INTRAPARTUM ASPHYXIA AND HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN A PUBLIC HOSPITAL: INCIDENCE AND PREDICTORS OF POOR OUTCOME

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This research report is submitted in fulfilment of the requirements for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Witwatersrand, Johannesburg

Johannesburg, 18 May 2015

DECLARATION

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

_____

Eduard Keith Bruckmann

__day of_____20_____in_____

DEDICATION

In loving memory of my father

Eduard Bruckmann[2nd]

1944 – 2013

PUBLICATIONS AND PRESENTATIONS

1. It was presented at the 33rd Conference on Priorities in Perinatal Care in Southern Africa; 11-14 March 2014, Capetown, Western Cape, South Africa.
2. It has been submitted to the South African Medical Journal and is accepted for publication (In Press) (see Appendix A).

ABSTRACT

OBJECTIVE: To determine the incidence of intrapartum asphyxia and hypoxic ischemic encephalopathy (HIE) and predictors of poor outcome in term and near term infants in a hospital from a developing country.

METHODS: Neonates with birth weight ≥2000g who required bag mask ventilation and were admitted with a primary diagnosis of intrapartum asphyxia from January-to-December 2011 were included. Medical records were retrieved, maternal and infant data were collected and analysed. Comparison between infants with severe HIE and/or died and those who survived normal or with mild to moderate HIE was performed.

RESULTS: There were 21086 live births with birth weight of ≥2000 grams over this period, the incidence of intrapartum asphyxia varied from 8.7 to 15.2/ 1000 live births and that of HIE from 8.5 to 13.3/ 1000 live births based on definition of intrapartum asphyxia used. Sixty percent of patients with HIE had moderate to severe HIE. Overall mortality rate was 7.8-12.3% (dependent on definition used) and 14.2% when including the deaths from labour ward. Mortality rate in infants with moderate and severe HIE was 7.1%, and 62.5% respectively. Odds of severe HIE and/or death were high if Apgar score was <5 at 10 minutes (OR 19.1; 95% CI 5.7;66.9), no spontaneous respiration at 20 minutes (OR 27.2; 95% CI 6.9;117.4), need for chest compressions (OR 8.37; 95% CI 3.71;19.1), need for adrenalin (OR 81.2; 95% CI 13.2;647.7) and pH<7 (OR 5.33; 95% CI 1.31;25.16). Predictors of poor outcome (namely severe HIE and/or death) were Apgar score at 10 minutes (p=0.004), adrenaline (p=0.034) and low serum bicarbonate (p=0.028).

CONCLUSION: Incidence of intrapartum asphyxia in term and near-term infants is higher than that reported in developed countries. Low Apgar score at 10 minutes and the need for adrenalin remain important factors in predicting poor outcome in infants with intrapartum asphyxia.

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Dr Kebashni Thandrayen for helping me with the statistical analysis.

Lastly to the mothers and babies we serve, may we continue to strive for improvement and to provide care of the highest possible quality.

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ABBREVIATIONS

AAP: American academy of paediatricians

ACOG: American College of Obstetricians and Gynaecologists

BMV: Bag Mask Ventilation

CHBAH: Chris Hani Baragwanath Academic Hospital

CRP: C-Reactive Protein

CS: Caesarean Section

CTG: Cardiotocograph

FBC: Full Blood Count

HIE: Hypoxic Ischemic Encephalopathy

HIV: Human Immunodeficiency Virus

ICU: Intensive Care Unit

LP: Lumbar Puncture

NICU: Neonatal Intensive Care Unit

PCO_2: Partial pressure of Carbon Dioxide

PO_2: Partial Pressure of Oxygen

RPR: Rapid Plasma Reagen

U&E: Urea and Electrolytes

WHO: World Health Organisation

PART A- PROTOCOL

Introduction

There are different criterions that have been used to make a diagnosis of intrapartum asphyxia, some simple and some more complex. The more strict or complex criteria to diagnose intrapartum asphyxia is that described by the American Academy of Paediatrics (AAP) and American College of Obstetrics and Gynaecology (ACOG) in 1996.[1] These criteria state that the following must be present for the diagnosis of intrapartum asphyxia; 1) profound metabolic or mixed academia (pH<7) in an umbilical artery blood sample, 2) persistence of an Apgar score of 0-3 for longer than 5 minutes, 3) neonatal neurologic sequelae (e.g., seizures, coma, hypotonia), 4) multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines). Simple criterion that have been used to diagnose intrapartum asphyxia have included the failure to initiate regular respiration within a minute of birth, Apgar score less than 7 at 5 minutes, and the need for bag mask ventilation or resuscitation at birth.[2] These simple criteria are based on the fact that newborn infants usually initiate breathing without assistance and usually cry after delivery. By one minute after birth most infants are breathing normally. Successful transition from intrauterine to extrauterine life requires a newborn baby to initiate spontaneous breathing at time of birth. Most term infants will initiate spontaneous respiration without any form of assistance. It has been reported that 5-10% of newborns will require stimulation, 3-6 % will require bag mask ventilation and less than 1% will require chest compressions, intubation and adrenaline.[3]

Intrapartum asphyxia is one of the major causes of death and/ or neurologic impairment in children, therefore using a less strict definition that can be used even in clinical settings where one has no access to do blood gases may increase the sensitivity of diagnosis of intrapartum asphyxia. The newborns who fail to initiate spontaneous respiration are more likely to die or have brain damage. Among the patients who die, a number of them will die during the neonatal period depending on the severity of brain injury. Globally, it is estimated that about 3.3 million neonates died in 2009.[4] In South Africa there were 14 000 neonatal deaths in 2008. About a quarter of neonatal deaths are due to intrapartum asphyxia. The fifth perinatal care survey in South Africa reported that the causes of death among infants who died from intrapartum asphyxia 50% were due to hypoxic ischemic encephalopathy, 28% due to meconium aspiration syndrome and 18% due to persistent pulmonary hypertension of the newborn.[5] Though it is known how many neonatal deaths are due to intrapartum asphyxia in South Africa, there have been no reports as to how many babies are diagnosed with a problem of intrapartum asphyxia in our healthcare facilities and how many survive with complications associated with intrapartum asphyxia especially Hypoxic Ischemic Encephalopathy (HIE) which is more likely to be associated with long term neurologic impairment. Fifteen to 20% of those infants with HIE die in the neonatal period and 25-30% of those infants who survive develop permanent neurodevelopmental deficits e.g. cerebral palsy.[6]

Hypoxic ischemic encephalopathy is divided into 3 grades of severity that have a predictable outcome.[7, 8] Unfortunately, the grade of HIE can only be assigned when the encephalopathy is established. With newer interventions, the outcome could possibly change appreciably which is why early therapeutic intervention in the asphyxiated

babies may be imperative to decrease cerebral injury and prevent further complications. Therefore, there remains a need to identify characteristics that are associated with severe HIE or death in asphyxiated infants as these infants might benefit from therapeutic hypothermia. The factors associated with poor outcome have been identified in previous studies but most of these studies have been conducted in developed world. It is possible that the factors associated with poor outcome in developed countries are not the same as those in developing countries. For example infection has been identified to result in abnormal neurodevelopmental outcome and its role in patients who develop HIE post-asphyxia is not known and infections are more prevalent in developing countries than in developed countries. Therefore understanding the burden and outcomes of intrapartum asphyxia is important, so that one can be able to assess how much assistance is required towards its reduction and to identify factors associated with poor outcomes.[9]

Poor outcome and characteristics of asphyxiated babies are dependent on numerous antenatal antecedents which can affect the fetus at different gestational ages from a specific gestational age e.g. term or preterm, to those affecting the fetus at any gestational age. In this study the focus will be on some of the antecedent factors associated with term/ near term babies born with asphyxia neonatorum which include parity/gravity, maternal age, patient booked/booking bloods, maternal conditions e.g. pregnancy induced hypertension/pre-eclampsia, diabetes mellitus and chorioamnionitis/ intrauterine infection/ inflammation. Some aspects of the impact of obstetric care will be looked at namely mode of delivery (caesarian section, normal vaginal delivery, and breech), assisted delivery and cardiotocograph (CTG) performed and interpretation thereof. The antenatal events are either directly responsible for brain damage to the

infant or make the infant more vulnerable to the normal asphyxiating events during delivery.[10]

Justification for the study

The number, characteristics, and outcome of patients who require resuscitation in developing countries are not well documented. A number of patients who need resuscitation at birth might benefit from therapeutic hypothermia, therefore it is important to determine characteristics of patients who die or develop severe HIE. Chris Hani Baragwanath Academic Hospital where this study will be conducted has about 23000 births a year, making it one of the busiest hospitals in the country. It caters for different types of patients, the majority (about two thirds) being high risk patients and about a third low risk patients and with some of them presenting in advanced stage of labour. The large number of births in relation to the number of midwives, obstetric and paediatric doctors places a high burden on perinatal care which results in delays in detecting those who need assistance and further care. In this environment it is more likely that the number of babies who need resuscitation (defined as need for bag mask resuscitation) are most likely to be higher than that reported in the literature. Delays in detecting those with fetal distress are more likely associated with high risk of brain injury despite resuscitation. The characteristics of those who need resuscitation and have signs of brain injury and/ or death or factors associated with poor outcomes in asphyxiated patients in our hospital are not known.

Objectives

- To determine the number of patients admitted with diagnosis of intrapartum asphyxia at CHBAH.
- To describe the characteristics of patients diagnosed with intrapartum asphyxia.
- To determine the number of patients who have HIE secondary to intrapartum asphyxia
- To determine the number of patient who die from asphyxia-related complications
- To compare the characteristics of patients who had severe HIE or death to those who survived to hospital discharge with no HIE or mild to moderate HIE

Definitions

- Near-term and term infants -- Gestational age >33 weeks according to obstetric records and/ or weight >2000grams
- Intrapartum asphyxia -- patient who required bag mask ventilation (BMV) or more at birth and subsequently admitted to TICU (level 2 nursery) or NICU (level 3 nursery) with a diagnosis of asphyxia.
- No HIE - No diagnosis of HIE or signs suggestive of HIE documented in the patients' notes
- HIE I, II, III – according to label in the hospital record or according to presence of signs that define HIE I, II, III in Sarnat staging (see Table1)

Table 1 Sarnat and Sarnat classification for Hypoxic Ischemic Encephalopathy

	Grade 1	**Grade 2**	**Grade 3**
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
Bronchial and Salivary	Sparse	Profuse	Variable
Secretions			
GI Motility	Normal or decreased	Increased; diarrhoea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)

Methods

Study Design

It will be a descriptive study, conducted through a retrospective review of medical records of neonates born at >33 weeks and/ or weighing ≥2000 g who required resuscitation with at least bag mask ventilation at birth and were admitted to level 2 or 3 nursery with a primary diagnosis of intrapartum asphyxia from 1st January to 31st December 2011.

Sample Population

The sample population includes all neonates born at a gestational age >33 weeks and/ or weighing ≥2000 g born at Chris Hani Baragwanath Academic Hospital (CHBAH)

Inclusion Criteria

Neonates who required resuscitation with at least bag mask ventilation and admission to levels 2 or 3 nursery NICU or died in labour ward with a diagnosis of intrapartum asphyxia

Exclusion Criteria

- Infants born before arrival to CHBAH
- Infants weighing <2000 g
- Infants with severe congenital abnormalities
- Twin pregnancies

Procedures/ Data Collection

Records of patients who were admitted to high care or Neonatal Intensive Care Unit (NICU) from 1 January to 31 December 2011 will be reviewed to select those that have the information that met the above criteria. Records with information that met the above criteria will be included in the study. The data will be collected and entered onto a prepared data sheet (appendix A). The data sheet will capture demographic information (Maternal age, parity, maternal Human Immunodeficiency Virus (HIV) and Rapid Plasma Reagen (RPR) status, infants' birth weight, gender, Apgar score), presence of abnormal neurologic signs, clinical diagnoses, duration of stay and investigations (blood gases, Full Blood Count (FBC) +Platelets, C-Reactive Protein (CRP), Lumbar Puncture (LP), Urea and Electrolytes (U&E), Creatinine, Ca+Mg+PO4), died or survived.

Data Analysis

Data will be entered into a Microsoft Excel spreadsheet and basic statistical analysis will be performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages, means and standard deviations and medians and ranges will be used for demographic data. For analysis looking at comparisons between those who died or with severe HIE and those who survived with no or mild to moderate HIE, Chi square or Fischer's exact test will be used to compare categorical variables and Student t-test or Mann Whitney U test will be used to compare the continuous variables using STATA. A statistician will be consulted for further assistance if needed.

Significance

The findings of this study will be shared with both obstetric and paediatric teams to highlight any improvements to perinatal care of mother and baby. Identifying the incidence of intrapartum asphyxia, characteristics related to maternal factors and obstetric care and outcome of infants with intrapartum asphyxia will assist in highlighting the need to improve obstetric care and/or paediatric care in our hospital and South Africa at large.

Limitations

The study is a retrospective audit of records and thus relies on data from existing records. These records may not be complete and some might be missing and therefore might weaken the validity of the findings. Infants who died in labour ward (36) were not included in the statistical calculation due to the absence of the files.

Ethical Considerations

The proposal for this study will be submitted to the CHBAH Protocol Review Committee and Human Research Ethics Committee (HREC) of the University of the Witwatersrand for approval. As this is a retrospective audit, no consent will need to be obtained from individual patients. Data sheets will only contain a study number. The patient's name and file numbers will be stored in a separate database at a different, secure location so that only the investigator and the supervisor will have access to this information. The study will not be started until clearance from the ethics and hospital committee has been received.

Cost/Funding

The cost involved in the study is for stationery, printing and binding. This cost will be borne by the investigator as there is no funding for this study.

Time Lines

	Feb 2012	Mar 2012	Apr 2012	May 2012	Jun 2012	Jul 2012	Aug 2012	Sep 2012	Oct 2012	Nov 2012
literature review										
protocol preparation										
protocol assessment										
ethics approval										
post graduate approval										
data collection										
data analysis										
write-up report										
write-up paper										

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PART B- MAIN RESEARCH REPORT

CHAPTER 1.0 – LITERATURE REVIEW

1.1 Introduction

Intrapartum asphyxia is defined biochemically as a condition of impaired respiratory gaseous exchange that results in hypoxemia, hypercapnia and metabolic acidosis. Metabolic acidaemia defined as a base deficit of >12 mmol/L or pH <7 has been associated with the presence of intrapartum asphyxia episodes; therefore it has been used to define intrapartum asphyxia biochemically.[1] The problem with this definition is that a number of normal babies have metabolic acidosis therefore used on its own there is a risk that it might overestimate or underestimate the incidence of intrapartum asphyxia.[2]

Lower thresholds have been shown to be more sensitive. Clinically, the need for bag mask ventilation (BMV) at birth and/or an Apgar score <7 have been used to define intrapartum asphyxia.[3] Since, in many developing countries there are no facilities to do blood gas measurement, base deficit is not used as part of the definition and only the clinical definition is used. Using the clinical definition alone to describe the incidence of asphyxia might also overestimate the incidence as infants who do not initiate respiration are not always asphyxiated intrapartum. Therefore assessing incidence of intrapartum asphyxia using a combination of clinical definition of need for BMV, Apgar score <7 at 5 minutes and metabolic acidaemia (base deficit of >12 mmol/L and/or pH <7.0) is more likely to provide information as to the true incidence of intrapartum asphyxia in the studied population.

Neonates with intrapartum asphyxia often have ongoing respiratory depression requiring respiratory support in a neonatal intensive care unit. Where resources are limited, there is competition for these interventions resulting in rationing and offering them to those who are more likely to survive with minimal morbidity. Therefore it is important to determine factors that are associated with severe morbidity and mortality as they might assist in decision-making with regard to who should be offered these limited resources.

1.2 Definitions

1.2.1 Perinatal asphyxia

Intrapartum asphyxia can be defined as "a clinical situation of damaging acidaemia, hypoxia, and metabolic acidosis". This definition is not cause specific but by adding the prerequisite for an identifiable significant event capable of interrupting oxygen supply to the fetus or infant a more accurate definition can be formed.[4] Simple criterion that have been used to diagnose asphyxia have included failure to start regular respiration within a minute of birth, Apgar score less than 7 at 5 minutes, and need for bag mask ventilation or resuscitation at birth.[3] The simple criteria are based on the fact that newborn infants usually initiate breathing without assistance and usually cry after delivery. A stricter and more complex system for the diagnosis of intrapartum asphyxia was described by the American Academy of Paediatrics (AAP) and American College of Obstetrics and Gynaecology (ACOG) in 1996. The definition states that all of the following must be present for the diagnosis of intrapartum asphyxia; profound metabolic or mixed academia(pH <7) in an umbilical artery blood sample, persistence of an Apgar score of 0-3 for longer than 5 minutes, neonatal neurologic sequelae (e.g.,

seizures, coma, hypotonia) and multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines).[5]

However, it was later demonstrated that many neonates who were neurological injured as a result of intrapartum asphyxia were not detected with the use of these criteria. In 1999, both the International Cerebral palsy Task Force and the American College of Obstetricians and Gynaecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy further reinforced the criteria by adding an extension to the ACOG criteria. These included the following updates.[6]

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (ph<7 and base deficit >12 mmols/l)
2. Onset of neonatal encephalopathy within 24 hours
3. Cerebral palsy of spastic quadriplegic or dyskinetic type
4. Exclusion of other identifiable aetiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders

The above essential criteria where further updated in 2003 by the ACOG and AAP by including 5 additional criteria that if present together with the above 4 essential criteria point toward an intrapartum timing of asphyxia on their own are nonspecific to asphyxial insult namely

1. A sentinel hypoxic event occurring immediate before or during labour
2. A sudden and sustained fetal bradycardia or other evidence of a non-reassuring fetal status
3. Apgar score of 0-3 beyond 5 minutes
4. Multisystem failure with 72 hours of birth

5. Early imaging study showing evidence of acute non focal cerebral abnormality

Using these criteria, all 4 essential criterion must be met before an intrapartum hypoxic cause of cerebral palsy can be considered whereas at least 3 of the 5 additional criterion have to be present to suggest an acute event rather than longer standing hypoxia or other chronic pathology.[7] If any one of the essential criteria is not fulfilled, it might show that intrapartum hypoxia was not the cause of cerebral palsy. This is vital since labelling an infant with hypoxic-ischemic encephalopathy from intrapartum asphyxia without these criteria may cause one to misdiagnose the real cause of the neurological problem and mismanage the neonate thereafter. Intrapartum asphyxia is one of the major causes of death and/ or neurologic impairment in children, therefore using a less strict definition that can be used even in clinical settings where one has no access to do blood gases will assist in highlighting the problem of intrapartum asphyxia.

1.2.2 Hypoxic ischemic encephalopathy

Neonatal encephalopathy is a clinically defined syndrome of impaired neurological function in the infant at or near term during the first week after birth. It presents with impaired initiation and maintenance of respiration, depression of tone and reflexes, altered level of consciousness and often seizures. When metabolic acidaemia has been conclusively proven by umbilical blood gases, fetal blood gases and or both, it must be established whether this is secondary to chronic hypoxia or whether an acute hypoxia has occurred during labour or birth in a previously healthy fetus.[8] Hypoxic ischemic encephalopathy is divided into 3 stages of severity that have an expected outcome

which includes mild HIE (Grade I) which consists of jitteriness and irritability, moderate HIE (Grade II) which consists of lethargy or abnormal tone (with or without seizures) and severe HIE (Grade III) which consists of coma or abnormal tone and multiple seizures.[9, 10] Unfortunately, the grade of HIE can only be assigned when the encephalopathy is established and at that grade no intervention can change the hypoxic injury already sustained but early therapeutic intervention may be imperative to decrease cerebral injury and prevent further complications. Therefore, there remains a need to identify characteristics that are associated with severe HIE or death in asphyxiated infants as these infants might benefit from therapeutic hypothermia.

1.3 Incidence

1.3.1 Perinatal asphyxia

Intrapartum asphyxia is one of the major causes of death and/ or neurologic impairment in children. The newborns who fail to initiate spontaneous respiration are more likely to die or have brain damage. Among the patients who die, a number of them will die during the neonatal period depending on the severity of brain injury. Globally, it is estimated that about 3.3 million neonates died in 2009.[11] In South Africa there were 14 000 neonatal deaths in 2008. About a quarter of neonatal deaths are due to intrapartum asphyxia. The fifth perinatal care survey in South Africa reported that the causes of death among infants who died from asphyxia 50% were due to hypoxic ischemic encephalopathy, 28% due to meconium aspiration syndrome and 18% due to persistent pulmonary hypertension of the newborn.[12]

In 2010, The World Health Organization (WHO) published the leading causes of death in South African children under the age of 5 years. In this group 34% of deaths were in the neonatal period which included prematurity (20%), intrapartum asphyxia and trauma (8%), sepsis/other infectious disorders and congenital abnormalities. The latest neonatal mortality rate in 2012 was reported to be 15/1000 live births. In relation to developed country e.g. USA, 48% of under 5 deaths are in the neonatal period with a neonatal mortality rate of 4/1000 live births of which only 3% are due to intrapartum asphyxia. (WHO: World Health Statistics. Geneva, WHO, 2012.). Though it is known how many neonatal deaths are due to intrapartum asphyxia in South Africa, there has been no reports as to how many babies are diagnosed with a problem of intrapartum asphyxia in our healthcare facilities and how many survive with complications associated with intrapartum asphyxia especially HIE which is more likely to be associated with long term neurologic impairment.

Whichever definition one uses, the incidence of intrapartum asphyxia in this report is very high compared to that reported in developed countries, which is at 1-5 / 1000 live births[13-15]. Compared to developing countries it is similar to that reported in Iceland (9.4/ 1000 live births)[16], lower than that reported in Nigeria (28/ 1000 live births)[17] but higher than that reported from Papua New Guinea (5.5/ 1000 live births)[18, 19]. We did not collect data on modifiable factors that might contribute to this high incidence of intrapartum asphyxia.

1.3.2 Hypoxic ischemic encephalopathy

Hypoxic ischemic encephalopathy refers to the CNS dysfunction associated with intrapartum asphyxia, and is often the prime concern while managing asphyxiated neonate as it can kill the neonate and can cause significant long-term neuromotor sequelae in those that survive. The overall incidence of HIE is variously reported as between 1-6 per 1000 births, but the sequelae of who survive is known to have a graded effect dependent upon severity of encephalopathy.[20] The incidence of moderate and severe forms of the disease is thought to be around 0.5-2/1000 births. Consequences of HIE ranging from cognitive, behavioural and memory problems to seizures and cerebral palsy of varying degrees and death, whilst rare in mild forms of HIE, are very high in the most severe forms.[20] In another study based in South Africa by Horn, et al the incidence of HIE varied from 2.3 to 4.3 per 1000 live births; mild HIE ranged from 0.4 to 1.3 per 1000 live births, and of moderate-severe HIE ranged from 1.5 to 3.7 per 1000 live births.[21]

1.4 Mortality

Regarding mortality and morbidity of various HIE grades, Morris et al noted that the outcome of those with the most severe form of the condition is poor, with a high portion of grade 3 HIE infants dying or surviving only to palliative care.[20] Morbidity in the form of abnormal neurological signs at discharge was highly prevalent in the moderate group, and almost universal amongst the most severe group.[17] In similar vein Shankaran, et al found that those with moderate encephalopathy have a 10 percent risk

of death, and those who survive have a 30 percent risk of disabilities. Sixty percent of infants with severe encephalopathy die, and many who survive are handicapped.[22] In Saudi Arabia fifteen to 20% of the infants with HIE die in the neonatal period and 25-30% of survivors develop permanent neurodevelopmental abnormalities e.g. cerebral palsy.[23] In severe hypoxic-ischemic encephalopathy, the mortality rate is reportedly 25-50%. Multi-organ failure is the cause of most deaths which occur in the first week of life. Those infants with severe neurologic disabilities often die in their infancy secondary to aspiration pneumonia or systemic infections. [24]

1.5 Factors associated with poor outcome

The factors associated with poor outcome have been identified in previous studies but most of these studies have been conducted in developed world. It is possible that the factors associated with poor outcome in developed countries are not the same as those in developing countries. Numerous studies have reported clinical predictors within hours of birth for poor outcome. These include depression at birth, resuscitation and the responses (e.g. 5 minute Apgar score of < 3, age of establishment of spontaneous breathing, use of extensive resuscitation), and postnatal clinical status (age at onset of seizures, depressed level of consciousness).[25]

1.5.1 Apgar Score

One of the factors associated with poor outcome is the Apgar score. The Apgar score was first developed in 1952 by Dr. Virginia Apgar, an obstetric anaesthesiologist.[26] Her goal was to develop a scoring system using signs observed that would gauge a neonate's transition after birth. It helps to quickly and subjectively assess the condition of the newborn infants.

The scoring system gained universal acceptance after it was shown to predict survival particularly at 5 minutes. It was then criticized when it was used as a predictor of birth asphyxia and long-term neurologic outcome. The problem was it didn't take into account many factors which can affect the score e.g. prematurity, intubation, and administration of drugs to the mother which all result in low scores that are not indicative of asphyxia.[27]It is important to remember that a low Apgar score does not point to the cause of the poor condition which may result from numerous different factors of which intrapartum hypoxia is only one. On its own, the Apgar score is a poor predictor of neurological outcome, although the risk of poor outcome increases with decreasing Apgar score and increasing duration of low Apgars.[28] Casey, et al examined whether the Apgar score was still good enough to predict survival during the neonatal period and if it remained pertinent in paediatric practice 50 years later. They found that among both preterm and term infants, those with a five minute Apgar score of 0 to 3 had a highest risk of death. These results were in keeping with the original reports by Apgar.[29] The importance of the Apgar score was further shown in the study by Laptook, et al where they look at whether the Apgar score at 10 minutes showed a greater correlation with death or disability in early childhood after perinatal hypoxic-

ischemic encephalopathy. They found that there was a 45% increase in the odds of death or disability in those infants with Apgars at 10 minutes of 7 or less in early childhood.[30] This further reflected the importance of the Apgar score in combination with other predictors of outcome in prognosticating infants after a perinatal insult has occurred. These studies showed that even 50 years later the Apgar score remains a pertinent tool in assessing the need for resuscitation at birth and remains a important tool in identifying those infants who are at risk of perinatal asphyxia and their complications thereof.

1.5.2 Time to spontaneous respiration

Infants are usually breathing well by one minute after birth. The successful transition from intrauterine to extra uterine life requires a newborn baby to initiate spontaneous breathing at time of birth. Most term infants will initiate spontaneous respiration without any form of assistance. It has been reported that 5-10% of newborns will require stimulation, 3-6 % will require bag mask ventilation and less than 1% will require chest compressions, intubation and adrenaline.[31] Time to spontaneous respiration has been shown to be a good predictor of poor outcome in infants requiring resuscitation. Shah, et al looked at predictors of outcome of term infants with severe asphyxia comparing three variables namely base deficit, chest compressions and time to spontaneous respiration. They found that at an age of respiration more than 30 minutes had a profound (2.3 times) increase in poor outcome with regards to neurological complications, asphyxia related complications and/or death.[32] Pappas, et al also showed that time to spontaneous respiration of more than 10 minutes was strongly

associated with poor outcome after adjustment to the level of $PC0_2$ levels.[33] Klinger, et al found that there was 2.2 times greater risk for severity for those infants with prolonged time to initiation of respiration with a mean time of 30 minutes.[34] Ekert, et al also showed in their study that an onset of respiration of > 10 minutes had a 5.1 times greater likelihood of severe adverse outcomes.[35] This highlights the importance of time to spontaneous respiration in predicting severity of outcome.

1.5.3 Need and extent of resuscitation

Ten percent of newborns may require some assistance to begin breathing at birth whereas less than 1% require extensive resuscitative measures. Although the vast majority of newly born infants do not require interventions to make the transition from intrauterine to extra uterine life, a sizable number will require some degree of resuscitation. Those newborns that will need resuscitation at birth can be identified prior to birth by careful consideration of risk factors. If the possible need for resuscitation is anticipated, more skilled personnel should be alerted and the essential equipment prepared.[36]

1.5.3.1 Bag Mask Ventilation

Ersdal, et al looked at early initiation of basic resuscitation interventions including face mask ventilation to minimize birth asphyxia related mortality in low-income countries. They found that the majority of newborn infants delivered in a rural institution in Sub-Saharan Africa, spontaneously started breathing within one minute and a substantial

number of apnoeic babies began breathing in response to basic stimulation/suction and/or BMV with a positive short term outcome in the majority of infants. They also found that 50% of the apnoeic infants responded to stimulation and suctioning only with a good outcome in this group. Those infants who received BMV regained spontaneous respiration within four to five minutes of delivery. Death was significantly more likely with more prolonged ventilation as well as when there was a delay in initiating BMV. Another important observation was that almost 10% of newborns died in the group that received BMV. [37]

1.5.3.2 Chest compressions and/ or adrenaline

Both chest compressions and adrenaline have been shown to predict the severety of outcome of term infants with intrapartum asphyxia as seen by the following two studies. Shah, et al found that the administration of chest compressions for more than 10 min showed a 3.2 time increased risk of neurological injury and/or death. They also found that the use of epinephrine during the resuscitation had a 2.6 time greater risk of poor outcome post resuscitation.[32] In similar vein Ekert, et al found that chest compressions at 10 minutes showed a 3.4 times greater risk for poor outcome which could be used as early marker (among others) of severity of asphyxia and HIE.[35]

1.5.4 Blood gas analysis

Blood gas analysis is very important in the diagnosis of intrapartum asphyxia when available. This should be done within one hour after birth. After an hour the newborn's system may have compensated for the acidaemia. This will result in not accurately

evaluating the newborn for the criteria of intrapartum asphyxia and therefore a significant event might be missed. It is important to evaluate both the respiratory and metabolic components of each sample. An isolated respiratory acidosis is usually the result of a short-lived impairment of the uteroplacental or fetoplacental circulation and usually does not result in adverse outcome. Prolonged insufficiency on the other hand results in progressive metabolic acidosis due to anaerobic glycolysis. Consequently most severe fetal acidosis is mixed.

1.5.4.1Base deficit and pH

Base excess values have a significantly greater usefulness than umbilical cord pH values, because base excess does not change significantly with respiratory acidosis and demonstrates a linear correlation to the degree of metabolic acidosis. The change in hydrogen ion concentration associated with a fall in pH from 7.0 to 6.9 is almost twice that which leads to a fall in pH from 7.3 to 7.2. The base deficit provides a more linear measure of the degree of accumulation of metabolic acid and is adjusted for variation in PCO_2.[38] Low, et al initially used a measure of buffer base (<36.1 mEq/L or nearly equivalent base deficit <12) as an indicator of metabolic acidosis which is associated with newborn complications. After intrapartum asphyxia (buffer base, <34 mmol/L), the incidence of major or minor deficits was 20% which increased to 80% among infants with the most severe metabolic acidosis (buffer base,<22 mmol/L). Therefore it can be presumed that asphyxial injury does frequently not occur until fetal base deficit is ≤12 mmol/L. Notably, most newborns with a base deficit of <12 mmol/L do not demonstrate neurologic injury. Even at levels of severe acidosis (base deficit, <16 mmol/L), most newborns either die or survive normally, with only a small proportion resulting in

cerebral palsy.[39] Perlman, et al looked at base deficit as predictor of poor outcome too and found that a base deficit more than 16 had a two time greater risk for neurological abnormality and/or death.[25] It was also noted that serious adverse complications in the newborn period are rare after birth with umbilical cord pH greater than 7.0 or base excess less than minus 12 mmols/l. On follow up of those infants with cord pH above 7.0, no adverse effects where seen on cognitive outcome. Even at pH less than 7.0 most infants will still recover fully without remarkable consequences. In this respect, cord pH or base excess alone are poor predictors of outcome. Sehdev, et al looked at neonatal morbidity in infants with pH < 7.00. He found that those infant who had a base deficit >16 and a 5 minute Apgar score of <7 concurrently, identified 79% of neonates having complications.[40] Armstrong and Stenson have noted that Goodwin, et al found that hypoxic ischemic encephalopathy occurred in 12% of infants with cord pH 7.0, 33% with cord pH 6.9, 60% with cord pH 6.8 and 80% with cord pH 6.7 or less.[41]

1.5.4.2 Partial pressure of oxygen and carbon dioxide

Hypercarbia will contribute to the degree of acidosis that will be found in the initial blood gas analysis. This can lead to the misdiagnosis of perinatal asphyxia if only pH is used as inclusion criteria. Therefore pH will need to be adjusted for the level of pCO_2 before a definitive assessment can be made. On the other hand it can have a direct influence on severity of hypoxic ischemic encephalopathy. Both pH and pCO_2 affect vascular tone, cerebral blood flow, cerebral oxygenation and may thereby modulate neuronal injury in neonates with HIE. PCO_2 also contributes to decreased partial pressure of arterial oxygen and decrease oxygen release which has further detrimental effects.[34]

With regards to hyperoxaemia after severe intrapartum asphyxia, increased toxic free oxygen radicals secondary to high PaO_2 mediate the adverse effects on the brain. Also hyperoxaemia becomes even more detrimental to the brain during the period of reperfusion.[34] Pappas, et al found in the effect of hypocarbia on HIE with a low $PaCO_2$ concentration within the first 16 hours of life were associated with an increase in death or disability. This was directly related to the degree and severity of hypocarbia.[33] Klinger, et al looked at hyperoxaemia and/or hypocapnia during the first 2 hours of life and assessed whether this added to the risk of brain injury after intrapartum asphyxia. They found that adjusting for the severity of intrapartum asphyxia, peak PaO_2 values exceeding 26.6 kPa (200 mm Hg) and $PaCO_2$ values of 2.6 kPa (20 mm Hg) or lower during the first 20 to 120 minutes of life were associated with death or adverse neurodevelopmental outcome.[34] The risk of adverse outcome was greatest in subjects who had both. There was three times increase in risk for poor outcome with either severe hyperoxaemia or severe hypocapnia but more significant was a 4 time greater risk in those infant who had both severe hyperoxaemia and severe hypocapnia.[34] Therefore, normoxia and normocapnia should be maintained with closer monitoring and individualised oxygen supplementation and ventilation to avoid exacerbation of the damage sustained.

In this study we sought to assess the incidence of intrapartum asphyxia and hypoxic ischemic encephalopathy (HIE) (according to the presence of signs that define HIE 1,2,3 in Sarnat staging)(Table 1)[10], infant characteristics and factors associated with severe HIE and mortality in term and near-term neonates diagnosed with intrapartum asphyxia in a setting where there is a high patient load and resources are limited.

CHAPTER 2.0 METHODS

2.1 Study design: A retrospective, descriptive study of neonates born at term or near-term (defined as those with birth weight ≥2000 grams) and admitted with a diagnosis of intrapartum asphyxia.

2.2 Study setting: The study was conducted at CHBAH a public government hospital. This hospital serves the population of Soweto and the surrounding areas. Until April 2014, it was the only hospital in Soweto. It is also a referral centre for all clinics conducting births in Soweto and surrounding areas. These clinics conduct about 8 000 births per year while the hospital conducts about 23 000 births per year, with a total of just over 30 000 births per year for the cluster. In 2011, the hospital had two operating theatres for obstetric surgery including caesarean sections (CS) and twelve neonatal intensive care (ICU) beds.

2.3 Study Population: Infants who were born weighing ≥ 2000g and required resuscitation with at least a bag mask ventilation (BMV) and were admitted with a diagnosis of intrapartum asphyxia were included. The study period was from 1st January to 31st December 2011. Infants who died in labour ward soon after birth were excluded as their records either were missing or had incomplete information. Patients who were born before arrival to hospital, twin pregnancies (due to the increased risk for complications of which one is intrapartum asphyxia) and those infants with severe congenital abnormalities were also excluded.

2.4 Study Procedure: Hospital records of newborn infants who met the inclusion criteria were retrieved and the following data were collected: birth weight, gender, gestational age, growth, Apgar score, resuscitation required, time to spontaneous respiration, arterial blood gas done within the first hour of birth and diagnosis of hypoxic ischemic encephalopathy. Maternal records were also reviewed for maternal age, parity, maternal human immunodeficiency virus results, antenatal care, maternal disease, mode of delivery, presence of foetal distress or meconium stained amniotic fluid and records of cardiotocograph. Means, standard deviations, medians and ranges were used to describe continuous variables while frequencies and percentages were used to describe categorical variables. The Chi square or Fischer's exact tests and Student t-test were used to compare the categorical variables and continuous variables respectively between infants with normal or mild to moderate HIE and those with severe HIE or died. Differences between the two groups were considered statistically significant at a *p*-value of <0.05. The extent of association of different variables with severe HIE or death was reported using odds ratios (ORs) and the precision using 95% confidence intervals (CIs). In order to determine predictors of severe HIE or death, variables with *p*-values <0.05 on the univariate logistic regression were included in the multivariate logistic regression. STATA version 10.0. was used to perform the statistical analysis. The approval to conduct the study was obtained from the hospital protocol review committee and the University of the Witwatersrand Human Research Ethics Committee.

CHAPTER 3.0 RESULTS

3.1 Incidence of asphyxia

There were 23035 total live-births of which 21086 weighed ≥2000grams at birth. Of those weighing ≥2000g, 357 had a diagnosis of intrapartum asphyxia of which 321 were admitted and 36 died in labour ward before admission. Since the records of the latter were either missing or had incomplete information, they were excluded from the more detailed analysis but where included in the calculation of overall mortality rate only since my be reasonable to assume these infants died of asphyxia. The incidence of intrapartum asphyxia varied from 8.7 to 15.2/1000 deliveries depending on the definition of intrapartum asphyxia used (Table 2).

Table 2 Incidence of asphyxia according to different definitions of intrapartum asphyxia (n=21086 live births >2000g)

Definition	**Number of babies with intrapartum asphyxia**	**(per 1000 live births)**
Need for BMV at birth	321	15.2[13.7,17.0]
BMV and Base deficit >12 mmol/L	261	12.4[11.0,14.0]
BMV and Apgar score <7 at 5 minutes	218	10.3[9.1,12.0]
BMV, Apgar score <7 at 5 minutes and Base deficit >12 mmol/L	183	8.7[7.5,10.0]

BMV – Bag Mask Ventilation **95% CI – 95% Confidence interval**

3.2 Maternal characteristics

Demographic and clinical characteristics of mothers giving birth to infants diagnosed with intrapartum asphyxia are shown in Table 3. Most of the mothers (95.6%) attended antenatal care. Average maternal age was 25 years and 57.6% where pregnant for the first time. Just over a quarter of mothers (25.9%) where positive for human immunodeficiency virus (HIV). Among the mothers who had maternal illness recorded, the common diagnosis was pregnancy induced hypertension accounting for 75.9% of mothers with recorded illness and 19.6% of mothers giving birth to infants with a diagnosis of intrapartum asphyxia. Thirty four percent of babies with intrapartum asphyxia where born to mothers with meconium-stained amniotic fluid. The mode of delivery was CS in 38% of cases, with the most common reason for performing the CS was foetal distress (68.9%). Electronic monitoring with cardiotocograph was recorded in 77.6 % of mothers of which 47% where abnormal. In mothers with abnormal CTG, the common abnormality was late deceleration (76.9%) followed by early deceleration (6.8%) and foetal bradycardia (6.8%).

Table 3 Characteristics of mothers who delivered infants with intrapartum asphyxia

Variables	Numbers (%)
Maternal age	25.17 ± 6.4*
Number of first pregnancies	185 (57.6)
Number with positive HIV test	83 (25.9)
Number received antenatal care	307 (95.6)
Maternal illness	
- Hypertension	63 (19.6)
- Other medical conditions	20 (6.2)
Mode of delivery	
- Caesarean section	122 (38.0)
- Vaginal delivery	171 (53.2)
- Assisted vaginal delivery	28 (8.7)
Number with meconium stained amniotic fluid	110 (34.3)
Documented electronic monitoring during labour CTG)	
- Yes	249 (77.6)
- No	72 (22.4)
Number with normal CTG in monitored patients	132/ 249 (53)
Number with abnormal CTG in monitored patients	117/ 249 (47)
- Late decelerations	90/ 117 (76.9)
- Early decelerations	8/ 117 (6.8)
- Fetal bradycardia	8/ 117 (6.8)
- Beat to beat variability	3/ 117 (2.6)
- Suspicious tracing	8/117 (6.8)

* - Mean ± SD CTG – Cardiotocograph

3.3 Infant characteristics

Average birth weight was 3084 grams with an average gestation of 39 weeks.(Table 4)

3.3.1 Apgar scores

Apgar scores were done at 1 minute and 5 minutes in 99.5% and at 10 minutes in 72.6% of babies. At 5 minutes 68.0% had an Apgar score of <7. Of those infants with documented Apgar score at 10 minutes, 29.7% had an Apgar of <7.

3.3.2 Resuscitation and time to spontaneous respiration

During resuscitation, the majority (90%) of babies diagnosed with intrapartum asphyxia responded to BMV only, while 10% required extensive resuscitation in the form of chest compressions (7%) and adrenaline (3%). Among the infants who had time to spontaneous respiration recorded, 60% took >5 minutes to attain spontaneous respiration.

3.3.3 Blood gases

All infants were resuscitated with 100% oxygen. The majority of infants had blood gas analysis performed within an hour after delivery. The percentage of infants who did not have blood gas data recorded where roughly 7.5% and where excluded in the total number used in the analysis of the blood gas parameters.

On blood gas analysis the mean partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) were 145 and 36 mmHg respectively. Only 24% had pH < 7.00, 58% of infants had PaO_2 of >100 mmHg, 53% had hypocarbia, $PaCO_2$<35 mmHg and 80% had a base deficit >12 mmol/L. Only 59.8% of infants had a lactate documented in their file but since it is a good indicator of tissue hypoxia it is an important measurement to include in the analysis. Of those documented, 97.4% of the readings where found to be >7.5 mmol/l.

Table 4 Characteristics of infants diagnosed with intrapartum asphyxia

Variables	Number (%)
Birth weight	3084 ± 448*
Gestational age	38.5 ± 2.2*
Sex	
- Male	192 (59.8)
- Female	129 (40.2)
Apgar score at 5 minutes	
- < 5	75 (23.4)
- 5-7	143 (44.6)
- ≥7	101 (31.5)
Apgar score at 10 minutes	
- Recorded	233(72.6)
- < 5	19 (8.2)
- 5-7	50 (21.5)
- ≥7	164 (70.3)
- Not recorded	88 (27.4)
Resuscitation required	
- BMV only	288 (89.7)
- BMV and CC	23 (7.2)
- BMV + CC + Adrenalin	10 (3.1)
Time to spontaneous breathing	
- <5 minutes	105 (32.7)
- 5-10 minutes	89 (27.7)
- 10-20 minutes	42 (13.1)
- >20 minutes	27 (8.4)
- Not recorded	58 (18.1)
pH	7.09 ±0.16*
- Number with pH <7.00	77 (24.0)
- Number with pH 7.00 - 7.25	182 (56.7)
- Number with pH >7.25	38 (11.8)
- Not recorded	24(7.5)
paO_2	145.63 ± 79.92*
- Number with paO_2 <50 mmHg	16 (5)
- Number with paO_2 50 – 100 mmHg	92 (28.7)
- Number with paO_2 >100 mmHg	186 (57.9)
$paCO_2$	36.66 ± 16.71*
- Number with $paCO_2$ <35 mmHg	170 (53.0)
- Number with $paCO_2$ 35 – 45 mmHg	64 (19.9)
- Number with $paCO_2$ >45 mmHg	62 (19.2)
Base deficit	18.09 ± 5.26*
- Number with Base deficit ≤12mmol/L	35 (10.9)
- Number with Base deficit >12mmol/L	261 (81.3)

* - Mean ± SD BMV- Bag Mask Ventilation CC- Chest Compression

3.4 Incidence of hypoxic ischemic encephalopathy and mortality

The incidence of HIE ranged from 8.5 - 13.3/ 1000 live births depending on the definition of perinatal asphyxia used (Table 5). Defining perinatal asphyxia as Apgar score at 5 minutes <7 and base deficit >12 mmol/L, 179 patients (55.8%) developed signs of hypoxic ischemic encephalopathy, giving an incidence of 8.5/1000 live births compared to 13.3/1000 live births when using need for bag mask ventilation. Among those who developed HIE, 59% had moderate to severe HIE. The overall mortality rate including the deaths from labour ward was 14.2%. The mortality rate excluding the deaths from labour ward came to 7.8%, with the rates in infants with HIE ranging from 8.9% to 12.3%, depending on the definition of intrapartum asphyxia used. Only 1.4% of infants with HIE 1 died compared to 7.1% and 62.5% in those with HIE 2 and 3 respectively, defining intrapartum asphyxia with inclusion of metabolic acidaemia. There were no deaths among those who did not develop HIE. Sixty four percent of the deaths were primarily due to HIE, and 20% were due to HIE and MAS (Meconium Aspiration Syndrome) with or without PPHN (Persistent Pulmonary Hypertension of the Newborn and 24% were due to sepsis. Co-morbidities found in patients with asphyxia included renal dysfunction 31.2%; clinically presumed sepsis 24.6% and positive blood culture 13.9%.

Table 5 Incidence of hypoxic ischemic encephalopathy and mortality rate in patients with intrapartum asphyxia defined as:

	Need for bag mask ventilation			**Apgar score <7 and base deficit >12 mmols/L**		
	Total n (%)	Incidence (per 1000 live births)	Number died, n(%)	Total n (%)	Incidence (per 1000 live births)	Number died, n (%)
No HIE	40 (12.5)	-	0 (0)	4 (1.3)	-	0 (0)
HIE I	131 (40.8)	6.2	2 (1.5)	71 (22.1)	3.4	1 (1.4)
HIE II	122 (38.0)	5.8	7 (5.7)	84 (26.2)	4.0	6 (7.1)
HIE III	28 (8.7)	1.3	16 (57.1)	24 (7.5)	1.1	15 (62.5)
All HIEs	281 (87.5)	13.3	25 (8.9)	179 (55.8)	8.5	22 (12.3)
Overall Mortality Rate including deaths in labour ward = 14.2 %						

HIE- Hypoxic Ischemic Encephalopathy

3.5 Association with HIE severity

The comparison of HIE 1 and 2 with HIE 3 and /or death was made between the two groups for all patients with intrapartum asphyxia defined as need for BMV. On univariate analysis factors, there was no statistical significant differences in maternal characteristics and CTG readings between those with no HIE or mild to moderate compared to those with severe HIE or those who died. The infant factors that were associated with poor outcome (severe HIE or death) were low Apgar scores at 5 and 10 minutes, need for chest compressions and adrenalin, delay in time to spontaneous respiration, low pH, high base deficit and low bicarbonate. Median Apgar score was lower at 5 minutes (4 vs. 6, $p<0.01$) and 10 minutes (5 vs. 8, $p<0.01$), time to spontaneous respiration was longer (15.4 min. vs. 6.2 min, $p<0.01$), pH was lower (6.9 vs. 7.1, $p<0.01$), base deficit was higher (22.8 vs. 17.5 mmol/l) and bicarbonate was lower (8.9 vs. 11.6 mmol/l) in

Table 6 Factors associated with severe hypoxic ischemic encephalopathy HIE or death in infants with intrapartum asphyxia

	HIE 1-2 (n=256)	**HIE 3 and/or Death (n=37)**	**P- value***	**P-value****
Median Apgar at 5 minutes	6[IQR, 5-7]	4[IQR, 3-5]	<0.001	0.99
Median Apgar at 10 minutes	8[IQR, 7-8]	5[IQR, 4-7]	<0.001	0.004
Need for chest compressions	61/256(23.8%)	22/37 (59.5%)	<0.001	0.35
Need for adrenalin	1/256 (0.39%)	9/37 (24.3%)	<0.001	0.03
Time to spontaneous respiration (minutes)	6.17 ± 5.71	15.36 ± 11.93	<0.001	0.69
pH	7.11 ± 0.14	6.92 ± 0.18	<0.001	0.54
PaO_2 (mmHg)	145.25 ± 76.00	148.75 ± 108.35	0.82	N.S.
$PaCO_2$ (mmHg)	34.94 ± 13.89	49.91 ± 27.69	<0.001	0.33
Bicarbonate (mmol/L)	11.59 ± 2.84	8.91 ± 2.72	<0.001	0.03
Base Deficit (mmol/L)	17.48 ± 4.88	22.74 ± 5.79	<0.001	0.30
Lactate (mmol/L	15.90 ± 4.34	18.26 ± 3.68	0.008	0.61
Glucose (mmol/L)	6.79 ± 2.30	6.93 ± 4.48	0.82	N.S.

* - Univariate analysis ** - Multivariate analysis N.S. = Not significant
± - Standard deviation IQR – Inter-quartile range

infants with severe HIE and/ or death compared to those who survived to hospital discharge with no HIE or mild to moderate HIE (Table 6). Factors showing statistically significant differences in univariate analysis were included in a multivariate analysis to determine factors that could independently predict severity of HIE or death. Only Apgar score at 10 minutes (p=0.004), adrenaline (p=0.034) and bicarbonate levels in the first hour after birth (p=0.02) were found to be predictors of severe HIE and/or death.

3.6 Severity of different variables and odds of developing severe HIE or death

The odds of having severe HIE or death was greater if Apgar score at 5 minutes was <5 (OR 9.33; 95% CI 2.83 - 34.03); Apgar score at 10 minutes was 5-7 (OR 3.05; 95% CI 1.08 - 8.62) or was <5 (OR 19.1; 95% CI 5.66 - 66.9) compared to Apgar scores of >7; if required chest compressions (OR 8.36; 95% CI 3.71 – 19.1); if required adrenalin, (OR 81.2; 95% CI 13.2 - 647.7) and time to spontaneous respiration was more than 20 minutes (OR 27.2; 95% CI 6.89 - 117.4)**.** When arterial blood gas was done within the first hour of life the odds of having severe HIE and/or death were higher if the pH was <7 (OR 5.33; 95% CI 1.31 - 25.16, PaO_2 <60 mmHg (OR 9.65; 95% CI 1.87 - 55.12) and $PaCO_2$ >45 mmHg (OR 3.98; 95% CI 1.11 - 15.56) (Table 7).

Table 7 The odds ratio for developing severe hypoxic ischemic encephalopathy and/ or death with severity of different variables.

Variables	Odds ratio [95% Confidence interval]
Apgar Score at 5 minutes	
>7	Reference
5 to 7	1.79 [0.50, 7.01]
<5	9.33 [2.83, 34.03]
Apgar Score at 10 minutes	
>7	Reference
5 to 7	3.05 [1.08, 8.62]
<5	19.13 [5.66, 66.89]
Extent of Resuscitation	
BMV only	Reference
Chest Compressions	8.36 [3.71, 19.1]
Adrenaline	81.2 [13.17, 647.7]
Time to Spontaneous Respiration	
<5 minutes	Reference
5 to 10 minutes	2.18 [0.55, 9.24]
10 to 20 minutes	3.41 [0.74, 16.20]
>20 minutes	27.19 [6.89, 117.38]
pH	
>7.25	Reference
7.0 – 7.2	1.48 [0.35, 7.13]
<7.0	5.33 [1.31, 25.16]
PaO_2 (mmHg)	
60 - 100	Reference
>100	2.40 [0.63, 10.74]
<60	9.65 [1.87, 55.12]
$PaCO_2$ (mmHg)	
35 - 45	Reference
>45	3.98 [1.11, 15.56]
<35	0.75 [0.19, 3.07]

BMV- Bag Mask Ventilation

CHAPTER 4.0 DISCUSSION

The recent development of induced hypothermia to reduce the risk of mortality and disability in infants with intrapartum asphyxia prompted this study to assess the burden of intrapartum asphyxia (incidence of intrapartum asphyxia) and the numbers that might require cooling (incidence of moderate to severe HIE) in a setting where there is high patient load but limited resources. Defining intrapartum asphyxia as need for BMV, Apgar score <7 at 5 minutes and base deficit >12 mmol/l within an hour post-delivery, the incidence of asphyxia was 8.7/ 1000 live births. Most studies reporting on incidence of intrapartum asphyxia from developing countries do not include blood gases, and use only need for assistance with respiration and/or Apgar score <7 at 5 minutes. Using the definition of need for assistance with breathing or Apgar score <7 at 5 minutes the incidence of intrapartum asphyxia in this study was 15.2/1000 or 10.3/1000 live births respectively. Whichever definition is used, the incidence of intrapartum asphyxia in this study is very high compared to that reported in developed countries, which are at 1-5/1000 live births.[13, 14] We did not collect data on modifiable factors that might contribute to this high incidence of intrapartum asphyxia. A perinatal care survey conducted in SA in 2008-9 reported that delay in seeking medical care, inadequate monitoring during labour and lack of facilities are modifiable factors that were identified in neonates who died from intrapartum asphyxia.[12]

The overall incidence of encephalopathy in infants with Apgar score <7 and base deficit >12mmol/L was 8.5/1000 live births, with 60% being due to HIE 2 and 3. The overall incidence reported in this study was higher than that reported in Sweden, a developed country and Kathmandu, Nepal, a developing country where the incidence was reported to be 1.8/ 1000 live births and 6.4/1000 live births respectively[42, 43]but lower than that

of 28.1/1000 that reported from Sarlahi, Nepal.[44] It has been reported that among infants diagnosed with HIE, 15-20% will die in the neonatal period and 25-30% of survivors develop permanent neurodevelopmental abnormalities including cerebral palsy.[14] In this study 62% and 7% of infants with HIE 3 and HIE 2 respectively died before hospital discharge. Some of the infants with HIE 2 and most of those with HIE 3 who survive to hospital discharge will have a severe neurologic outcome. Therefore this high incidence of HIE in this report is a major concern and highlights the need for improvement in the healthcare system so that there is a reduced incidence of asphyxia and less HIE. It is also important to treat those with moderate to severe HIE with induced hypothermia to reduce neurologic disability and mortality.

Predictors of severe HIE and/or deaths were low Apgar score at 10 minutes, need for adrenaline and low bicarbonate. Shah, et al reported similar findings and that need for chest compression, high base deficit and delayed onset of respiration more than 20 minutes in infants with intrapartum asphyxia was associated with poor outcome. This study reported that the rates of severe adverse effects were 64% if one predictor was present and 76% if two were present and 93% if all three were present.[32] The finding that Apgar score at 10 minutes is a predictor of poor outcome is helpful as the Apgar score is easy to perform and is widely used in labour and delivery rooms both in developed and developing countries. Though Apgar score has not been helpful in predicting infants who will develop cerebral palsy, especially in the era of using induced hypothermia for asphyxia,[45] it has been shown to be of great assistance in predicting survival in both preterm and term infants. Laptook, et al reported that each point decrease in Apgar score at 10 minutes was associated with a 45% increase in the odds of death or disability, and concluded that Apgar score at 10 minutes provided useful

prognostic information before other evaluations are available.[30] Presence of metabolic acidaemia or low bicarbonate is of additional value to Apgar score in predicting poor outcome, as Apgar score is often not done in real time and therefore can be unreliable. A base deficit of >16mmol/L has previously been reported to be a predictor of poor outcome.[10] Casey, et al also reported that a combination of low Apgar score (0-3) and cord pH <7.0 increased the risk of mortality in both preterm and term infants.[29] Sehdev, et al reported that a base deficit >16 mmol/L and a 5 minute Apgar score of <7 concurrently, identified 79% of neonates who would develop complications.[40]

Study limitations

One of the chief limitations of this study is that it is a retrospective study. Therefore the diagnosis of intrapartum asphyxia and encephalopathy was mainly based on what was recorded in the patient's hospital file. This might have led to overestimation of the true incidence of HIE especially as some clinical findings might be affected by the experience of a person conducting the examination. This overestimation is potentially affected by junior doctors commonly labelling infants with intrapartum asphyxia as having HIE.

Another limitation was the exclusion of the 36 deaths in labour ward. These were included in the overall mortality rate calculation but were excluded in the total number of asphyxiated infants and in the calculation of the incidence of intrapartum asphyxia amongst others. Since the files of these patients could not be found, details surrounding the deaths were unclear. It might have been concluded that these deaths were due to severe intrapartum asphyxia but unfortunately it was unknown if there were any underlying confounding factors (e.g. congenital abnormalities, etc.) which could of

contributed to the cause of death other than perinatal asphyxia. This may have potential consequences especially with the calculation of incidence, since adding these deaths could increase number of asphyxiated infants by roughly 10% and therefore increasing the incidence of intrapartum asphyxia.

A further limitation was that important data with regards to time to spontaneous respiration, blood gas analysis and Apgar score at 10 minutes where not found in 18.1%, 7.5% and 27.4% respectively. This missing data would be valuable in the statistical analysis and fine tune it more, making the analysis more complete. Due to the absence of the data, the analysis was performed with the numbers available and analysed as closely as it could.

Despite these limitations this study highlights the burden of intrapartum asphyxia and encephalopathy in our hospital and the need to attend to factors that might be contributing to this high incidence of intrapartum asphyxia. In addition it identifies areas in our management that might be contributing to high incidence of HIE namely use of 100% oxygen and identifies information that might help when rationing use of intensive care beds and therapeutic hypothermia.

CHAPTER 5.0 CONCLUSION AND RECOMMENDATIONS

The incidences of both intrapartum asphyxia and hypoxic ischemic encephalopathy are very high in this CHBAH. As moderate to severe hypoxic-ischemic encephalopathy is more likely to be associated with abnormal neurodevelopmental outcomes and disability, factors that contribute to a high incidence of intrapartum asphyxia must be avoided. Those infants at risk of developing encephalopathy must be offered neuro-protective treatment, namely induced hypothermia. Where arterial blood gas analysis,

intensive care facilities and induced hypothermia are not available or are limited, Apgar score <5 at 10 minutes, need for chest compressions and need for adrenalin can be of assistance in predicting poor outcome and in predicting need for counselling of families with a neonate with intrapartum asphyxia regarding prognosis and further interventions. Understanding the burden and outcomes of intrapartum asphyxia is important, so that one can be able to assess how much assistance is required towards its reduction and to identify factors associated with poor outcomes. Intrapartum asphyxia must be prevented as it is associated with high mortality rate especially in those with severe HIE, and survivors are more likely to have abnormal neurodevelopmental outcome. In addition to resuscitation and basic post-resuscitation care, induced hypothermia (neuro-protection) should be used in those with moderate to severe HIE in order to reduce mortality rate and incidence of abnormal neurodevelopmental outcome.

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PART C- APPENDIX

3.1 Appendix A – Publication acceptance letter

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27th January 2015

Eduard Bruckmann;

The article

INTRAPARTUM ASPHYXIA AND HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN A PUBLIC HOSPITAL: INCIDENCE AND PREDICTORS OF POOR OUTCOME

Eduard Bruckmann,MBChB; SithembisoVelaphi, MBChB, FC Paed

has been accepted for the April edition of the South African Journal of Medicine

S Afr Med J 2015;105(4):xxxx.

(page numbers still to be determined).

Signed:

Professor Janet Seggie

Editor-In-Chief

South African Medical Journal

Health & Medical Publishing Group

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3.2 Appendix B – Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Eduard Buckmann

CLEARANCE CERTIFICATE	**M120960**
PROJECT	The Number, Characteristics and Outcome of Neonates with Asphyxia Born and Admitted at Chris Hani Baragwanath Hospital
INVESTIGATORS	Dr Eduard Buckmann.
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	28/09/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 28/09/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Professor Sithe Velaphi

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

3.3 Appendix C – Publication

Intrapartum asphyxia and hypoxic ischaemic encephalopathy in a public hospital: Incidence and predictors of poor outcome

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Objective. To determine the incidence of asphyxia and hypoxic ischaemic encephalopathy (HIE) and predictors of poor outcome in a hospital in a developing country.
Methods. Neonates of birth weight ≥2 000 g who required bag-and-mask ventilation and were admitted with a primary diagnosis of asphyxia from January to December 2011 were included. Medical records were retrieved and maternal and infant data collected and analysed. Infants who had severe HIE and/or died were compared with those who survived to hospital discharge with no or mild to moderate HIE.
Results. There were 21 086 liveborn infants with a birth weight of ≥2 000 g over the study period. The incidence of asphyxia ranged from 8.7 to 15.2/1 000 live births and that of HIE from 8.5 to 13.3/1 000, based on the definition of asphyxia used. In 60% of patients with HIE it was moderate to severe. The overall mortality rate was 7.8%. The mortality rate in infants with moderate and severe HIE was 7.1% and 62.5%, respectively. The odds of severe HIE and/or death were high if the Apgar score was <5 at 10 minutes (odds ratio (OR) 19.1; 95% confidence interval (CI) 5.7 - 66.9) and if there was no spontaneous respiration at 20 minutes (OR 27.2; 95% CI 6.9 - 117.4), a need for adrenaline (OR 81.2; 95% CI 13.2 - 647.7) and a pH of <7 (OR 5.33; 95% CI 1.31 - 25.16). Predictors of poor outcome were Apgar score at 10 minutes (p=0.004), need for adrenaline (p=0.034) and low serum bicarbonate (p=0.028).
Conclusion. The incidence of asphyxia in term and near-term infants is higher than that reported in developed countries. Apgar score at 10 minutes and need for adrenaline remain important factors in predicting poor outcome in infants with asphyxia.

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Asphyxia is defined biochemically as a condition of impaired respiratory gaseous exchange that leads to hypoxaemia, hypercapnia and metabolic acidosis. Metabolic acidaemia, defined as a base deficit of >12 mmol/L, has been associated with episodes of intrapartum asphyxia and has therefore been used to define asphyxia biochemically.[1] The problem with this definition is that a number of normal babies have metabolic acidosis, and if it is used on its own there is a risk that the incidence of asphyxia may be overestimated.[2] Clinically, the need for bag-and-mask ventilation (BMV) at birth and/or an Apgar score <7 have been used to define intrapartum asphyxia.[3] Since in many developing countries there are no facilities to do blood gas measurement, base deficit is not used as part of the definition and only the clinical definition is used. Using the clinical definition alone to describe the incidence of asphyxia may also overestimate the incidence, as infants who do not initiate respiration are not always asphyxiated intrapartum. Assessing the incidence of asphyxia using a combination of clinical definition of need for BMV, Apgar score <7 at 5 minutes and metabolic acidaemia (base deficit >12 mmol/L) is therefore more likely to provide information on the true incidence of asphyxia in any population. Neonates with asphyxia often have ongoing respiratory depression requiring respiratory support in a neonatal intensive care unit (NICU). Where resources are limited, there is competition for these interventions, resulting in rationing and their being offered to infants who are more likely to survive with minimal morbidity. It is therefore important to determine factors that are associated with severe morbidity and mortality, as they could assist in decision-making on who should be offered these limited resources.

In this study we sought to assess the incidence of asphyxia and hypoxic ischaemic encephalopathy (HIE) according to the presence of signs that define HIE 1, 2 and 3 in Sarnat staging (Table 1),[4] infant characteristics and factors associated with severe HIE and mortality in term and near-term neonates diagnosed with asphyxia in a setting where there is a high patient load and resources are limited.

Methods

Study design. A retrospective, descriptive study of neonates born at term or near term (defined as birth weight ≥2 000 g) and admitted with a diagnosis of asphyxia.

Study setting. Chris Hani Baragwanath Academic Hospital (CHBAH), Johannesburg, South Africa (SA), a public government hospital. This hospital serves the population of Soweto and the surrounding areas. Until April 2014, it was the only hospital in Soweto. It is also a referral centre for all clinics conducting births in Soweto and surrounding areas. These clinics conduct about 8 000 births per year and the hospital about 23 000 births per year, with a total of just over 30 000 births per year for the cluster. In 2011, the hospital had two operating theatres for obstetric surgery including caesarean sections (CSs), and 12 NICU beds.

Study population. Infants who were born weighing ≥2 000 g, required resuscitation with at least BMV and were admitted with a diagnosis of asphyxia were included. The study period was from 1 January to 31 December 2011. Infants who died in the labour ward soon after birth were excluded, as their records were either missing or had incomplete information. Infants born before arrival to hospital, twins and infants with severe congenital abnormalities were also excluded.

Table 1. Sarnat and Sarnat[4] classification of HIE

	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalised sympathetic	Generalised parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased; diarrhoea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)

Table 2. Incidence of asphyxia according to different definitions of asphyxia (*N*=21 086 live births)

Definition	Infants with asphyxia, *n*	Incidence /1 000 live births
Need for BMV at birth	321	15.2
BMV + base deficit >12 mmol/L	261	12.4
BMV + Apgar score <7 at 5 min	218	10.3
BMV, Apgar score <7 at 5 min + base deficit >12 mmol/L	183	8.7

Study procedure. Hospital records of newborn infants who met the inclusion criteria were retrieved and the following data were collected: birth weight, gender, gestational age, growth, Apgar score, resuscitation required, time to spontaneous respiration, arterial blood gas done within the first hour of birth, and the diagnosis of HIE. Maternal records were also reviewed for maternal age, parity, maternal HIV results, antenatal care, maternal disease, mode of delivery, presence of fetal distress or meconium-stained amniotic fluid and cardiotocographic records. Means, standard deviations (SDs), medians and ranges were used to describe continuous variables, while frequencies and percentages were used to describe categorical variables. The χ^2 test or Fischer's exact test and Student's *t*-test were used to compare the categorical variables and continuous variables, respectively, between infants with no or mild to moderate HIE and those with severe HIE or who died. Differences between the two groups were considered statistically significant at a *p*-value of <0.05. The extent of association of different variables with severe HIE or death was reported using odds ratios (ORs) and the precision using 95% confidence intervals (CIs). In order to determine predictors of severe HIE or death, variables with *p*-values <0.05 on the univariate logistic regression were included in the multivariate logistic regression. STATA version 10.0. was used to perform the statistical analysis.

Approval to conduct the study was obtained from the hospital protocol review committee and the University of the Witwatersrand Human Research Ethics Committee.

Results

Incidence of asphyxia

Of a total of 23 035 liveborn infants, 21 086 weighed ≥2 000 g at birth. Of those weighing ≥2 000 g, 357 had a diagnosis of asphyxia, of whom 321 were admitted and 36 died in the labour ward before admission; since records of the latter were either missing or had incomplete information, they were excluded. The incidence of asphyxia ranged from 8.7 to 15.2/1 000 deliveries, depending on the definition of asphyxia used (Table 2). Using the definition combining need for BMV, Apgar score <7 at 5 minutes and base deficit >12 mmol/L (representing a truer reflection of intrapartum asphyxia) the incidence was 8.7/1 000 live births, compared with 15.2/1 000 using need for BMV alone.

Maternal characteristics

Demographic and clinical characteristics of mothers giving birth to infants diagnosed with asphyxia are shown in Table 3. Most of the mothers (95.6%) had attended antenatal care. The average maternal age was just over 25 years, and 57.6% were pregnant for the first time. Just over a quarter of mothers (25.9%) were positive for HIV. Among the mothers who had maternal illness recorded, the most common diagnosis was pregnancy-induced hypertension, accounting for 75.9% of mothers with recorded illness and 19.6% of mothers giving birth to infants with a diagnosis of asphyxia. Of babies with asphyxia, 34.3% were born to mothers with meconium-stained amniotic fluid. The mode of delivery was CS in 38.0% of cases, with only 8.7% of deliveries being assisted vaginal deliveries. The most common reason for performing CS in mothers of asphyxiated infants was fetal distress (68.9%) followed by prolonged second stage of labour (7.3%), cephalopelvic disproportion (6.3%) and cord prolapse (4.1%). Electronic monitoring with a

Table 3. Characteristics of mothers who gave birth to infants with asphyxia (*N*=321)

Variables	
Maternal age (years), mean (SD)	25.17 (6.4)
First pregnancies, *n* (%)	185 (57.6)
Positive HIV test, *n* (%)	83 (25.9)
Received antenatal care, *n* (%)	307 (95.6)
Maternal illness, *n* (%)	
Hypertension	63 (19.6)
Other medical conditions	20 (6.2)
Mode of delivery, *n* (%)	
CS	122 (38.0)
Vaginal delivery	171 (43.2)
Assisted vaginal delivery	28 (8.7)
Meconium-stained amniotic fluid, *n* (%)	110 (34.3)
Documented electronic monitoring during labour (CTG), *n* (%)	
Yes	249 (77.6)
No	72 (22.4)
Normal CTG in monitored patients, *n* (%)	132/249 (53)
Abnormal CTG in monitored patients, *n* (%)	117/249 (47)
Late decelerations	90/117 (76.9)
Early decelerations	8/117 (6.8)
Fetal bradycardia	8/117 (6.8)
Beat-to-beat variability	3/117 (2.6)
Suspicious tracing	8/117 (6.8)

cardiotocograph (CTG) was performed in 77.6% of cases; tracings were normal in 53% and abnormal in 47%. In mothers with an abnormal CTG, the common abnormality was late deceleration (76.9%), followed by early deceleration (6.8%) and fetal bradycardia (6.8%).

Infant characteristics (Table 4)

Apgar scores

The average birth weight was 3 084 g and the average gestation 38.5 weeks. Apgar scores were done at 1 and 5 minutes in 99.5% of the infants and at 10 minutes in 72.6%. At 5 minutes 68.0% had an Apgar score of <7. Of infants with a documented Apgar score at 10 minutes, 29.7% had a score of <7.

Resuscitation and time to spontaneous respiration

During resuscitation, the majority (89.7%) of infants diagnosed with asphyxia responded to BMV only, while just over 10% required extensive resuscitation in the form of chest compressions (7.2%) and adrenaline (3.1%). Of the infants who had time to spontaneous respiration recorded, 50.0% took >5 minutes to attain spontaneous respiration.

Blood gases

All infants were resuscitated with 100% oxygen. The majority of infants had blood gas analysis performed within an hour after delivery. The mean partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) were 145.6 mmHg and 36.6 mmHg, respectively, suggesting overzealous BMV. Only 24.0% of infants had a pH of <7.00, 57.9% had a PaO_2 of >100 mmHg, 53.0% had hypocarbia ($PaCO_2$ <35 mmHg), and 81.3% had a base deficit of >12 mmol/L. The lactate level, which is a good indicator of tissue hypoxia, was found to be >7.5 mmol/L in 97.4% of cases in which it was documented.

Table 4. Characteristics of infants diagnosed with asphyxia (*N*=321)

Variables	
Birth weight, mean (SD)	3 084 (448)
Gestational age, mean (SD)	38.5 (2.2)
Gender, *n* (%)	
Male	192 (59.8)
Female	129 (40.2)
Apgar score at 5 min, *n* (%)	
<5	75 (23.4)
5 - 7	143 (44.6)
≥7	101 (31.5)
Apgar score at 10 min, *n* (%)	
Recorded	233 (72.6)
< 5	19/233 (8.2)
5-7	50/233 (21.5)
≥7	164/233 (70.3)
Not recorded, *n* (%)	88 (27.4)
Resuscitation required, *n* (%)	
BMV only	288 (89.7)
BMV + CC	23 (7.2)
BMV + CC + adrenaline	10 (3.1)
Time to spontaneous breathing (min), *n* (%)	
<5	105 (32.7)
5 - 10	89 (27.7)
10 - 20	42 (13.1)
>20	27 (8.4)
Not recorded	58 (18.1)
pH, mean (SD)	7.09 (0.16)
pH <7.00 , *n* (%)	77 (24.0)
pH 7.00 - 7.25, *n* (%)	182 (56.7)
pH >7.25, *n* (%)	38 (11.8)
PaO_2 (mmHg), mean (SD)	145.63 (79.92)
PaO_2 <50, *n* (%)	16 (5)
PaO_2 50 - 100, *n* (%)	92 (28.7)
PaO_2 >100, *n* (%)	186 (57.9)
$PaCO_2$ (mmHg), mean (SD)	36.66 (16.71)
$PaCO_2$ <35, *n* (%)	170 (53.0)
$PaCO_2$ 35 - 45, *n* (%)	64 (19.9)
Base deficit (mmol/L), mean (SD)	18.09 (5.26)
Base deficit ≤12, *n* (%)	35 (10.9)
Base deficit >12, *n* (%)	261 (81.3)

CC = chest compressions.

Incidence of HIE and mortality

The incidence of HIE ranged from 8.5 to 13.3/1 000 live births, depending on the definition of asphyxia used (Table 5). Defining

asphyxia as an Apgar score of <7 at 5 minutes and base deficit of >12 mmol/L, 179 patients (97.8%) developed signs of HIE (according to Sarnat and Sarnat staging[4]), giving an incidence of 8.5/1 000 live births, compared with 13.3/1 000 live births when asphyxia was defined as need for BMV. Among those who developed HIE, 59.0% had moderate to severe HIE. The overall mortality rate was 7.8%, with the rates in infants with HIE ranging from 8.9% to 12.3%, depending on the definition of asphyxia. Only 1.4% of infants with HIE 1 died, as opposed to 7.1% and 62.5% of those with HIE 2 and 3 respectively, defining asphyxia with inclusion of metabolic acidaemia. There were no deaths among those who did not develop HIE. Sixty-four per cent of the deaths were primarily due to HIE, and 16.0% were due to HIE and meconium aspiration syndrome, with or without persistent pulmonary hypertension of the newborn; 24.0% were due to sepsis. Comorbidities in patients with asphyxia included renal dysfunction in 31.2%, clinically presumed sepsis in 24.6% and positive blood culture in 13.9%.

Comparison of mild to moderate HIE with severe HIE and/or death

Comparison was made between the above two groups for all patients with asphyxia defined as need for BMV. On univariate analysis, there were no statistically significant differences in maternal characteristics and CTG readings between those with no HIE or mild to moderate HIE compared with those with severe HIE or who died. The infant factors that were associated with poor outcome (severe HIE or death) were low Apgar scores at 5 and 10 minutes, need for adrenaline, delay in time to spontaneous respiration, low pH, high base deficit and low bicarbonate. The median Apgar score was lower at 5 minutes (4 v. 6; $p<0.01$) and 10 minutes (5 v. 8; $p<0.01$), time to spontaneous respiration was longer (15.4 minutes v. 6.2 minutes; $p<0.01$), pH was lower (6.9 v. 7.1; $p<0.01$), base excess was higher (22.8 v. 17.5 mmol/L) and bicarbonate was lower (8.9 v. 11.6 mmol/L) in infants with severe HIE and/or who died compared with those with either no HIE or mild to moderate HIE who survived to hospital discharge (Table 6). Factors showing statistically significant differences in univariate analysis were included in a multivariate analysis to determine factors that could predict severity of HIE or death. Only Apgar score at 10 minutes ($p=0.004$), need for adrenaline ($p=0.034$) and bicarbonate levels in the first hour after birth ($p=0.02$) were found to be predictors of severe HIE and/or death.

Severity of different variables and odds of developing severe HIE or death

The odds of having severe HIE or death increased if the Apgar score at 5 minutes was <5 (OR 9.33; 95% CI 2.83 - 34.03); if the Apgar score at 10 minutes was 5 - 7 (OR 3.05; 95% CI 1.08 - 8.62) or <5 (OR 19.1; 95% CI 5.66 - 66.9) compared with a score of >7; if chest compressions were required (OR 4.51; 95% CI 1.06 - 18.0); if adrenaline was required (OR 81.2; 95% CI 13.2 - 647.7); and if time to spontaneous respiration was >20 minutes (OR 27.2; 95% CI 6.89 - 117.4). When arterial blood gas was measured within the first hour of life, the odds of having severe HIE and/or death were increased if the pH was <7 (OR 5.33; 95% CI 1.31 - 25.16); if the PaO_2 was <60 mmHg (OR 9.65; 95% CI 1.87 - 55.12); and if the $PaCO_2$ was >45 mmHg (OR 3.98; 95% CI 1.11 - 15.56) (Table 7).

Table 5. Incidence of HIE and mortality rate in patients with asphyxia, depending on definition used

	Need for BMV			Apgar score <7 + base deficit >12 mmol/L		
	Total *N* (%)	Incidence /1 000 live births	Died *n* (%)	Total *N* (%)	Incidence /1 000 live births	Died *n* (%)
No HIE	40 (12.5)	-	0 (0)	4 (2.2)	-	0 (0)
HIE 1	131 (40.8)	6.2	2 (1.5)	71 (38.8)	3.4	1 (1.4)
HIE 2	122 (38.0)	5.8	7 (5.7)	84 (45.9)	4.0	6 (7.1)
HIE 3	28 (8.7)	1.3	16 (57.1)	24 (13.1)	1.1	15 (62.5)
All HIEs	281 (87.5)	13.3	25 (8.9)	179 (97.8)	8.5	22 (12.3)

Table 6. Factors associated with severe HIE or death in infants with asphyxia

	No HIE or HIE 1 - 2 (*N*=256)	HIE 3 and/or death (*N*=37)	*p*-value	
			Univariate	Multivariate
Median Apgar at 5 min	6	4	<0.001	0.99
Median Apgar at 10 min	8	5	<0.001	0.004
Need for CCs, *n* (%)	19/256 (7.4)	4/37 (10.8)	0.36	N/A
Need for adrenaline, *n* (%)	1/256 (0.4)	9/37 (24.3)	<0.001	0.03
Time to spontaneous respiration (min), mean (SD)	6.17 (5.71)	15.36 (11.93)	<0.001	0.69
pH, mean (SD)	7.11 (0.14)	6.92 (0.18)	<0.001	0.54
PaO_2 (mmHg), mean (SD)	145.25 (76.00)	148.75 (108.35)	0.82	N/A
$PaCO_2$ (mmHg), mean (SD)	34.94 (13.89)	49.91 (27.69)	<0.001	0.33
Bicarbonate (mmol/L), mean (SD)	11.59 (2.84)	8.91 (2.72)	<0.001	0.03
Base deficit (mmol/L), mean (SD)	17.48 (4.88)	22.74 (5.79)	<0.001	0.30
Lactate (mmol/L), mean (SD)	15.90 (4.34)	18.26 (3.68)	0.008	0.61
Glucose (mmol/L), mean (SD)	6.79 ± 2.30	6.93 (4.48)	0.82	N/A

CCs = chest compressions; N/A = not applicable.

Table 7. ORs for developing severe hypoxic ischaemic encephalopathy and/or death according to severity of different variables

Variables	OR (95% CI)
Apgar score at 5 min	
>7	Reference
5 - 7	1.79 (0.50 - 7.01)
<5	9.33 (2.83 - 34.03)
Apgar score at 10 min	
>7	Reference
5 - 7	3.05 (1.08 - 8.62)
<5	19.13 (5.66 - 66.89)
Extent of resuscitation	
BMV only	Reference
CCs	4.51 (1.06 - 17.98)
Adrenaline	81.2 (13.17 - 647.7)
Time to spontaneous respiration (min)	
<5	Reference
5 - 10	2.18 (0.55 - 9.24)
10 - 20	3.41 (0.74 - 16.20)
>20	27.19 (6.89 - 117.38)
pH	
>7.25	Reference
7.0 - 7.2	1.48 (0.35 - 7.13)
<7.0	5.33 (1.31 - 25.16)
PaO_2 (mmHg)	
60 - 100	Reference
>100	2.40 (0.63 - 10.74)
<60	9.65 (1.87 - 55.12)
$PaCO_2$ (mmHg)	
35 - 45	Reference
>45	3.98 (1.11 - 15.56)
<35	0.75 (0.19 - 3.07)

CCs = chest compressions.

Discussion

The recent development of induced hypothermia to reduce the risk of mortality and disability in infants with asphyxia prompted this study to assess the burden of asphyxia (incidence of asphyxia) and the numbers of infants who might require cooling (incidence of moderate to severe HIE) in a setting where there is a high patient load but limited resources. Defining asphyxia as need for BMV, Apgar score <7 at 5 minutes and base deficit >12 mmol/L within an hour after delivery, the incidence of asphyxia was 8.7/1 000 live births. Most studies reporting on the incidence of birth asphyxia in developing countries do not include blood gases, and use only need for assistance with respiration and/or Apgar score <7 at 5 minutes. Using the definition of need for assistance with breathing or Apgar score <7 at 5 minutes, our incidence of asphyxia was 15.2/1 000 or 10.3/1 000 live births, respectively. Whichever definition is used, the incidence of asphyxia in this study is very high compared with that reported in developed countries (~1 - 5/1 000 live births.[5,6] We did not collect data on modifiable factors that may have contributed to this high incidence. A perinatal care survey conducted in SA in 2008/9 reported that delay in seeking medical care, inadequate monitoring during labour and lack of facilities were modifiable factors identified in neonates who died from asphyxia.[7] We postulate that these same factors contribute to our high incidence of asphyxia.

The overall incidence of encephalopathy in infants with Apgar scores <7 and base deficit >12 mmol/L was 8.5/1 000 live births, with 60% of cases being due to HIE 2 and 3. The overall incidence reported in this study was higher than the incidences reported from Sweden, a developed country, and Kathmandu in Nepal, a developing country (1.8 and 6.4/1 000 live births, respectively[8,9]), but lower than the 28.1/1 000 reported for Sarlahi, Nepal.[10]

It has been reported that of infants diagnosed with HIE, 15 - 20% will die in the neonatal period and 25 - 30% of survivors will develop permanent neurodevelopmental abnormalities including cerebral palsy.[6] In our study, 62% and 7% of infants with HIE 3 and HIE 2, respectively, died before hospital discharge. Some infants with HIE 2 and most of those with HIE 3 who survive to hospital discharge will have a poor neurological outcome.

The high incidence of HIE in this report is a major concern and highlights the need for improvements in the healthcare system to reduce the incidence of asphyxia and HIE. It is also important to treat infants with moderate to severe HIE with induced hypothermia to reduce neurological disability and mortality.

Predictors of severe HIE and/or death were low Apgar score at 10 minutes, need for adrenaline and low bicarbonate. Shah *et al.*[11] reported similar findings, and that need for chest compressions, high base deficit and delay in onset of respiration beyond 20 minutes in infants with asphyxia were associated with poor outcome; rates of severe adverse effects were 64% if one predictor was present, 76% if two were present and 93% if all three were present. The finding that Apgar score at 10 minutes is a predictor of poor outcome is helpful, as the Apgar score is easy to perform and widely used in labour and delivery rooms in both developed and developing countries. Although the Apgar score has not been helpful in predicting which infants will develop cerebral palsy, especially in the era of induced hypothermia for asphyxia,[12] it has been shown to be very useful in predicting survival in both preterm and term infants. Laptook *et al.*[13] reported that each point decrease in Apgar score at 10 minutes was associated with a 45% increase in the odds of death or disability, and concluded that Apgar score at 10 minutes provided useful prognostic information before other evaluations are available.

The presence of metabolic acidaemia or low bicarbonate is of additional value to the Apgar score in predicting poor outcome, as the Apgar score is often not done in real time and can therefore be unreliable. A base deficit of >16 mmol/L has previously been reported to be a predictor of poor outcome.[10] Casey *et al.*[14] also reported that a combination of low Apgar score (0 - 3) and cord pH of <7.0 increased the risk of mortality in both preterm and term infants, whereas Sehdev *et al.*[15] reported that a base deficit of >16 and a 5-minute Apgar score of <7 together identified 79% of neonates who would develop complications.

Study limitations

The chief limitation of this study is that it is retrospective. The diagnoses of asphyxia and encephalopathy were therefore mainly based on what was recorded in the patient's hospital file. This may have led to overestimation of the true incidence of HIE, especially as some clinical findings could be affected by the experience of a person conducting the examination, e.g. junior doctors commonly labelling infants with asphyxia as having HIE. Our study nevertheless serves to highlight the burden of asphyxia and encephalopathy at CHBAH, which possibly reflects the incidence in other public sector hospitals in SA.

Conclusion

The incidences of both asphyxia and HIE are very high at CHBAH. As moderate to severe HIE is likely to be associated with abnormal neurodevelopmental outcomes and disability, factors that contribute to a high incidence of asphyxia must be avoided. Infants at risk of developing encephalopathy must be offered neuroprotective treatment, i.e. induced hypothermia. Where arterial blood gas analysis, NICU facilities and induced hypothermia are not available or are limited, an Apgar score of <5 at 10 minutes and the need for adrenaline can be of assistance in predicting poor outcome and the need for counselling of families with a neonate with asphyxia.

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INTRAPARTUM ASPHYXIA AND HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN A PUBLIC HOSPITAL: INCIDENCE AND PREDICTORS OF POOR OUTCOME

Eduard Keith Bruckmann