in mortality and morbidities, and it is the standard of care for the treatment of RDS in preterm infants (Aftab and Gerdes, 2013). Study done by Khodapanahandeh showed that premature babies with RDS has risk to develop IVH (Khodapanahandeh *et al.*, 2008). Study was done by Sajjadian 2010 noted that 5% of premature babies who had respiratory distress associated with developed IVH (Sajjadian *et al.*, 2010).

#### 2.3.1.4 Respiratory support

Mechanical ventilation has a definite effect on survival of sick new-borns. Careful use of it can decrease the mortality and morbidity to a great degree. Positive pressure ventilators are the basis of providing mechanical ventilation in neonatal intensive care units (Nabi, 2005). Up to 50% of newborn treated in intensive care units were reported to require some type of mechanical respiratory support (Khemani *et al.*, 2009; Wolfler *et al.*, 2011).

Current policies, aim to maintain and support spontaneous breathing and carefully avoid hypoxia and hypocapnia (Putensen *et al.*, 2001). For lung protection relatively small tidal volumes and sufficient positive end-expiratory pressures (PEEP) are used (Jauncey-Cooke *et al.*, 2010). These strategies have been shown to improve the neonatal outcome by improving gas exchange, reducing the duration of ventilator support and preventing ventilator-induced lung injury (Vanpee *et al.*, 2007). Early establishment of nCPAP in the management of RDS in premature babies, can significantly decrease the use of mechanical ventilation (MV) and surfactant therapy, which can reduce the complications (BalaJi *et al.*, 2015).

Ventilated neonatal breathing in asynchrony with the ventilator poses a threat of complications during mechanical ventilation, for example pneumothorax or IVH (Cools and Offringa, 2007).

#### 2.3.1.5 Pneumothorax

Pneumothorax is a life-threatening situation with high morbidity and mortality. It is defined as the occurrence of air between visceral and the parietal pleura (Antony, 2004). Pneumothorax is more common in the neonatal period and can arise spontaneously in non-ventilated babies It can be expected in premature babies if there is no improvement within a short time of resuscitation or if asymmetric chest movement is identified during resuscitation (Hill *et al.*, 1982). Rapid diagnosis is required by urgent portable X-ray. Treatment consists of immediate intervention for life saving and better outcome (Hassan *et al.*, 2015). New ventilator techniques have played a role in decreasing air leaks (Malek *et al.*, 2011). Surfactant, and high-rate low-tidal-volume reduce the incidence of pneumothorax in VLBW (Vellanki *et al.*, 2012). Numerous reports have indicated that pneumothorax is frequently associated with, or followed by IVH (Cooke *et al.*, 1993). All pneumothorax produced by RDS can exacerbate or induce IVH (Pishva *et al.*, 2012).

#### 2.3.1.6 Surfactant Therapy

Exogenous surfactant replacement is considered the standard of care in the treatment of premature babies. Authors have called surfactant replacement therapy the best important discovery in paediatric medicine in the past 30 years (Thomas *et al.*, 2014). Surfactant is a lipoprotein complex, originating in the lungs, which decreases alveolar collapse by developing a layer between the alveolar surface and the alveolar gas in the lungs, decreasing surface tension (Berry, 1991). Premature infants are not able to produce enough own surfactant because the type II alveolar epithelial cells are not matured. The alveoli may not inflate or collapse on expiration,