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Developmental motor outcomes of children aged nine to twenty-four months with hypoxic ischaemic encephalopathy based on the Thompson score

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2019

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DEVELOPMENTAL MOTOR OUTCOMES OF CHILDREN AGED NINE TO TWENTY-FOUR MONTHS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY BASED ON THE THOMPSON SCORE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Occupational Therapy

Johannesburg, 2019

DECLARATION

I, Tasha Nicolson, declare that this research report is my own work. It is being submitted in partial fulfilment of the degree of Master of Science in Occupational Therapy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed: _____

on the _____ day of _____, 2019

For my mother

Patricia Margaret Nicolson

1948-2014

ABSTRACT

Hypoxic ischaemic encephalopathy (HIE) is the occurrence of impaired neurological function in a new-born, associated with asphyxia at birth. It may be considered mild, moderate or severe depending on the presence or absence of various clinical signs. The incidence of HIE in South Africa ranges from 0.4 – 3.7 per 1000 live births. In the moderate and severe form, HIE is known to cause functional motor deficits, cognitive deficits, intellectual impairment, language, learning and executive skills limitations and/or social impairments.

This study was a quantitative cross-sectional study investigating the motor outcomes, as measured by the Peabody Developmental Motor Scales: second edition (PDMS-2), of 28 children with various severities of HIE. The severity of the HIE was measured by the Thompson HIE score. Participants were between the ages of nine and twenty-four months and attended the Mowbray Maternity Hospital Neurodevelopmental High-Risk Clinic. There were thirteen participants with mild HIE, seven participants with moderate HIE and eight participants with severe HIE.

Demographic and perinatal factors were comparable across groups. Results of the study showed that all participants functioned within the normal range for all subtests of the PDMS-2. The mild and moderate HIE groups were comparable in all areas and therefore were combined and compared to the severe group. This comparison showed that the severe HIE group performed worse in all subtests with small to large effect sizes. It is therefore important for occupational therapists to ensure that children with severe HIE, according to the Thompson HIE score receive comprehensive assessment and follow up treatment. This assessment and treatment should focus on fine motor development, particularly VMI.

ACKNOWLEDGEMENTS

To my husband and beautiful children, thank you for your unending support and love and for keeping me inspired on this journey even when it felt impossible to reach the finish line.

To Lizelle Jacobs, your patience as a supervisor was tested and always prevailed. Thank you for your kindness and support throughout this process.

To Dr Thompson, thank you for being so welcoming to me at the clinic. Your dedication to your patients is an absolute inspiration. Thank you for being such a thoughtful guide around the complexities of the health system and the condition that is HIE.

To Denise Franzsen, thank you for always being available to help. Your knowledge is unparalleled and I am so grateful that I was a beneficiary of it.

To the participants of this study and their families, thank you for agreeing to take part and helping me to learn about this condition.

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Operational Definitions

Occupational therapy (OT) is defined as the therapeutic use of everyday life activities (occupations) for the purpose of enabling participation in roles, habits, and routines within the home, school, workplace, and community sphere.[1] These interventions may be with an individual or with a group.

Hypoxic ischaemic encephalopathy (HIE) is defined as a clinical syndrome of neonatal encephalopathy where hypoxia, ischaemia or both have been identified as the cause. The syndrome causes hypotonia, poor reflexes, difficulty with feeding, seizures, and reduced respiration and level of consciousness in the neonate.[2, 3]

Cerebral palsy (CP) is defined as a group of permanent disorders affecting the development of movement and posture that result in activity limitation and are attributed to non-progressive disturbances in early life.[4] It also results in cognitive deficits and intellectual impairment, language, learning and executive skills limitations and/or social skills impairments.[4]

Peabody Developmental Motor Scales -2 (PDMS-2) is a standardised motor assessment used to assess gross and fine motor development in the paediatric population.[5]

Thompson score: A score that was developed at Groote Schuur Hospital in Cape Town, South Africa to determine the severity of hypoxic ischaemic encephalopathy (HIE) that was standardised by Dr Clare Thompson in 1997. The assessment is performed on infants in the first two weeks of life and is based on clinical signs.[6]

Developmental motor outcomes: refers to both fine and gross motor outcomes as measured, in this study, by the PDMS-2.[5]

Abbreviations

ADHD – Attention deficit hyperactivity disorder

ADL – Activities of daily living

aEEG – Amplitude integrated electroencephalogram

AIMS – Alberta Infant Motor Scale

BGT – Basal ganglia thalamic

BSID – Bayley Scales of Infant Development

CP – Cerebral palsy

DCD – Developmental coordination disorder

FMQ – Fine Motor Quotient

GMQ – Gross Motor Quotient

GSH – Groote Schuur Hospital

HIE – Hypoxic ischaemic encephalopathy

IQ – Intelligence quotient

M-ABC – Movement Assessment Battery for Children

MMH – Mowbray Maternity Hospital

MRI – Magnetic resonance imaging

NE – Neonatal encephalopathy

NVD – Normal vaginal delivery

OT – Occupational therapy

OPA – Occupational performance areas

PDMS-2 – Peabody Developmental Motor Scales – Second Edition

PLIC – Posterior limb of the internal capsule

RDS – Respiratory distress syndrome

TMQ – Total motor quotient

VMI – Visual-motor integration

Chapter 1: Introduction

1.1 Introduction

Neonatal encephalopathy (NE) is considered a "constellation of neurologic signs" that are noted in the first week of life.[7] When these signs are found in association with intrapartum asphyxia, which is impaired respiratory gas exchange accompanied by acidosis, it is termed hypoxic ischaemic encephalopathy (HIE).[7] Clinical manifestations of HIE range from minor tone abnormalities to absent primitive reflexes and include breathing irregularities requiring ventilation, seizures, coma and death and are used to classify the severity of HIE.[8, 9] The most widely used classification system is a modified Sarnat score. These scores are based on the original classification score by Sarnat and Sarnat, which was published in 1976. The scores are based on the presence/absence of various clinical signs, including neuromuscular control, complex reflexes, autonomic functions, seizures and electroencephalogram (EEG) results and group infants into mild, moderate or severe HIE categories.[10]

In South Africa intrapartum asphyxia accounts for ten to 26% of perinatal mortalities whilst the incidence of HIE ranges from between 0.4 to 1.3 and 1.5 to 3.7 per 1000 live births for mild and moderate-severe HIE respectively.[2, 11] Long term outcomes of HIE are well correlated to severity, with infants with mild HIE having minimal limitations, 15% – 75% of infants with moderate HIE having minor to notable limitations and over 90% of those with severe HIE experiencing marked disability, particularly cerebral palsy (CP), or death.[7-9, 12] CP is the term for a group of permanent disorders that result in the development of movement and posture deficits impacting on activity participation.[4] It also results in cognitive deficits and intellectual impairment, language, learning and executive skills limitations and/or social skills impairments.[4]

The provision of medical interventions such as therapeutic hypothermia, which is the lowering of the temperature of the deep brain structures to between 32 and 34˚C, significantly improves outcomes in the child with HIE.[13] In addition to the various medical interventions, rehabilitation/habilitation interventions such as physiotherapy, speech therapy and occupational therapy have also been found to improve the outcomes of infants with HIE.[14]

These therapies can reduce or ameliorate the long-term effects of HIE, which include varying degrees of functional motor deficits, cognitive deficits, intellectual impairment, language, learning and executive skills limitations and/or social skills impairments.[15] These long-term effects may result in activity limitations and participation restrictions for the child and their family, which is why occupational therapy can be beneficial.[4]

Occupational therapy supports health and participation in life through occupation or everyday activity, which may be shared or individual in nature or may involve organisations or populations. These activities or occupations are sorted into various areas namely, activities of daily living (ADLs), instrumental ADLs, rest and sleep, education, work, play, leisure and social participation. Occupational therapy interventions may involve therapeutic use of self or therapeutic use of occupations and activities.[16]

In paediatric occupational therapy this is all performed within the context of family centred practice, where the family is considered to be an integral part of the child's therapeutic team.[17] Specific paediatric occupational therapy interventions for HIE include, but are not limited to: promoting gross movement; facilitating use of the hands; enhancing and modifying the environment in order for the child to explore; fostering self-regulation and social play skills; promoting interaction between the child and his/her family and peers; promoting independent function in self care activities such as eating and drinking, dressing and grooming; and improving community participation.[18]

Research has indicated that the earlier intervention is initiated for infants at high risk for developmental disability, the more beneficial it is likely to be, noting that therapy offered before the age of nine months of age has been shown to be more beneficial than that offered after.[14, 19] Early intervention does not only benefit the child directly but can assist the caregiver as well by reducing maternal stress often experienced after the birth of a medically complex infant.[20] For early intervention to happen, however, those who would benefit most from therapy must be identified early so appropriate referral and therapy can be provided. This identification requires that an outcome measure, used at birth, be identified as an appropriate indicator of difficulties with performance skills that would necessitate occupational therapy.

However, the early referral of infants with HIE to occupational therapy is challenging as there is minimal research identifying at birth which infants are most likely to present with impairments that would benefit specifically from occupational therapy.

1.2 Statement of the problem

Currently the majority of assessments that exist for HIE are mostly either based on the Modified Sarnat Score, which has been criticised for not being very specific in the moderate range, or rely on expensive equipment such as MRIs, which are not readily available in the resource poor settings of South Africa.[14, 21, 22] There are also no standardised referral criteria to occupational therapy for early intervention services for children with HIE.[14, 21, 22]

This difficulty with early identification and referral to occupational therapy means that children are often referred much later than nine months and frequently have secondary musculoskeletal impairments and significant participation restrictions, which make therapy less effective.[17] Their caregivers are also more likely to have suffered psychosocial stressors, which have been found to impact on their mental wellbeing and development of a positive relationship with their infant.[23, 24] In order to improve referral to rehabilitation/habilitation services a measure needs to be identified that can guide early referral.

The Thompson HIE score, developed in South Africa, is a simple and cost effective assessment that is used in the first two weeks of the infant's life to assess the severity of their HIE.[6] While this score is used to assess the infant in the first week, it has been shown to be an indicator of the physical and cognitive problems the infant will likely present with in the long term and may be useful to occupational therapists and referring doctors in guiding the need for intervention.[6]

The Thompson HIE score has been found to be predictive of neurodevelopmental outcomes for infants using the Griffiths Mental Development but this research, by Thompson et. al. was done in 1996 with infants who had not received therapeutic hypothermia, which many infants with moderate or severe HIE in the Western Cape now have access to.[6]

1.3 Purpose of the study

This study investigated the gross and fine motor outcomes of children aged nine to twenty-four months with various severities of HIE. Using children at or older than nine months is critical as this marks the onset of important milestones in motor skills, including standing and skillful grasping. This research adds to the 1997 research by Thompson et.al. by determining the gross and fine motor outcomes of children according to their grade of HIE based on the Thompson HIE score. The Thompson HIE score could be used as an early indicator as to which children would benefit from early referral to occupational therapy.

1.4 Aim of the study

The aim of this study was to determine the gross and fine motor outcomes of children, aged nine to twenty-four months, diagnosed with HIE at birth based on their Thompson HIE scores in order to determine if the Thompson HIE score would be a good guide as to the need for early occupational therapy intervention for these children.

1.5 Objectives of the study

To describe the sample of children diagnosed with HIE according to demographic information, birth history and medical history.

To determine the gross and fine motor outcomes of children aged nine to twenty-four months of age previously diagnosed with HIE using the Peabody Developmental Motor Scales-2 (PDMS-2).

To establish the difference in the gross and fine motor outcomes of children, nine to twenty-four months of age, diagnosed with HIE in relation to the severity of their Thompson HIE scores.

1.6 Justification of the study

Children with HIE, particularly severe HIE, may suffer with neurological dysfunction that will remain with them throughout their lives. This includes varying degrees of functional motor deficits, including CP.[8, 12] Determining whether the Thompson HIE scores of children with HIE between nine and twenty-four months are associated with their gross and fine motor skills function may indicate that the Thompson score would be a good early predictor of the children's need for occupational therapy and other rehabilitation professionals such as physiotherapy and speech therapy. If this can be established then early referral of these children to occupational therapy can occur, essential if long-term outcomes are to be effectively addressed in therapy.

Chapter 2: Literature Review

2.1 Introduction

In this literature review, HIE will be defined and its prevalence, incidence and the neuropathophysiology behind it will be elaborated upon. The medical interventions for HIE will be described and its effect on development will be discussed in terms of the motor, cognitive, behavioural, language, communication and social development as well as effects on vision and hearing and how these factors affect the family as a unit. The Thompson HIE score will be described and occupational therapy assessment will be discussed with particular focus on the PDMS-2. Finally, treatment options will be discussed. The medical intervention of therapeutic hypothermia will be explained and rehabilitation therapies reviewed with specific focus on the role of the occupational therapist in the treatment of children with HIE.

2.2 Defining hypoxic ischaemic encephalopathy

Before the literature can be adequately reviewed the terms birth asphyxia, neonatal encephalopathy (NE), and HIE must be properly defined.

Birth asphyxia refers to a period of oxygen deprivation and/or excessive carbon dioxide caused by an interruption in breathing occurring before, during or just after birth.[9] Birth asphyxia can lead to significant central nervous system, respiratory, cardiovascular and renal complications.[25] Over the last 40 years the criteria for the diagnosis of birth asphyxia have significantly evolved. Previously there was a single criterion for the diagnosis of birth asphyxia, for example delayed respiration or pH level. From the 1950s the Apgar score was used but more recently multiple-criteria

definitions have evolved that use numerous clinical signs, for example reflexes, tone, and level of consciousness, to name but a few.[7]

Neonatal encephalopathy (NE) is not determined by a single event/sign but rather a number of different neurologic signs noted within the first seven days of birth.[7] The aetiology of NE is varied with genetic, metabolic and infective conditions presenting with similar signs.[2] When there is evidence that asphyxia is the cause of the encephalopathy the condition is then termed hypoxic ischaemic encephalopathy (HIE).[2, 7] The most common causes of intrauterine asphyxia, leading to HIE, are brought on by circulatory problems or inflammatory processes. Circulatory problems include clotting of placental arteries, placental abruption. These together with inflammatory processes lead to diminished exchange of oxygen and carbon dioxide as well as severe lactic acidosis.[26]

Hypoxic ischaemic encephalopathy is diagnosed clinically through the determination of a variety of markers including clinical parameters such as tone, reflexes, seizures, respiration and level of consciousness as well as test results such as blood gas pH of >7 or a base deficit of ≥12 mmol/l in the first hour of life.[2, 9] In well-resourced countries magnetic resonance imaging (MRI), cranial ultrasound or amplitude integrated electro-encephalogram (aEEG) may also be used to assist diagnosis of HIE.[3, 27] Hypoxic ischaemic encephalopathy can occur in both the term and preterm infant. In a 2016 review it was suggested that preterm HIE may well be more prevalent than term HIE.[28] However this is difficult to determine as the additional neurological complications associated with preterm birth such as periventricular leukomalacia make it difficult to single out the specific sequelae of HIE and for this reason most of the literature focuses on term infants, i.e. those born between 37 and 41 weeks, diagnosed with HIE.[28, 29]

2.3 Prevalence of hypoxic ischaemic encephalopathy

Birth asphyxia is a significant worldwide problem but is one that impacts developing countries disproportionately. Globally studies have shown that 23% of neonatal deaths occur as a result of birth asphyxia, with a massive 98% of these occurring in

low and middle-income countries.[30] An illustration of this is the incidence of neonatal deaths as a result of birth asphyxia in Sweden and France, which is approximately six per 1000 live births and 0,86 per 1000 live births respectively compared to Nepal where the incidence of birth asphyxia is 29,9 per 1000 live births.[9, 31, 32] Sadly, neonatal deaths were found to have made the least progress towards achieving the Millennium Developmental Goals with deaths occurring in the neonatal period increasing in the decade from 2002 to 2012 from 38% to more than 41%.[2] A large portion of these are as a result of birth asphyxia.[2]

In South Africa infant mortality rates are between 42,5 and 59,1 per 1000 live births with most of these occurring in the poorer provinces, namely the Eastern Cape, North West and Free State.[33] Birth asphyxia accounts for approximately 16% of these deaths with the incidence of 7,21 and 5,65 per 1000 live births at district and referral hospitals respectively.[33] This makes it the third leading cause of perinatal mortality in South Africa following spontaneous preterm labour and unexplained preterm labour.[33, 34] It has been noted however that incidence rates from South Africa may actually be much higher due to the number of rural home births where complications may never be reported to a health care facility.[11]

As is evident by the above figures, most studies report on the incidence of birth asphyxia rather than on neonatal encephalopathy or HIE specifically. Ideally research into HIE should use specific and internationally agreed upon criteria to identify the condition. Frequently though, especially in low resource settings, the equipment and therefore the data are not available or not all the criteria can be fulfilled, yet no other explanation can be found.[3]

In a 2013 study investigating HIE in the South African population it was found that when different criteria were applied the incidence of moderate to severe HIE increased from 1,5 to 3,7 per 1000 live births and the incidence of mild HIE increased from 0,4 to 1,3 per 1000 live births.[2] In the first case more stringent criteria were used including blood gas and base deficit. In the second case the presence of

one or more intrapartum-related abnormalities in association with neonatal encephalopathy without other causes, was used to determine HIE.[2]

In another example, a 2002 study evaluating incidence of HIE in the Southern Cape region of South Africa using strict criteria, found the incidence to be 3,8 per 1000 live births whereas a more recent study using more general criteria, found the incidence to be 9 per 1000 live births.[2] Although the rates may vary between studies and according to differing criteria, it is clear that HIE is a significant public health problem for South Africa.

A 2015 study evaluated both the direct and indirect costs associated with a diagnosis of HIE and the subsequent development of CP which occurs in approximately 28-41% of children with HIE.[35, 36] This paper notes that the cost of medical intervention alone for most children with CP is massive, mostly because of the associated comorbidities. A child with CP may have any or even all of these interventions; gastrostomy, fundoplication, botulinum toxin therapy, anticonvulsant therapy, hip surgery and intrathecal baclofen, scoliosis surgery, orthoses, wheelchairs, respite care, rehabilitation therapies and specialised education. This doesn't include the indirect cost of loss of potential not only in terms of future earnings of the individual but also the loss of earnings of the child's parents, one of whom may no longer be able to work or may not be able to work full time. In 2003 these costs were calculated at around $800 000 - $900 000 per child with CP. The costs of those that develop learning disabilities is less but is still approximately $455 000.[37] This makes it clear that HIE and the subsequent development of CP or learning disabilities are important public health considerations.[35] In order to understand this complex condition it is necessary to understand how it develops and what the consequences of this are.

2.4 Neuropathophysiology following hypoxic events

The more research that is done and the more refined and sophisticated the imaging techniques get, the more it is becoming apparent that HIE is not a single event but rather an evolving process.[26, 38] HIE staging often improves in the first few hours

after resuscitation and halting of the initial hypoxic cell death but there often follows a deterioration over the next 48-72 hours due to cerebrovascular and metabolic derangement.[3] These derangements lead to oxidative stress and inflammatory processes that create excitotoxicity and mediate changes in the blood brain barrier which allow for further excitotoxicity, phagocytosis and neuronal cell death.[3, 26] These effects have been shown in MRI studies that demonstrate how the lesion size increases over the first few days and are backed by diffusion weighted imaging which shows small areas of restricted diffusion starting in the putamen and thalamus which increase to involve larger areas of the brain over a three to four day period.[26] These three to four days are considered a window of opportunity to ameliorate the secondary effects of the initial hypoxic brain injury, specifically through the use of therapeutic hypothermia which will be discussed later in the chapter.[26]

There are two dominant patterns of injury as a result of asphyxia. The first is a watershed pattern, which affects white cortical matter in the vascular watershed areas. The second pattern affects the deep grey nuclei specifically of the basal ganglia and thalamus (BGT). Both patterns can include more extensive areas of the brain when severe.[39] Studies have shown that the pattern of injury, as seen on MRI, is more predictive of outcome than the extent of the injury.[4]

The white matter watershed pattern is seen in 45% of cases and is associated with a partial prolonged asphyxia.[39] Infants with this kind of injury, where the deep grey matter is unaffected, tend to normalise neurologically more quickly and have relatively good motor development but are often susceptible to cognitive deficits, squints, seizures and behavioural problems, most of which are only identified after the age of 30 months.[3, 39] It is for this reason that children with any degree of HIE should ideally be followed up beyond their first year and perhaps even into their third despite normal neurological findings.

The basal ganglia/thalamus pattern is seen in 25% of cases and is associated with acute/profound asphyxia.[4, 39] It is thought that these areas are more susceptible to acute perinatal injury due to their high metabolic rate leading to an increased

demand for energy, increased concentration of glutamate receptors and the fact that they are actively myelinating at term age.[29] While all the structures in this area may be affected by HIE it is the posterior limb of the internal capsule (PLIC) that is most predictive of outcome with more severe involvement leading to more severe disability.[40] This pattern is associated with briefer neonatal seizures and earlier feeding and visual function but more severe motor deficits, which are generally evident in the first year of life and frequently lead to an athetoid type of CP.[3, 4] The more severe the motor impairment is, the more likely these children are to suffer from learning disabilities and epilepsy.[27]

The remaining 30% suffer from severe diffuse injuries that don't conform to one particular pattern and are more likely to present with severe motor and cognitive disabilities that require intensive medical intervention.[29]

2.5 Medical intervention for children with hypoxic ischaemic encephalopathy

Evidence for current best practice in medical intervention is therapeutic hypothermia, which is the lowering of the temperature of the deep structures in the brain, namely the basal ganglia, to between 32˚C and 34˚C, generally for 72 hours with initiation within 6 hours after birth.[41] This can be achieved in two ways. Whole body therapeutic hypothermia lowers the core temperature of the body and relies on this being the same as deep brain temperatures whereas selective head therapeutic hypothermia lowers the deep brain temperature and although this may have an effect on core temperature, this is not the objective. This is achieved through servo controlled fans, mattresses, and gel packs to name but a few.[3]

The mechanism of action of therapeutic hypothermia is via the inhibition of the cellular death cascade, reduction of the oxidative damage caused by reperfusion, the reduction of damage to the blood-brain barrier and limiting of inflammation associated with the initial insult.[3, 26] To date the only adverse effects noted have been mild and include bradycardia and increased thrombocytopenia.[3]

This procedure has been shown to reduce the incidence of death and moderate to severe disability in children who have suffered birth asphyxia.[38, 42-44] The first study to determine this was the CoolCap study, which found a 10% reduction in mortality and a 16% reduction in severe disability in infants with mild and moderate HIE. This effect however was not seen in those children with severe HIE.[3] In a large-scale randomized controlled trial investigating moderate hypothermia, termed the Total Body Hypothermia (TOBY) trial published in 2009, therapeutic hypothermia was found to increase the likelihood of surviving without a secondary impairment.[45] Specifically the chance of developing any type of CP was 28% in the cooled group versus 41% in the uncooled group.[45] Other studies have found similar improvements of between 16 and 18% reductions in mortality or severe disability in both moderate and severe HIE with confirmation of this in a 2013 Cochrane database review by Jacobs et al.[26, 41] In the review eight studies comprising of 917 children between the ages of 18 and 24 months showed significant improvements in mortality and neurodevelopmental disability.[41]

At Mowbray Maternity Hospital (MMH) the criteria for the provision of therapeutic hypothermia are as follows: the infant will be cooled if they are >36 weeks gestational age, >2000g weight, <6 hours old at initiation of hypothermia and if seizures or voltage suppression is evident on an aEEG or the HIE is clinically severe or seizures are clinically evident. Further criteria include: if there is a base deficit of 16 or more in the first hour of life on cord or infant arterial blood; if the child has a ten min Apgar score of < 7 or the child requires some form of assisted ventilation at ten minutes of age plus the mother's obstetric history is suggestive of intrapartum hypoxia. The infants are not cooled if there is a major congenital abnormality, active bleeding, obvious sepsis, persistent pulmonary hypertension, severe hypoglycaemia or an electrolytic abnormality.[46]

2.6 Effects of hypoxic ischaemic encephalopathy on childhood development

There are many different factors that affect the way a child develops. These include: personal factors such as genetics, body structure, and sex; perinatal factors such as gestation, Apgar scores, birth weight, provision of breastfeeding, mode of delivery; physical and psychological health; personality; as well as environmental factors such as socio-economic status, culture, education and family environment.[20]

Of particular importance with regards to this study are perinatal factors. Infants born at or after 37 weeks gestation are considered to be full term. Those born at 34 to 36 weeks are considered late preterm and those born before 34 weeks are considered preterm.[47] It is well known that preterm infants often suffer with significant delays in overall development including cognitive, motor and social development.[48] Late preterm infants, however, are considered to have near-normal development unless they required admission to the NICU. A recent study of Canadian born late preterm infants found that late preterm infants who had been admitted to the NICU performed below average in tests of social and cognitive function at 12 months corrected age. Interestingly, they had similar test results to infants born full term who required NICU admission.[47] These findings suggest that it is the illness or the time spend in the NICU that hampers later development rather than the late-preterm birth itself.[47]

A factor closely associated with gestation is birth weight. Normal birth weight is considered to be above 2500g, low birth weight is considered to be between 1500g and 2500g and very low birth weight is considered to be below 1500g.[49] While those with very low birth weight show definite delay in motor development, social development and cognitive development, the effect of low birth weight is slightly less evident.[50] One study published in 2003 found that children born with low birth weight i.e. below 2500g were at a slightly increased risk of school related difficulties, particularly those relating to cognition.[51] A later study, published in 2010 also showed some delays in gross motor, fine motor and problem solving skills.[52]

The mode of delivery is also significant in HIE. Most studies show an increased rate of caesarean section delivery with higher than average rates of between 34% and 42% being noted in the literature.[2, 53, 54] This is due to the nature of the conditions precipitating HIE such as cord prolapse, prolonged second stage and foetal distress. Certain precipitating factors for a caesarean section are also more prevalent in children diagnosed with HIE. One study found that severe uterine rupture was the most common antenatal complication associated with a subsequent HIE diagnosis followed by placental abruption and cord prolapse.[55]

Certain medical complications after birth are also strongly associated with HIE. Seizures, in particular, are considered to be one of the most reliable indicator of later neurodevelopmental disorders in children with HIE, most notably abnormal EEG findings at six hours are associated with a high positive predictive value for abnormal neurodevelopmental outcomes at five years old.[53]

The Apgar score, developed in the 1950's, is the most commonly used assessment tool for the new-born as it can be administered rapidly and is easily understood.[56] Newborn infants are given a score out of ten at one minute after birth, five minutes after birth and ten minutes after birth.[25] This score relates to various clinical factors namely activity, pulse, grimace, appearance and respiration with scores of less than seven being considered abnormal.[56] While the Apgar score is widely used, there are limitations to its use as a diagnostic tool, such as the fact that it is influenced by gestational age, maternal drug provision and the neonate's maturity.[25] So while it is generally not used in isolation, it is still useful as an early indicator of neonatal function.[25] Children with HIE generally present with low Apgar scores. A South African study found Apgar scores in children with HIE to be on average 6,25 at five minutes.[2] Apgar scores, particularly those under three at ten minutes postpartum, have been shown to be highly correlated with death and severe disability in infants with HIE.[57] A recent study in Sweden examined the risk of developing epilepsy and CP in a cohort of over a million children. They found that a five-minute Apgar score of between six and seven coupled with a ten minute Apgar score of between seven and eight resulted in a hazard ratio of 15. In other words, children with those Apgar

scores were 15 times more likely to develop CP and twice more likely to develop epilepsy.[56]

This study focuses specifically on motor development between the ages of 9 and 24 months for a number of reasons. Gross and fine motor developmental milestones are the most obvious in younger children where the progression of milestone achievement is both rapid and extensive. For example, in the space of 18 months an infant typically will go from only briefly being able to lift their heads to rolling, sitting, standing and walking. In their fine motor development they will progress from reflexive grasp to voluntary grasp to manipulation of small parts.[58] Although the cognitive, perceptual, social and language development is occurring at an equally rapid pace the outcome of this development is only easily recognisable when the child gets closer to two years of age.[59]

The development of perception, cognition and social competency is also closely linked to a child's gross and fine motor development and is deeply affected by limitations in these areas.

2.6.1 Motor development and its link to cognitive and social development

From the 1930s onward the study of infant motor development began. Initially motor development was seen as a result of central nervous system maturation without much variation between individuals.[60] From the 1980s, with the uprising of the dynamical systems model, motor development began to be seen as a process greatly affected by experience and environment.[60] More recently, research is focused on the dynamic interplay between the environment and its impact on the neural pathways of cognition and movement and how these result in a continuum of development.[60]

Prior to the development of the dynamical systems model in the 1980s motor development was seen as being wholly independent of cognitive and social development but there are now many examples of how motor, cognitive and social

development are inextricably linked.[61] In a 2016 study investigating the relationship between motor, social and cognitive skills in pre-kindergarten children with developmental disabilities, three reasons for this interconnectedness are explained.

Firstly, motor development, especially fine motor development, requires substantially similar networks as those required for cognitive development. For example, the prefrontal cortex, an area strongly associated with cognitive ability is linked not only to the cerebellum and basal ganglia, which have distinct motor learning roles, but also has strong connections to the amygdala, which is highly involved in aspects of social behaviour and motor planning and execution. Secondly, automaticity theory proposes that the ability to perform a motor task without paying full attention to it i.e. when a motor output becomes automatic means that there are additional attention resources that can be utilized for the performance of a second task which makes the performance of this task easier. And thirdly, the embodied cognition theory posits that as motor skills develop they allow the individual to interact more fully with the environment as well as seek out new environments. This facilitates the development of additional motor skills as well as the necessity for advancing cognitive and social interaction skills. An example of this is the study of locomotion. As infants begin to move they not only increase their repertoire of movements but also place themselves in new and challenging environments which affords increased learning and social engagement opportunities.[62]

There are now many studies looking into the interconnectedness of these systems both with typically developing children and children at high risk for or with a developmental disability such as HIE.[62, 63] A 2016 population based, long-term follow-up study assessed the neuromotor development of typically developing infants at nine to twenty weeks and then assessed their behavioural executive functioning at four years, their non-verbal intelligence at six years and their neuropsychological functioning at between five and ten years. The authors found that early abnormal neurodevelopment was not predictive of non-verbal intelligence, language comprehension or overall executive functioning but was significantly associated with

a reduced performance of tasks requiring attention shifting, planning, visuospatial processing, sensorimotor function, immediate memory and inhibition.[63]

This finding was mirrored in a 2016 study examining the motor, cognitive and social skills of children with developmental disabilities. This study found that poor gross motor skills were linked to reduced self-worth; poor attention and working memory, decreased perceived scholastic ability and increased probability of low academic achievement.[62] In this study fine motor skills were found to be more predictive than gross motor skills in terms of cognitive and social skills.[62]

2.6.1.1 Motor development of children with hypoxic ischaemic encephalopathy

Most studies into outcomes following HIE separate the subjects according to the severity of HIE, specifically mild, moderate and severe. Outcomes across studies for motor development for children diagnosed with mild and severe HIE, particularly in developing nations, generally show consensus that mild HIE results in near typical motor development while severe HIE often results in a diagnosis of CP and a mortality rate of approximately 90%.[9] Overall the incidence of a diagnosis of CP across all severities of HIE is between 28 and 41% depending on whether the child received therapeutic hypothermia or not but functional motor and cognitive problems are much more common.[7, 36]

When one considers moderate HIE however, the outcomes vary widely with rates of motor disability identified as 5 – 15%, 40%, 30 – 60%, and 60 – 75% across four different large studies.[7, 8, 12, 40] The discrepancy in outcomes between HIE studies is as a result of different outcome measures being used and frequent conflation of birth asphyxia or neonatal encephalopathy with a true HIE diagnosis.[64] Furthermore, studies tend to cluster dysfunctions together, for example, speaking of motor function without delineating if they mean fine motor function, locomotion, or gross motor skills.[64] Most commonly though it is the discrepancy between the different definitions of HIE being used. Many long-term follow-up studies include subjects in the study based on the diagnostic criteria available at the time of initiating the study. For

example, the study by Lindstrom et.al., which was published in 2012 but was actually begun in 1984, this study used a low Apgar (<7 at five min), which has more recently shown to have a low specificity for HIE.[54] Despite more reliable HIE criteria, more recent studies into HIE outcomes are still difficult to make generalisable as therapeutic hypothermia (cooling), the gold standard of care for moderate and severe HIE, alters outcomes and so studies need to be evaluated not only of grade of HIE but also interventions received.[41]

Almost all studies subsequent to 2000 have shown that while the motor system is frequently affected there are extensive delays and limitations in other systems as well, particularly cognition, which may affect the child's ability to actively participate in daily life, which is important to consider as occupational therapists.

The link between this motor and cognitive dysfunction includes difficulties in visual-motor integration (VMI). Visual-motor integration refers to the child's ability to co-ordinate visual perception with hand and finger movements.[65] Robertson and Finer who published their seminal paper into the long-term outcomes of children with HIE in 1989 found that visual-motor integration was significantly delayed in children with moderate and severe HIE. One of the only more recent studies into VMI in children with HIE was published in 2008 and found that VMI was among the lowest scoring outcomes in adolescents with HIE along with attention and executive function.[66]

2.6.1.2 Visual-motor integration in children with hypoxic ischaemic encephalopathy

While there have not been many studies into VMI in HIE, there are a number of studies investigating VMI in both typically developing and special needs populations.[65, 67, 68] These studies have had interesting results that are as applicable to HIE as to the study population. For example, a 2016 study investigated the connectomics of visuo-motor deficits in children with developmental coordination disorder (DCD), a motor disorder characterised by mild motor and cognitive dysfunctions affecting the child's home and learning environment. They found that VMI, which was also delayed in children with DCD, was related to deficits particularly

in the internal capsule.[67] These findings were also found in a 2010 study that showed the deficits in the internal capsule were strongly related to motor function in infants with HIE and the subsequent development of CP.[40]

The area that is perhaps most affected by poor VMI is in school. Individuals with VMI difficulties have been shown to have poorer later reading ability.[69] Another study has linked poor VMI skills to impaired working memory and reduced mathematical proficiency in school-aged children.[70] The first study was performed in France and the second in the United States of America but these findings have been found for children in South Africa as well.[69-71] A 2009 multi-centre study showed that there was a significant correlation between VMI ability and writing skills, particularly letter formation.[71] This was re-iterated in a 2013 study with similar findings of negatively affected executive function, maths and writing skills in children with poor VMI.[72] In yet another study, VMI performance was also shown to affect the child's ability to perform ADLs. VMI is therefore undeniably linked to cognitive function and overall participation in life activities both at home and in school. This is the case both in healthy children and those with conditions such as HIE.

2.6.2 Cognitive development and behaviour of children with hypoxic ischaemic encephalopathy

The effect of HIE on cognition is an ever-evolving study. Originally it was thought that HIE did not affect cognitive abilities. In fact in 2004 the American College of Obstetricians and Gynaecologists: Task Force on Neonatal Encephalopathy stated that neonatal encephalopathy can result in CP of spastic quadriplegic or dyskinetic types only and could not result in cognitive dysfunction independent of motor deficits.[4, 27] Recently, however, there have been numerous studies that are challenging this assumptions. These studies are finding that up to 80% of children with moderate NE suffer from cognitive deficits, with or without neuromotor deficits being present. This demonstrates that these children "grow into their deficits" despite normal examinations at 12 or 18 months of age.[4, 27, 39, 44, 73] The assessment of cognition in survivors of HIE is complex. Standardised tests are often not created

with motor and communication impairments in mind and testing may be further complicated by visual deficits, despite this cognitive testing is vitally important for the adequate provision of school and community-based resources.[40]

One study assessed the language and cognitive skills of children with neonatal encephalopathy (NE) at seven years of age.[74] They found that children with moderate NE were no different to the control group in general cognitive functioning but were behind in language and sensorimotor domains, presented with poorer narrative memory and sentence repetition, and were more likely to require extra support in the educational setting.[74] They also found, in the group with severe NE neonatally, that besides poorer general cognition and motor difficulties, these children were more likely to score significantly lower in episodic memory i.e. context-rich memory for events with relative preservation of semantic memory i.e. context-free memory for facts. The authors noted that further study should be done into specific memory dysfunction related to NE.[74]

One of the few studies that have been done with late adolescents with moderate HIE but not CP indicated a borderline to disabled intelligence quotient (IQ) with increased symptoms of inattention, short term memory dysfunction and problems with time perception and social function and up to 70% suffering from impaired cognitive executive function.[73]

As is evident from the above studies, most research into this domain is compiled based on children with moderate HIE. More and more, however, studies are identifying that children with mild HIE are also experiencing cognitive deficits. One such study found that despite normal outcomes at 3 years, children diagnosed with mild HIE scored significantly lower on tests of IQ.[53]

In addition to executive function deficits, behavioural problems such as attention deficit hyperactivity disorder (ADHD) have also been attributed to HIE. Research has found that the corpus callosum, an area of the brain responsible for connecting the cerebral hemispheres and associated with poor attention, hyperactivity and motor deficits, was thinned in 37% of children with mild HIE and 53% of children with

moderate HIE compared to just 16% of the control group placing them at a higher risk for a later diagnosis of ADHD.[75]

Both cognition and motor development are strongly associated with social skills and ADLs. In children with motor disabilities, those with poorer cognitive abilities had fewer playful behaviours and more limited self-care function.[76]

2.6.3 Activities of daily living development

ADLs are defined by the American Occupational Therapy Association's Occupational Therapy Framework: Domains and Processes (3rd ed.) as the activities involved in taking care of one's own body and includes toileting, dressing, eating, feeding, functional mobility, personal device care, personal hygiene and grooming and sexual activity.[1] Competent performance of ADLs is vital for participation in school, home and community spheres and significantly contributes to the child's development of self-esteem.[77]

Very few studies have described the outcome of asphyxiated children in functional terms, such as performance of ADLs.[7] Therefore, research done with children diagnosed with CP, a frequent outcome in children diagnosed with severe HIE, will be considered. Performance of ADLs in children with CP have been found to be associated with many factors such as their age, health condition, motivation, family values, culture and physical environment but the most significant predictors of ADL performance are gross and fine motor function and intellectual capacity.[77-79]

The level of physical ability of children with CP is predictive of their participation in self-care activities and engagement in play with higher motor functioning being related to increased independence in self-care tasks and better social functioning.[76] This relationship has been found in numerous studies.[77-79] Gross and fine motor function has also been found to be strongly related to intellectual function.[80]

The developmental trajectory of ADL performance of children with CP as well as slight fine motor dysfunction has been found to be smaller than typically developing children but still significant, whereas children with marked fine motor dysfunction

showed no significant improvement in ADL performance. As the level of fine motor proficiency reduces, so the developmental trajectory of ADLs becomes flattened.[77] ADL performance is vitally important to a child's social participation and self esteem and independence in ADLs also improves quality of life both for the child and their family.[81] Independence in ADL function is one of the outcomes addressed by occupational therapy and the multidisciplinary team.

2.7 Rehabilitation options for children with hypoxic ischaemic encephalopathy

2.7.1 Neuroplasticity and development after insult at birth

As a necessary consequence of the subject matter, most of the studies regarding rehabilitation strategies by the multidisciplinary team following early cortical injury rely on animal, specifically rodent, studies, which make generalisation to human subjects difficult.[26] Some strategies such as pharmacological interventions to stimulate stem cells will require significant refinement before they can be safely administered to human neonates but others are more readily and safely applied.[82] Early experiences, both pre- and postnatal, can significantly alter brain as well as behavioural development resulting in actual structural reorganization of neural networks.[82, 83] These changes are thought to be epigenetic in nature and thus are very varied depending on the child's age and the type of experiences they have, including experiences following cerebral lesions during development.[82] This propensity for neural reorganisation can be harnessed using motor learning strategies to improve neurodevelopmental outcomes in children with HIE.[84] This important work is carried out by the multidisciplinary team.

2.7.2 The multi-disciplinary team and occupational therapy

Rehabilitation, in paediatrics, is carried out by a large team who need to work together to ensure the optimal development and participation of the child. This team includes social workers, psychotherapists, physiotherapists, speech therapists and

occupational therapists. Each profession has their individual role in the child-family-society triad but each work towards the child's optimal engagement in life.[85, 86]

Occupational therapists are uniquely focused on occupation both as a treatment modality and as the goal of treatment. Occupational therapy is the therapeutic use of daily living activities (occupations) with individuals or within a group setting for the greater purpose of enhancing and enabling participation and quality of life.[1] The core philosophical assumption of the profession is that by virtue of our culture, environment, history and biological endowment, people of all ages and abilities require occupation to develop, survive and thrive and that in the pursuance of occupation, humans are able to express their totality.[87] Humankind could not exist without occupation and therefore humankind are occupational by nature.[87]

Compared to other mammals, human postnatal brain development is extremely protracted. Synaptic growth and increased synaptic density continue for at least the first decade of life and refinement of these, via the selective pruning of synapses, occurs for much longer. An example of this is the refinement of gait and hand function, which continues to approximately 15 years of age and that of cognition, which continues for much longer. As a result of that and despite the fact that early brain trauma is generally more severe than that experienced by adults, infants have a much higher potential for recovery.[88] Occupational therapists use this potential to direct recovery and optimise function.

This optimisation of function is done through the development of interventions based on the child's performance of and context for their unique occupations which include ADLs, examples of which include dressing; eating and washing; play; school participation; family interaction; social participation; sleep and rest; their engagement in leisure activities; and how al of these are afforded or constrained by their physical, social and cultural environments.[89]

Occupational therapy for children with neurological conditions is a vast and swiftly evolving field and is attempting to keep up with rapid and exciting changes in the concepts of neuroplasticity as well as theories of motor learning and cognitive

development and how best to harness these to improve the occupational performance of the children affected.[89] The body of research into occupational therapy interventions with children with neurodevelopmental delay is growing steadily but faces numerous challenges including the heterogeneity of the sample as well as of the intervention and outcome measures, the ethical dilemma of a control group in a paediatric population, small sample sizes, low methodological quality, and poor sensitivity of outcome measures.[15] Although, as at the time that this study was completed, there is no research specifically investigating occupational therapy for children with HIE there is research into the occupational therapists role in treatment of children with CP, a frequent and disabling outcome of HIE.

As the understanding of development moves away from neuro-maturation theories towards more neuroplasticity-based and dynamic systems theories so occupational therapy, too has moved towards more activity and goal oriented approaches.[90, 91] This treatment is directed towards both the child and family in order to treat the child holistically. The goals of this treatment are to improve school, family, social and community participation and quality of life.[15, 83, 92]

It is not only the intervention itself that is important but the timing of the intervention is important too. Whilst intervention at any time is beneficial, early intervention may provide the most benefit for children with perinatal brain injury. Early intervention, defined as intervention with children under the age of five years, at risk for developmental disabilities, involves many different components. These include improving child health and wellness, facilitating the acquisition of developmental skills, minimizing developmental delays and remediating existing and emerging disabilities, preventing functional deterioration, promoting parenting skills and education, and functioning of the family unit as a whole.[20, 21, 93]

A 2015 Cochrane systematic review into the benefits of early intervention for children who were born prematurely noted that early intervention post-discharge for these children improved motor outcomes up to preschool age and improved cognitive outcomes further into later school years.[94] In other research early intervention

programmes have also been found to improve school achievement, reduce developmental delay, improve independence, reduce criminal activity and improve earnings later in life for the individual as well as enhance parenting skills and reduce parental stress.[20, 21, 93]

This shows that the timing of occupational therapy is of particular importance but in a resource-limited setting such as South Africa where there are limited occupational therapists available and the ability of the child and their family to access these service is limited by time and financial restraints it is important to prioritise the treatment of those most in need of services. In order to do this a reliable indicator must be used that can determine which children would benefit most. In the Western Cape, the Thompson HIE score is regularly used to identify and grade the severity of children with HIE.

2.8 Baseline measure of hypoxic ischaemic encephalopathy

2.8.1 Thompson hypoxic ischaemic encephalopathy score

The Thompson HIE score is an assessment based on clinical signs performed in the child's first two weeks of life or until discharge from hospital, whichever comes first. As was mentioned in the introduction the Thompson HIE score is well suited to the South African context where resources are limited and expensive diagnostic tests such as an MRI are not readily available. Developed at Groote Schuur Hospital, it was tested by Thompson et al. in 1997 to determine its value in predicting the neurodevelopmental outcomes, using the Griffiths Mental Development, of infants who developed HIE after birth. They found a correlation coefficient of 0.7 for the correlation between the Griffiths general quotient and the Peak score of the Thompson HIE score.[6] In addition to this they found that the peak daily total scores (i.e. the highest total score measured) corresponded well with the Sarnat and Sarnat classification.[6] They found that peak scores of less than ten were graded as mild HIE, scores between 11 and 14 being graded as moderate HIE and those with a peak score of greater than 14 being graded as severe HIE.[6]

Since then, studies researching the Thompson score in infants who have received therapeutic hypothermia have found the peak scores to be slightly flatter. A 2013 study by Horn et al. found that a Thompson score at between three and five hours of less than or equal to seven had 100% sensitivity with specificity of 66.67%.[2] There are however no recent studies evaluating motor outcomes that include infants who received therapeutic hypothermia where the Thompson HIE score was used. The aim of this study therefore, was to determine if the Thompson HIE score can be used to identify children most in need of occupational therapy services.

2.9 Summary

In this review the complex definition of HIE was described. Distinction was made between birth asphyxia, neonatal encephalopathy and hypoxic ischaemic encephalopathy. It was shown that determining accurate prevalence is difficult due to the numerous criteria used to describe HIE. Despite this it has been shown that HIE is a major public health concern with a prevalence in South Africa of 1.5 – 9 per 1000 live births. The extensive costs associated with HIE were also enumerated.

HIE pathophysiology and the two major patterns of injury were described, namely the watershed pattern affecting the white cortical matter and often resulting in cognitive and behavioural problems and the basal ganglia-thalamic pattern often associated with athetoid.

The effects of HIE on a child's development were discussed. In terms of motor development, it is generally agreed upon that mild HIE has fairly typical motor development and severe HIE has a very high incidence of motor disability. When considering moderate HIE however, results are less certain with incidence of disability ranging from fifteen to seventy-five percent depending on the study and the criteria that were used. Many recent studies have shown that children may grow into their disability noting that, despite normal examinations at 18 months, many children went on to have lower than average IQ, memory dysfunction, poorer self-care and reduced social function as adolescents.

Treatment by the rehabilitation team was noted and the specific role of the OT discussed. Studies into the use of OT in children with CP face numerous challenges including heterogeneous outcome measures and interventions, ethical dilemmas with having a control group as well as poor sensitivity to change in most outcome measures amongst others. However, research has shown that activity and goal-directed approaches are most effective, especially when performed within a family-centred approach. Early intervention was shown to be beneficial in improving motor, cognitive and school function at preschool age as well as being of benefit to the family as a whole. Intervention needs to be directed at the most at-risk groups to be of maximum benefit. The Thompson HIE score was described as a possible means of determining which children with HIE would most benefit from OT services.

Chapter 3: Methodology

This chapter will discuss the choice of study design, and will elaborate on the study population and how the study sample was selected. Details of the research measurement tools and procedures will be discussed as well as how the data collected was analysed. Lastly ethical considerations will be outlined and procedures to address these described.

3.1 Study design

A quantitative, descriptive, cross sectional study design was used.[40] Descriptive research refers to research that does not manipulate variables but rather uses a single point in time to describe the sample being studied.[43] In this study data collection in the form of an assessment and interview took place at a specific moment in time and thus is considered to be cross sectional research.[40]

3.2 Study population

The study population was children previously diagnosed with HIE, aged between nine and twenty-four months from Mowbray Maternity Hospital (MMH) and Groote Schuur Hospital (GSH). It included all children with a diagnosis of HIE regardless of the severity, or whether or not they received therapeutic hypothermia.

3.3 Study sample

3.3.1 Selection and selection procedure

This was a convenience sample of children attending the paediatric outpatient clinic at MMH in Cape Town, as children from both MMH and GSH are followed up at this facility. The first 30 children who met the inclusion criteria, whose caregivers agreed to participate and who attended the paediatric clinic between 1 May 2016 and 30 October 2017 were included in the study. Two subjects were later excluded. One was excluded because of congenital disorders discovered after assessment and

another because despite a diagnosis of HIE on the referral, no HIE score could be found. 28 participants were thus included in the study.

3.3.2 Inclusion and exclusion criteria

Children were included/excluded based on the following:

Table 3.1: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Child must have been born full term (at or greater than 36 weeks gestation) Child must have a diagnosis of HIE with a Thompson HIE score on record Child must be between nine and twenty-four months of age	Primary caregivers of children who are not yet 18 years of age themselves or who cannot legally give informed consent for the child. Children with comorbidities that may affect the outcome of the study such as congenital abnormalities, hydrocephalus etc.

3.4 Research measurement instruments

3.4.1 Medical information:

The medical records information sheet (Appendix A) was compiled and included the following information: the child's age, subject code, HIE score, brief medical history in terms of additional morbidities, Apgar score at one, five and ten minutes, whether the child received therapeutic hypothermia or not, whether the child had in the past or was currently receiving any other interventions, and the child's birth weight measurements. This information was included based on common outcomes and

complications noted on the literature.[2, 6] The medical records information sheet was completed by the researcher via review of the child's hospital records.

The HIE grade i.e. mild, moderate or severe is determine by the Thompson HIE score. The Thompson HIE score is calculated using nine clinical signs, namely: tone, level of consciousness (LOC), seizures, posture, Moro reflex, suck reflex, grasping reflex, respiration and the status of the fontanel (Table 3.2).[6] These signs are given a daily rating by the attending doctor of 0-3 depending on their presentation (Table 1). These scores are then added to give a total score per day, which is done until the total score is nought (i.e. no abnormalities detected) or until the infant is discharged. Grading is based on the peak score with scores of less than ten being graded as mild, scores of 11 to 15 being graded as moderate and scores of 16 and above being graded as severe HIE.[6]

Table 3.2: The Thompson hypoxic ischaemic encephalopathy score

Sign	**Score 0**	**1**	**2**	**3**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Tone	Normal	Hyper	Hypotonic	Flaccid							
Level of conscious-ness	Normal	Hyperalert, stare	Lethargic	Comatose							
Fits	Normal	Infrequent < 3/day	Frequent >2/day								
Posture	Normal	Fisting, cycling	Strong, distal flexion	De-cerebrate							
Moro reflex	Normal	Partial	Absent								
Grasp	Normal	Poor	Absent								
Suck reflex	Normal	Poor	Absent ± bites								
Respiration	Normal	Hyperventilation	Brief apnoea	Intermittent positive pressure ventilation							
Fontanel	Normal	Full, not tense	Tense								

3.4.2 Peabody Developmental Motor Scales, Second Edition (PDMS–2):

When assessing the motor outcomes of children, occupational therapists use a number of different assessment measures. The most common assessments include the Alberta Infant Motor Scales (AIMS), Bayley Scales of Infant Development (BSID) – II or III, the PDMS-2, and the Movement Assessment Battery for Children (MABC-2). The AIMS only assesses children up to the age of 18 months and the MABC-2 only assesses from three years up.[95, 96] The BSID-2 is a norm-referenced assessment for children from one month to three and a half years with three scales, namely a mental, motor and behavioural scale. The BSID-2 has however found to have limited differentiation between fine and gross motor function, which is the purpose of the study and therefore makes it inappropriate. The PDMS-2 is also a norm-referenced assessment and consists of gross and fine motor scales divided into six subtests from birth to 5 years 11 months. While its evaluative properties i.e. its ability to measure change over time, are acceptable, its discriminative properties i.e. its ability to determine delay based on normative data are excellent.[97]

The Peabody Developmental Motor Scales were first developed by Folio and Fewell in 1983 and then revised and renamed the Peabody Developmental Motor Scales, Second Edition (PDMS-2) in 2000.[98] The PDMS-2 has six subtests based on Harrows taxonomy of psychomotor domains. These subtests are:

1. Reflexes: an 8-item subtest that measures the child's ability to automatically react to environmental events
2. Stationary: a 30-item subtest measuring a child's ability to sustain control of his or her body within its centre of gravity and retain equilibrium.
3. Locomotion: an 89-item subtest measuring the child's ability to transport his or her body from one base of support to another
4. Object Manipulation: a 24-item subtest measuring a child's ability to throw, catch and kick balls.

5. Grasping: a 26-item subtest measuring a child's ability to use his or her hands and fingers.
6. Visual Motor Integration: a 72-item subtest measuring a child's ability to integrate and use his or her visual perceptual skills to perform complex eye-hand coordination tasks.[5]

Scoring of the items is on a three-point scale where a score of 2 shows mastery in the item according to the specified criteria, a score of 1 shows a resemblance to the specified criteria for mastery but does not fully achieve them, a score of 0 is given when a child is unable to perform or unwilling to attempt the item.[5, 99] Folio and Fewell published their guide to interpreting PDMS-2 subtest standard scores in their 2000a Examiners Manual (Table 3.3):

Table 3.3: Guide to evaluating PDMS-2 score[5]

STANDARD SCORES	QUOTIENT SCORES	DESCRIPTION
17-20	135-165	Very superior
15-16	121-130	Superior
13-14	111-120	Above average
8-12	90-110	Average
6-7	80-89	Below average
4-5	70-79	Poor
1-3	35-69	Very poor

In total there are 249 items that can be tested which would be extremely time consuming but for three restrictions that are applied which are based on the age of the child being assessed. First the assessment is begun at an entry point based on the point at which 75% of the standardisation sample was able to successfully complete the task. Second there is a basal level where the last three items need to be graded a two. Third the ceiling level which is the point at which the child scores

three consecutive zeros. The resultant subtest score is then the basal score plus the scores achieved before the ceiling is reached[99]

In 2000 Folio and Fewell found that the PDMS-2 was a reliable test of motor development in children in their study which investigated internal consistency (Cronbach α =.89 – .97), test-retest reliability (.82 – .93) and inter-rater reliability (.96 – .99).[5] In a 2006 study, it was determined that the composite scores of the PDMS-2 had good test-retest reliability with intraclass coefficients of 0.88 to 1.00 and acceptable sensitivity (1.6 – 2.1) and responsiveness (1.7 – 2.3) as measured by the Guyatt responsiveness index for sensitivity to change (GRI-S) and the Guyatt responsiveness index for responsiveness (GRI-R) respectively.[100]

There are some issues worth noting with the PDMS-2. In particular there have been some studies that have noted that the PDMS-2 has low sensitivity for picking up minor motor dysfunction. One study into the concurrent validity of the Bayley Scales of Infant Motor Development (BSID)-2 and the PDMS-2 in children with developmental delay found that approximately half of the children showing appropriate development on the PDMS-2 were classified as being slightly delayed on the BSID-II.[101] This result was reproduced by another study in 2007 but this time with the M-ABC.[102] These results were applicable to both the gross and the fine motor scales of the PDMS-2. This was not assumed to be of particular importance to this study as previous studies noted marked motor dysfunction.

In addition to that the PDMS-2 has not been standardised on the South African population. A 2013 study showed that black urban South African children from Gauteng performed slightly above USA children on the BSID-III but no other studies were available for South Africa.[103] Studies using the PDMS-2 on other children from disadvantaged backgrounds show variable outcomes especially at differing ages. For example a 2009 study performed in India showed that children from a low socio-economic background there scored lower than the norm for fine motor function under 44 months but over 44 months showed an upward trend and eventually exceeded the norm-referenced scores.[104] The authors of this paper surmised that there may be

a number of reasons for this including cultural differences in the developmental expectations of caregivers in India, a difficulty with translation of the measure into local languages which may have allowed for more demonstration and thus altered the reliability of the scores and the lack of resources in most households in the area meaning that children may not be exposed to toys such as peg-boards and shape boards, particularly not until they are of school-going age[104] This lack of standardisation on the South African population is however unavoidable as there are currently no large standardised assessments of motor function that have been standardised on the South African population. The PDMS-2 has further been used successfully in many different studies in children from around the world.[98, 99, 104, 105]

In this study the raw scores from all of the subtests were recorded on the examiners record booklet (Appendix B) and the Fine and Gross Motor Quotients as well as the Total Motor Quotient were summarised on the profile sheet (Appendix C).

3.5 Data collection procedure

Dr Clare Thompson who runs the neuro-developmental follow up clinic at MMH identified children who met the research criteria. On the day of the child's clinic appointment, their caregivers were approached. The information sheet (Appendix D) was used to explain the purpose of the study to the caregivers and they were invited to participate. All of the caregivers, who were approached, agreed to participate in the study. The caregivers were then requested to sign informed consent for the researcher to assess the child (Appendix D) and access their medical folders (Appendix E). All assessments took place on the day of the child's neurodevelopmental clinic appointment.

Assessments took place with the caregivers present in a separate room adjacent to the High-Risk Neurodevelopmental clinic room either before or after the child's appointment with the doctors at the clinic. The children were assessed using the PDMS-2, which took approximately 45 minutes to complete. The child's medical folder was reviewed for the relevant information and to confirm the inclusion criteria

by the researcher and the medical record information sheet was completed and attached to the questionnaire after the assessment had taken place.

3.6 Data analysis

Descriptive and inferential statistics

Descriptive statistics have been used to describe the data. In order to do this the central tendencies, specifically the, median, and quartile ranges have been noted for the data gathered using the PDMS–2 as the sample was small and the data were not normally distributed. Median scores were used so that outlying figures did not skew the results due to the small sample size.[106]

The demographic factors for the groups which were divided into mild, moderate and severe HIE using Thompson scores were compared using Fischer exact tests and chi-square tests.

The difference in the PDMS-2 for the three groups were compared using a Mann Whitney U test. Non-parametric statistics were used due to the small samples in each group, which did not have normally distributed data. The significance was set at 0.05. Clinical significance was established using Cohen's r effect sizes for parametric data. Effect sizes (Cohen's r) were interpreted at 0 – 0.9 as a negligible effect, 0.1 – 0.23 as a small effect size, 0.24 – 0.37 as a moderate effect and greater than 0.38 as a large effect size.[107] A z-score of 1.645 obtained in relation to the Mann Whitney U tests can be considered as indicating significant differences at a 0,05 level and a z-score of 2.326 is significant at a 0.01 level.

The mild and moderate HIE group were compared initially and when no significant differences and small effect sizes were found their scores were combined. This combined group was then compared to the severe group. The Mann Whitney U test and Cohen's r effect sizes were calculated for this comparison.

3.7 Ethical considerations

Ethical clearance has been obtained from the University of the Witwatersrand Human Research Ethics Committee (Appendix F). The National Health Research Database (NHRD) has given approval for research to be conducted at MMH (Appendix G). Approval was obtained from the University of Cape Town Human Research Ethics Committee (Appendix H) and further extended (Appendix I). Written consent was requested (Appendix J) and obtained from the medical superintendent of Mowbray Maternity Hospital to perform the research at the hospital as well as for access to the hospital's medical records (Appendix K).

3.7.1 Description of risks and benefits:

This study posed minimal risk to the participants as only an assessment was done and no intervention was provided. No discomfort is associated with the PDMS-2 assessment procedure and it is considered a routine physical examination.

Potential benefits included the determination of early developmental difficulties. Where a child scored a -2 standard deviation below the mean the child was referred to their nearest community occupational therapy department and their caregivers were counseled by the researcher on the extent of the developmental delay, their specific concerns and available treatment options for their child. The family was also supplied with an information pamphlet about developmental delay and home-based strategies to stimulate appropriate developmental milestones (Appendix L). Other results were made available to the family on request.

3.7.2 Informed consent process

Caregivers attending the clinics were invited to participate in the study on the day of their existing appointment. Each participant's caregiver was given the information sheet (Appendix D), which was explained verbally to him or her by the researcher. This sheet was translated from English into Xhosa and Afrikaans and the caregivers were given the sheet in their language of choice. In the information sheet and in the

verbal discussions with the child's caregivers it was stated that participation in the study was completely voluntary, that no compensation could be received for participation and that they could refuse or withdraw at any time without any penalty whatsoever. If they agreed they were then requested to sign the informed consent sheets (Appendix E and F) giving consent for the researcher to access the child's medical records as well as assess the child using the PDMS-2. Both informed consent forms were available in English, Xhosa and Afrikaans.

3.7.3 Privacy and confidentiality

All information divulged to the researcher or interpreter by the caregivers or in accessing the medical records was kept strictly confidential at all times. No identifying information has been published or been accessed by any person other than the researcher. In order to ensure this, a list was drawn up with the children's names to which the researcher subsequently added subject codes. The subject codes list was only accessed by the researcher and was kept separately from all data, stored in a locked safe when not in use. No medical information forms or PDMS-2 record sheets contained any identifying information. Data will be stored for a period of six years in accordance with the Health Professions Council of South Africa (HPCSA) guidelines.

3.8 Conclusion

This was a quantitative, descriptive, cross-sectional study of twenty-eight infants with HIE between the ages of nine and twenty-four months attending the Mowbray Maternity Hospital's Neurodevelopmental High-Risk Clinic. Medical information, including the child's HIE score, was collected using the medical research information sheet (Appendix A) compiled by the researcher. The child's gross and fine motor skills were assessed using the PDMS-2. Descriptive and non-parametric methods were applied in the analysis of the data. Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee, The National Health Research Database (NHRD), the University of Cape Town Human Research Ethics Committee and the medical superintendent of Mowbray Maternity Hospital

gave consent for the research to be conducted at the Neurodevelopmental High-Risk Clinic. Informed consent and confidentiality were strictly adhered to.

Chapter 4: Results

4.1 Introduction

This chapter presents the results of this study including the demographics and medical history of the participants. Demographics such as age and gender are detailed. Medical information including the participant's birth history (gestation, Apgar scores, delivery, complications and HIE scores), in hospital treatment (therapeutic hypothermia, length of hospital stay) and the therapy received as well as the length of intervention will be presented. It further includes the results of the PDMS-2 for the different HIE groups (based on the Thompson HIE scores) of the children studied. This is done firstly by examining the sample as a whole and then by combining the mild and moderate HIE groups and comparing them to the severe HIE group and determining if differences exist between the groups in terms of the results of the PDMS-2 subtests and motor quotient scores.

4.2 Results

The study recruited 28 participants aged between nine and 24 months of age attending the Mowbray Maternity Hospital High Risk Neurodevelopmental Clinic. Thirty children were initially assessed but two children were later excluded: one based on congenital disorders discovered after assessment in the medical folder and the other due to an HIE diagnosis in the medical folder but no Thompson HIE scores. Participants were sorted into three separate groups based on their Thompson HIE score. Those with a peak score between zero and nine were included in the mild HIE group, those whose peak scores were between 11 and 14 were included in the moderate HIE group and those whose peak scores were between 15 and 20 were included in the severe HIE group. Of the 28 children, 46% (n=13) were graded as mild, 25% (n=7) as moderate and 29% (n=8) as severe according to the Thompson HIE score.

4.2.1 Demographics

4.2.1.1 Age and gender

The age of the participants ranged from nine to 21 months with the average age being 12 months and 27 days. More participants were assessed at 15 months (25%; n=7) than at any other age (mode). There was no significant difference (p=0.394) between the average age across the mild, moderate and severe HIE groups (Table 4.1). Overall there was a significant difference (p=0.022) for females between the three groups with more females in the mild HIE group (76,92%; n=10); and similar numbers of females in the moderate HIE group (43%; n=3) and the severe HIE group (50%; n=4). There were overall more females (61%; n=17) than males (39%; n=11) recruited to the study.

Table 4.1: Age and gender of each group

	TOTAL SAMPLE (n=28)		**MILD GROUP (n=13)**		**MODERATE GROUP (n=7)**		**SEVERE GROUP (n=8)**		**p-VALUE**
			Mean (SD)						
Mean age (m)	12.9 (3.27)		13.07 (4.05)		13.57 (2.50)		12.12 (2,53)		0.394
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	p-VALUE
Females	17	61	10	77	3	43	4	50	0.022*
Males	11	39	3	23	4	67	4	50	0.331

* significance $p \leq 0.05$ ** significance $p \leq 0.01$

4.2.2 Birth history

4.2.2.1 Gestation

The gestation period of the children varied between 36 and 41 weeks (Figure 4.1) with the highest percentage of children in the total sample born at 40 weeks (57%; n=16), which is considered to be the typical length of gestation (mild = 62%; n=8;

moderate = 42%; n=3 and severe = 63%; n=5). The mean gestation period of the mild, moderate and severe HIE participants was 39.54, 38.86 and 39.50 weeks respectively. Only one child was born at 36 weeks in the mild HIE group (8%) with all children in the moderate and severe HIE groups being born at or after 37 weeks.

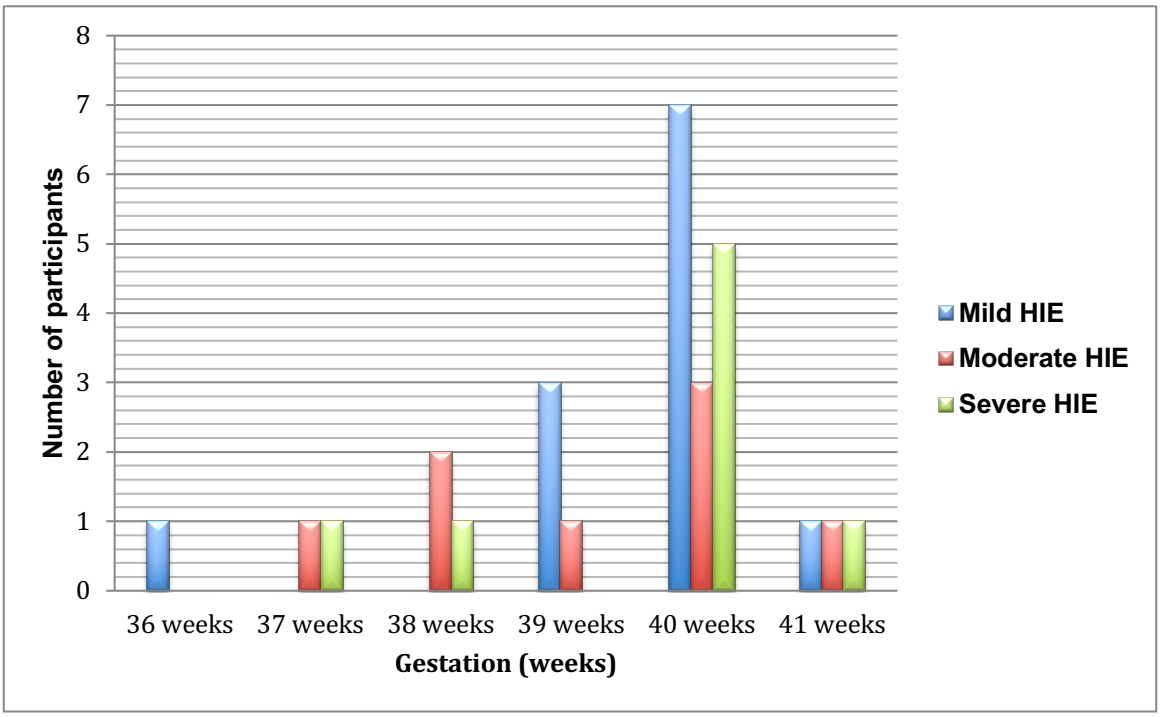


Figure 4.1: Gestation period of the participants according to mild, moderate and severe hypoxic ischaemic encephalopathy groups (n=28)

4.2.2.2 Mode of delivery and precipitating factors

The majority of the children were born via caesarean section (68%; n=19) with only two of these births being elective caesarean sections (11%). The most common noted precipitating factor associated with a woman receiving a caesarean section in the mild and moderate HIE group was foetal distress while cord prolapse was the most common factor in the severe HIE group. There was no noted precipitating factor in two births in the mild HIE group (8%), two births in the moderate HIE group (29%) and one birth in the severe HIE group (13%). There was a strong significant difference between the three groups in the number of children who experienced cord

prolapse during birth (p=0.000) (Table 4.2). Thirty-eight percent (n=3) of the severe HIE group experienced cord prolapse while only eight percent (n=1) of the mild HIE group and none of the moderate HIE group experienced cord prolapse.

Table 4.2: Mode of delivery and precipitating factors

	TOTAL SAMPLE (n=28)		MILD GROUP (n=13)		MODERATE GROUP (n=7)		SEVERE GROUP (n=8)		p-VALUE
Mode of delivery									
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Caesarean section	19	68%	10	77%	4	57%	5	63%	0.190
NVD	9	32%	3	23%	3	43%	3	38%	0.705
Precipitating factors									
Foetal distress	7	25%	3	23%	2	29%	2	25%	0.695
Cord prolapse	4	14%	1	8%	0	0	3	38%	0.000**
Prolonged labour	4	14%	2	15%	1	14%	1	13%	0.931
Placental abnormalities	2	7%	1	8%	1	14%	0	0	0.286
Elective	2	7%	2	15%	0	0	0	0	n/a
Abnormal presentation	2	7%	2	15%	0	0	0	0	n/a
Cephalopelvic disproportion	2	7%	1	8%	0	0	1	13%	0.823

* significance p ≤ 0.05 ** significance p ≤ 0.01

4.2.2.3 Birth weight

Birth weight of the participants ranged from 2300g to 4990g with the average weight being 3111g. Only three of the participants (11%) were defined as having low birth weight i.e. below 2500g. Information on birth weight was unavailable for five of the participants. When looking at the mean birth weight for the three groups, there was a statistically significant difference (p=0.000) with the mild HIE group having significantly higher birth weights. The mean birth weight in the mild HIE group was 3417,55 grams with the mean weight in the moderate and severe HIE groups at 3078,75 and 3049,29 grams respectively.

4.2.2.4 Apgar scores

There were no Apgar scores documented for one participant. The mean one-minute Apgar scores for the total sample were 3.97, mean five-minute scores were 6.4 and mean ten-minute scores were 7.64 (Figure 4.2). One-minute Apgar scores were lowest in the moderate HIE group at 3,71 with scores for the mild HIE group at 4,33 and for the severe HIE group at 3,88 but overall showed no significant difference between the groups (p=0.422). Five-minute Apgar scores were lowest in the severe HIE group at 5,75 and similar in the mild and moderate HIE groups at 6,92 and 6,57 respectively (p=0.414). Mean ten-minute Apgar scores were also lowest in the severe HIE group (7.00) and highest in the mild HIE group (8.67) with mean scores of 7.25 in the moderate HIE group. Unfortunately, ten-minute Apgar scores were not documented for all participants and were only available for 13 of the 28 participants of the study with no significant differences between the three groups (p= 0.317) using the available scores.

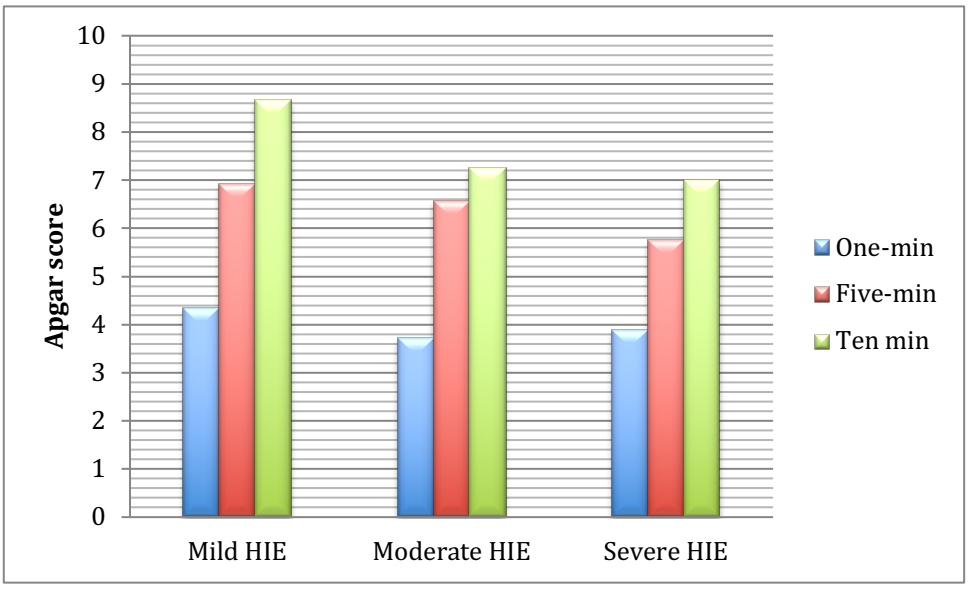


Figure 4.2: Mean Apgar score at 1, 5 and 10 min for the mild, moderate and severe groups (n=27)

4.2.3 Medical history

4.2.3.1 Thompson hypoxic ischaemic encephalopathy score

Thirteen of the twenty-eight participants were classified as having mild HIE (46%). Seven participants were classified as moderate HIE (25%) and eight as severe HIE (29%). Figure 4.3

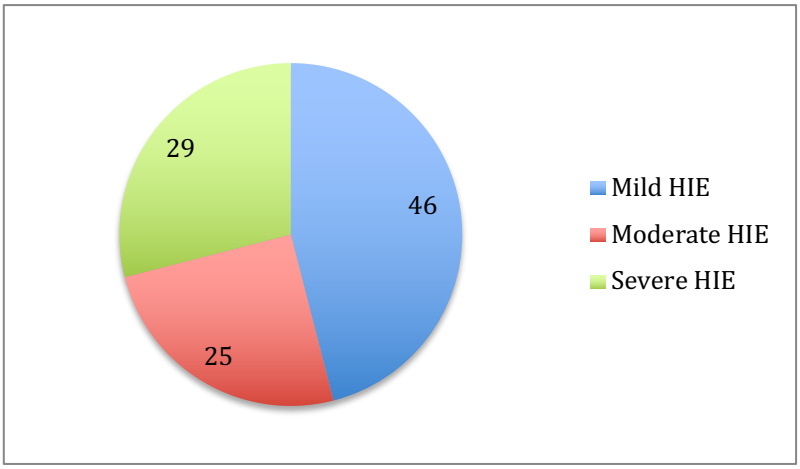


Figure 4.3 Participants' hypoxic ischaemic encephalopathy severity by percentage (n=28)

4.2.3.2 Therapeutic hypothermia

There was a significant difference (p=0.002) in the percentage of participants who received therapeutic hypothermia between the three groups of participants. The ratio of participants who did and did not receive therapeutic hypothermia in the mild HIE group was very similar with 6 (cooled) to 7 (uncooled). In the moderate and severe HIE groups there were a markedly larger number of participants cooled versus uncooled being 6:1 and 6:2 respectively. This resulted in 46% (n=6) of the mild HIE group, 86% (n=6) of the moderate HIE group and 75% (n=6) of severe HIE group receiving therapeutic hypothermia (Figure 4.4).

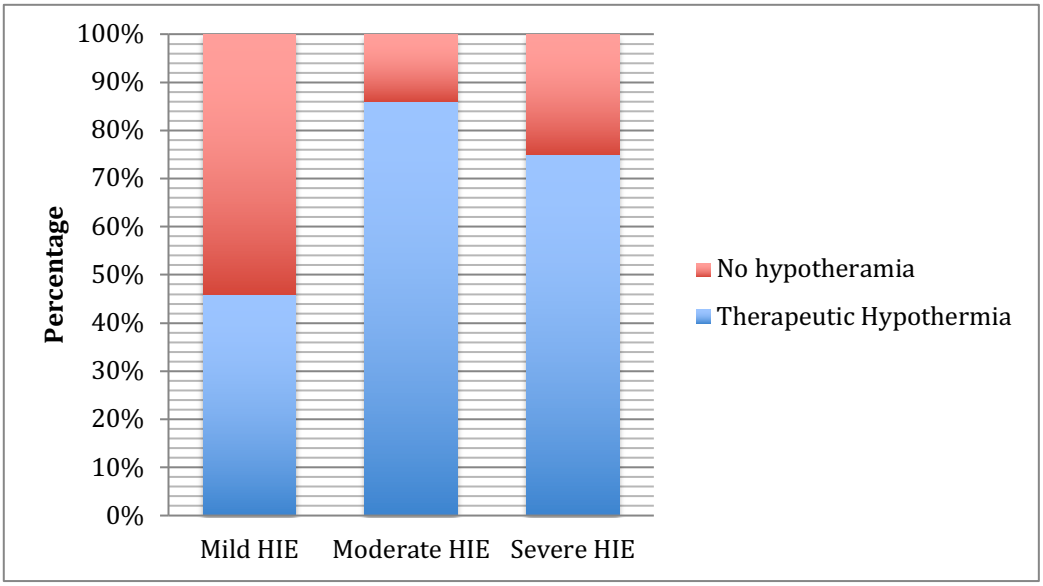


Figure 4.4: The percentage of participants receiving therapeutic hypothermia and those not receiving therapeutic hypothermia in the mild (n=13), moderate (n=7) and severe (n=8) groups

4.2.3.3 Complications

A variety of complications were experienced by the participants in the study (Table 4.3). The most common complications in the total sample were presumed sepsis (50%, n=14), prolonged ventilation (43%, n-12), respiratory distress syndrome (50%,

n=14) and seizures (39%, n=11). Significant differences were noted between the mild, moderate and severe HIE groups in presumed sepsis (p=0.018) with 69% (n=9) of the mild HIE group, only 14% (n=1) of the moderate HIE group and 13% (n=1) of the severe group experiencing presumed sepsis. Significance was also noted between the groups in terms of seizures (p=0.013) with 31% (n=4) of the mild HIE group, 57% (n=4) of the moderate HIE group and 38% (n=3) of the severe HIE group experiencing at least one seizure.

Table 4.3: Complications experienced based on severity of hypoxic ischaemic encephalopathy

	TOTAL SAMPLE (n=28)		MILD GROUP (n=13)		MODERATE GROUP (n=7)		SEVERE GROUP (n=8)		p - VALUE
	n	%	n	%	n	%	n	%	
Presumed sepsis	11	50%	9	69%	1	14%	1	13%	0.018*
Confirmed Sepsis	4	14%	1	8%	1	14%	2	25%	0.985
Prolonged ventilation	13	46%	4	31%	3	43%	6	75%	0.190
Respiratory distress syndrome	10	36%	5	38%	3	43%	2	25%	0.563
Seizures	11	39%	4	31%	4	57%	3	38%	0.013*
Macrosomia	3	11%	2	15%	0	0	1	13%	0.850
Meconium aspiration syndrome/ stained liquor	5	18%	2	15%	1	14%	2	25%	0.128
Retro-viral disease	2	7%	1	8%	1	14%	0	0	0.559
Retro-viral disease exposed	1	4%	0	0	1	14%	0	0	n/a
Neonatal jaundice	3	11%	1	8%	1	14%	1	13%	0.412
Other	12	43%	5	38%	3	43%	4	50%	0.435
None	3	11%	2	15%	1	14%	0	0	0.056

*significance $p \leq 0.05$ **significance $p \leq 0.01$

4.2.3.4 Length of hospitalisation

Length of hospitalisation after birth was unavailable for six of the twenty-eight participants. For more than half of the participants (57%; n=16) the length of stay was 1-2 weeks. There was a significant difference between the three groups in length of hospital stay of 1-2 weeks (p=0.002). Only 29% (n=2) of the moderate group stayed in hospital for 1-2 weeks while 69% (n=9) of the mild HIE group and 63% (n=5) of the severe HIE group stayed in hospital for 1-2 weeks. This significant difference needs to be interpreted with caution, as data on length of hospitalisation was missing for 71% (n=5) of the moderate HIE group participants (Table 4.4).

Table 4.4: Length of hospital stay according to severity of hypoxic ischaemic encephalopathy

Weeks	**TOTAL SAMPLE (n=28)**		**MILD GROUP (n=13)**		**MODERATE GROUP (n=7)**		**SEVERE GROUP (n=8)**		**p-VALUE**
	n	%	n	%	n	%	n	%	
0-1	1	4%	1	8%	0	0	0	0	n/a
1-2	16	57%	9	69%	2	29%	5	63%	0.002**
2-3	3	11%	2	15%	0	0	1	13%	0.850
3-4	1	4%	0	0	0	0	1	13%	n/a
4+	1	4%	0	0	0	0	1	13%	n/a
Unavailable	6	21%	1	8%	5	71%	0	0	

*significance p ≤ 0.05 **significance p ≤ 0.01

4.2.4 Therapy

Overall 61% (n=17) of the total sample received some degree of physiotherapy aimed at improving motor development. Three quarters of the participants in the severe HIE group (75%; n=6), less than half (43%; n=3) of the participants in the moderate HIE group and 62% (n=8) of the mild HIE group received physiotherapy intervention at the Mowbray Maternity Hospital High-Risk Clinic showing a statistically significant difference in the percentage of participants in the three groups who received physiotherapy (p=0.002). The participants did not receive occupational or speech therapy as part of their treatment at MMH. Some parents reported accessing occupational and speech therapy at other community health centres or hospitals. This information was not recorded as part of this study.

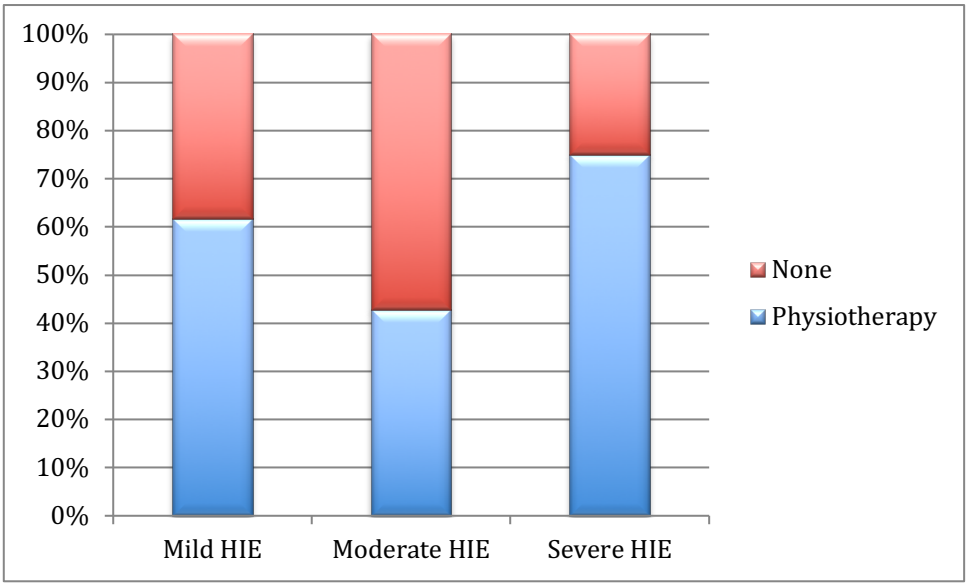


Figure 4.5 Physiotherapy received vs. no therapy in the mild, moderate and severe group

4.2.5 Peabody developmental motor assessment – 2 scores

When considering the PDMS-2 scores of the total sample it is noted that for all the subtests the median percentile scores are within the average range i.e. between the

25th and 75th percentiles (sample range = 37 – 63). This was confirmed by the z-scores, which are all within the normal range of 1 to -1 (range 0.35 to -0.8), as detailed in Table 4.5. These results need to be interpreted with caution as the total sample is skewed by the inclusion of a disproportionate number of participants with mild HIE (n=13) compared to those with moderate HIE (n=7) and severe HIE (n=8). This will be discussed in more detail later in 4.2.5.2.

Table 4.5 Summary of median, upper and lower quartile percentile scores, z-scores, mean and standard deviation (SD) of the Peabody Developmental Motor Scales -2 for the total sample (n-28)

SUBTEST	MEDIAN SCORES	LOWER QUARTILE	UPPER QUARTILE	Z-SCORE	Mean (SD)
Reflexes	37	37	50	-0.35	43.70 (13.74)
Stationary	63	50	75	0.35	63.35 (17.16)
Locomotion	37	25	50	-0.15	40.81 (20.71)
Object Manipulation	63	37	75	0.35	57.88 (19.98)
Grasp	50	37	75	0	53.38 (21.88)
VMI	50	37	50	0	43.46 (18.22)
GM Quotient	55	35	65	0.15	30.50 (3.62)
FM Quotient	50	31	61	0	19.73 (2.79)
TM Quotient	50	41	58	0	50.15 (5.60)

4.2.5.1 Therapeutic hypothermia

Many studies on outcomes of children with HIE, separate participants based on whether or not they received therapeutic hypothermia at birth as this generally affects the outcomes of the participants and therefore may skew results.[13, 45, 46] In this study when statistical analysis was done it was found that there was no statistically significant difference between the participants who had received therapeutic hypothermia and those who had not. This was applied to the sample as a whole as the sample size of those receiving therapeutic hypothermia in the moderate and severe HIE groups was too small. Only a small effect size was found for Reflexes (r=0.27) and for Locomotion (r=0.12). For this reason, both participants who did and did not receive therapeutic hypothermia were grouped together in the mild, moderate and severe HIE groups.

Table 4.6 Significance and effect size between participants who did and did not receive therapeutic hypothermia

SUBTEST	THERAPEUTIC HYPOTHERMIA		NO HYPOTHERMIA		p-VALUE	COHEN'S r
	MEDIAN	UPPER AND LOWER QUARTILE	MEDIAN	UPPER AND LOWER QUARTILE		
Reflexes	50	37-63	31	25-44	0.171	0.27*
Stationary	63	50-75	63	50-84	0.957	0.01
Locomotion	31	9-50	50	25-50	0.500	-0.12*
Object Manipulation	63	37-75	62	37-75	0.870	-0.03
Grasping	56	37-75	40	25-63	0.850	0.04
VMI	50	25-50	43	37-50	0.850	-0.04
Gross motor Quotient	52	35-65	56	55-65	1.000	0.00
Fine motor Quotient	54	35-65	42	27-58	0.808	0.05

Total motor Quotient	51	32-68	60	42-58	1.000	0.00

*Significance p≤ 0.05 **Significance p≤ 0.01 Cohen's r 0.10–0.23 – small effect size

0.24-0.37 – moderate effect size

>0.38 – large effect size

4.2.5.2 Descriptive statistics for the mild, moderate and severe groups

Overall the z-scores for all three groups fall into the normal distribution range of 1 to -1. It is noted however that the mild and the moderate HIE group have confined and similar ranges of z-scores at 0.35 to -0.35 and 0.65 to -0.35 respectively while the severe HIE group has a much broader range of z-scores at 0.20 to -0.60. In particular it is noted that in the severe HIE group Locomotion and VMI show lower z-scores of -0.56 and -0.60 respectively.

Table 4.7: Percentile median, upper and lower quartile and z-scores for the mild, moderate and severe groups

	MILD GROUP (n=13)			MODERATE GROUP (n=7)			SEVERE GROUP (n=8)		
PDMS SUB-TEST	**Median**	**Upper and lower Quartile**	**z score**	**Median**	**Upper and lower Quartile**	**z score**	**Median**	**Upper and lower Quartile**	**z score**
Reflexes	50	37-63	0	37	37-37	-0.35	37	25-50	-0.35
Stationary	63	63-84	0.35	63	50-75	0.35	57	38-69	0.20
Locomotion	37	25-50	-0.35	50	25-63	0	31	17-50	-0.56
Object manipulation	50	37-75	0	75	63-84	0.65	50	37-63	0
Grasping	63	50-75	0.35	50	37-75	0	50	21-50	0
VMI	50	37-63	0	50	37-50	0	25	21-50	-0.60
GM Quotient	55	45-65	0.10	61	35-73	0.31	43	25-58	-0.20
FM Quotient	58	42-65	0.20	50	35-65	0	35	22-46	-0.40
TM Quotient	50	45-68	0	58	32-73	0.20	37	25-52	-0.35

4.2.5.3 Comparison between the mild and moderate groups

Noting the similarities between the mild and moderate HIE groups, a Mann-Whitney U Test (with continuity correction) was performed where marked tests are significant at $p<0.05$. Effect size was determined by Cohen's r.

When comparing the mild to the moderate HIE group, small effect sizes for all sub-tests were evident except for VMI ($r=0.08$) and the Total Motor Quotient score ($r=-0.06$) which had negligible effect sizes and the Reflexes subtest that showed moderate effect size ($r=0.29$). In this comparison of mild and moderate HIE group test scores it is evident that there is no clear significant difference between the groups and thus they were combined to form the mild/moderate HIE group and compared with the severe HIE group, described in 4.2.5.4.

Table 4.8: Comparison of mild and moderate groups' Peabody Developmental Motor Assessment-2 subtest percentile scores

PDMS SUB-TEST	MILD GROUP (n=13)		MODERATE GROUP (n=7)			
	Median	Upper and lower Quartile	Median	Upper and lower Quartile	p - VALUE	EFFECT SIZE (Cohen's r)
Reflexes	50	37 -63	37	37-37	0.39	0.29**
Stationary	63	63 -84	63	50-75	0.41	0.18*
Locomotion	37	25-50	50	25-63	0.44	-0.17*
Object manipulation	50	37-75	75	63-84	0.41	-0.23*
Grasp	63	50-75	50	37-75	0.54	0.13*
VMI	50	37-63	50	37-50	0.71	0.08
GM Quotient	55	45-65	61	35-73	0.47	-0.16*
FM Quotient	58	42-65	50	35-65	0.63	0.11*
TM Quotient	50	45-68	58	32-73	0.78	-0.06

*Significance p≤ 0.05 **Significance p≤ 0.01 Cohen's r 0.10–0.23 – small effect size
0.24-0.37 – moderate effect size
>0.38 – large effect size

4.2.5.4 Comparison of combined mild and moderate group to severe group

The mild/moderate HIE group and severe HIE group were compared to each other using the Mann-Whitney U Test with continuity correction (significance at p <0,05).

Comparison of the mild/moderate and severe HIE groups shows small effect sizes for Reflexes, Locomotion and Object Manipulation. Moderate effect sizes for Stationary, Grasping, VMI, and Gross Motor Quotient scores and large effect sizes for Fine Motor and Total Motor Quotient scores. Despite the small effect size for Locomotion it is important to note that it was the second poorest performing subtest on the PDMS-2 (median percentile=31). The statistical significance and large effect sizes for the Fine Motor (r=0.45; p=0.02) and Total Motor (r=0.40; p=0.03) Quotient scores are likely a reflection of the moderate effect sizes shown in the Grasping (r=0.34) and VMI subtests (r=0.34) of the severe HIE group. The moderate effect size in the Grasping subtest is likely due to the Grasping subtest results in the mild/moderate group being above average (median percentile = 63) with the severe HIE group being average (median percentile = 50). In the VMI subtest on the other hand, which also shows a moderate effect size (r=0.34) median scores in the mild/moderate HIE group are at 50 with median scores of the severe group at 25 showing that the severe HIE group performed markedly below average on tests of VMI performance.

Table 4.9: Comparison of the of mild/moderate group to the severe groups' Peabody Developmental Motor Assessment-2 subtest percentile scores

PDMS SUB-TEST	MILD AND MODERATE GROUP (n=20)		SEVERE GROUP (n=8)			
	Median	Upper and lower Quartile	Median	Upper and lower Quartile	p-VALUE	EFFECT SIZE (Cohen's r)
Reflexes	44	37-57	37	25-50	0.46	0.22*
Stationary	63	56-84	56.5	38-69	0.12	0.28**
Locomotion	44	25-57	31	17-50	0.31	0.19*
Object manipulation	63	43-79	50	37-63	0.42	0.19*
Grasping	63	43-75	50	21-50	0.07	0.34**
VMI	50	37-57	25	21-50	0.07	0.34**
GM Quotient	58	40-65	43	25-58	0.08	0.33**
FM Quotient	58	38-65	35	22-46	0.02*	0.45**
TM Quotient	53	43-69	37	25-52	0.03*	0.40**

*Significance p≤ 0.05 **Significance p≤ 0.01 Cohen's r 0.10–0.23 – small effect size
0.24-0.37 – moderate effect size
>0.38 – large effect size

Figure 4.5 shows the two groups median percentile scores for each subtest and motor quotient scores. The severe HIE group (red line) shows markedly lower scores overall for the PDMS-2 subtest and Motor Quotient scores in comparison with the

mild/moderate HIE group (blue line). Trend lines between the two groups are similar although the VMI subtest scores are proportionately lower in the severe HIE group and as a result of that so are the Fine Motor Quotient scores for this group.

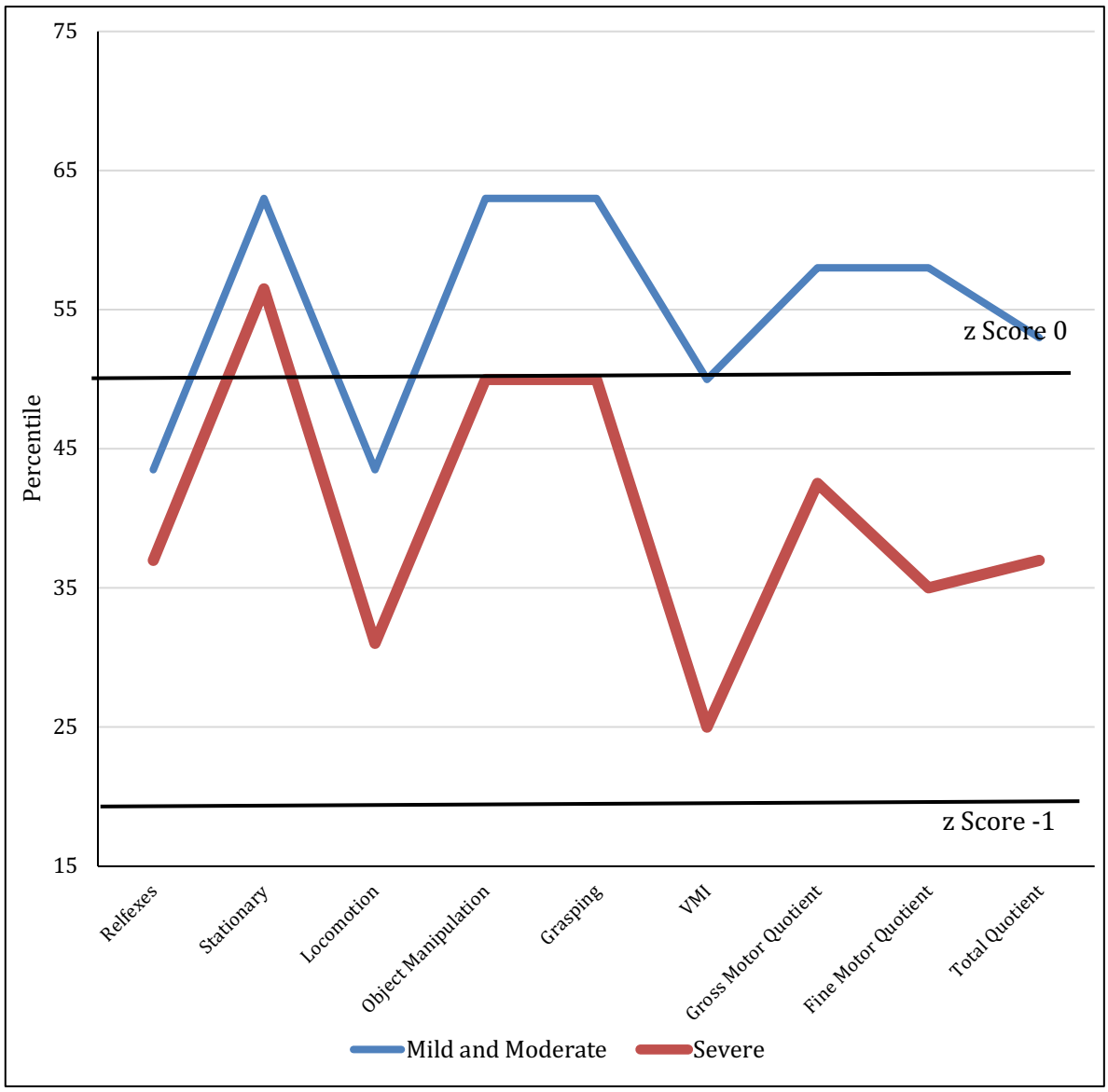


Figure 4.6: Comparison of mild/moderate to severe groups' percentile scores

4.3 Summary of results

Results were analysed for 28 participants between nine and twenty-one months of age with mild, moderate or severe HIE. Significantly more participants were female, particularly in the mild HIE group. Gestation varied between thirty-six and forty-one weeks with most children in all three groups born at forty weeks. Most of the participants were delivered via caesarean section with foetal distress and cord prolapse being the most common precipitating conditions. Participants were born at a mean birth weight of 3111g with only three participants being born under 2500g. Significantly higher birth weight was found in the mild HIE group.

Apgar scores were lower in the moderate group with an average score of six at five minutes across the total sample with no significant difference between the groups. Significantly more participants in the moderate and severe HIE group received therapeutic hypothermia. Complications were experienced in all but three participants. The most common complications were sepsis, prolonged ventilation, respiratory distress syndrome and seizures. Significantly more participants in the mild HIE group experienced presumed sepsis while more participants in the severe group experienced prolonged ventilation, though this was not significant. More seizures were noted in the moderate HIE group. Participants in the severe HIE group were more likely to spend longer in hospital although data were missing for the majority of the moderate group. Significantly more participants in the severe HIE group received physiotherapy.

In terms of PDMS-2 results, overall the total sample showed typical development in all subtests. When the groups were compared the mild and moderate HIE groups were found to have similar PDMS-2 scores and a Mann-Whitney U test was performed which showed no statistically significant difference between the two groups and so they were combined to form the mild/moderate HIE group. The PDMS-2 results of the mild/moderate HIE group were compared to the results of the severe HIE group.

In this comparison between the mild/moderate and severe HIE groups small to large effect sizes were found in all of the six PDMS-2 subtests. Small effect sizes were found for the Reflexes, Object Manipulation and Locomotion subtests. Moderate effect sizes were found in Grasping, VMI, and Gross Motor Quotient scores. Large effect sizes and significant p-values were noted for Fine Motor and Total Motor Quotients, likely as a result of poor performance in the Grasping and VMI subtests. The null hypothesis was accepted for the mild and moderate HIE group, but rejected when the mild and moderate HIE group were compared to the severe HIE group.

Chapter 5: Discussion

5.1 Introduction

In this chapter the results of the study will be discussed and elaborated upon based on both the demographics of the participants and the results of the PDMS-2 assessment and how these relate to the Thompson HIE score.

5.2 Participant demographics

The first objective of this study was to describe the study sample in terms of demographics, birth and medical history. These factors will be discussed first.

5.2.1 Age and gender

The participants in the study were between the ages of nine and twenty-one months at the time of assessment with no significant differences between the three HIE groups. This age range was chosen, as it is an important period for both gross and fine motor development. In terms of gross motor development, it is an age where the child should progress from merely being able to sit to being able to get up, walk, run and eventually begin jumping. In terms of fine motor development the child progresses from simple grasps to more complex grasps and object manipulation.[89] In addition to this, the literature suggests follow up of the child with HIE at approximately eighteen months of age when it is more likely for either neurotypical development to be demonstrated or for neurological sequelae to be easily identifiable due to the fact that most children at eighteen months should be walking, manipulating smaller objects and using some degree of speech to communicate.[3, 27] Although the majority of participants in this study were 15 months of age, they all functioned within normal ranges in terms of their motor development.

The female participants in this study slightly outnumbered males at 61%. In research with this population it is generally the other way around with males with an HIE diagnosis slightly outnumbering females at approximately 60%.[2] This may be as a

result of the distribution of participants across severities. Research has shown that in addition to brain injury being more likely in male babies it is also more likely to be severe.[26] The result of this is that there are generally more females diagnosed with mild HIE and more males with moderate and severe HIE.[26] In this study, with a higher proportion of participants in the mild HIE group it is then reasonable to expect that there would be a higher percentage of females than in studies where there are similar numbers between the severities.

5.3 Birth history of participants

5.3.1 Gestation

The incidence of HIE in infants born prematurely is thought to be between one and two per 1000 live births and may actually exceed the incidence of HIE in term infants but study of these children is extremely challenging as there are numerous other co-morbidities associated with prematurity.[28] For this reason near or full term gestation (greater than or equal to 36 weeks) was chosen as an inclusion criterion, which is in keeping with other similar studies.[2, 45] Thus, the gestation period of participants enrolled in this study was between 36 and 41 weeks with more than 50% of participants being born at 40 weeks. Only one child was born late-preterm (36 weeks). Children born late preterm mostly have typical neurodevelopmental outcomes although this is often reduced if they have required an admission to the NICU.[47] Regardless, the inclusion of this one late preterm participant is unlikely to have altered the outcomes overall.

5.3.2 Mode of delivery

While babies born via elective or pre-labour caesarean section rarely develop any kind of encephalopathy, emergency caesarean section is strongly correlated with a diagnosis of HIE.[27, 30] In this study there was an unusually high rate of caesarean section deliveries (68%) with only two of these being born via elective caesarean. This is higher than has been reported in international studies.[53, 54] It is also substantially higher than has been reported by another study where part of the

sample was from the same hospital. In this study, only 34% of the participants were delivered via caesarean section.[2]. Reasons for this are unclear but the aforementioned study was performed in 2013 and the obstetric protocols may have changed since then. There was no statistical difference between the mild, moderate and severe HIE groups in terms of caesarean section deliveries.

Significant difference was noted between the three groups in the likelihood of cord prolapse having been a complication during birth. More participants in the severe HIE group suffered from cord prolapse during birth compared to the mild and moderate HIE groups. Literature on the topic notes that cord prolapse is the third most common sentinel event associated with an HIE diagnosis but not that it is associated with severity of HIE and therefore this difference between the groups is unlikely to skew the PDMS-2 results.[55]

5.3.3 Birth weight

Low birth weight is a risk factor for developmental delay in both cognitive and motor domains.[51] Although participants in the mild HIE group had a significantly higher birth weight (3417.56g) than those in the moderate (3078.75g) and severe (3049.29g) HIE groups, the average birth weight of the participants was 3111g. This resembles that of other similar studies and is average for most full term births.[2, 64, 108] This result is thus unlikely to skew the results.

5.3.4 Apgar score

In this study, the mean five-minute Apgar score for the total sample was 6.4, which is in keeping with the South African study by Horn et. al. that reported a mean five-minute Apgar score of six.[2] Mean one-minute Apgar scores have been shown to have limited reliability in determining future adverse outcomes so research generally focuses on the five- and ten-minute Apgar scores.[109] In both of these there was a trend for children in the mild HIE group to have the highest scores and those in the severe HIE group to have the lowest scores. This is expected as Apgar scores have been shown to be higher in those with less severe insults and lower in those with

more severe insults.[25] The mean five-minute Apgar score of 6.4 and the mean ten-minute score of 7.25 are of particular interest. A 2018 study found that children with a five-minute Apgar score of five to six and a ten-minute Apgar score of between seven and eight have an hazard ratio of 15 for CP and of two for epilepsy and are therefore 15 times more likely to develop CP and twice more likely to develop epilepsy than children with full Apgar scores.[56] This information must be interpreted with caution due to the ten-minute Apgar scores missing in more than 50% of the sample but is still important to consider as both of these conditions significantly affect a child's neurodevelopmental outcomes and their participation in everyday activities.[56]

5.4 Medical history

5.4.1 Thompson hypoxic ischaemic encephalopathy score

The Thompson HIE score classifies infants as mild, moderate or severe based on the peak scores that the infant has received over a two-week period or until such time as the Thompson score is zero. A peak score of above 15 is considered to be severe, between 11 and 15 is considered to be moderate and below 11 is considered to be mild.[6] In this study there were more children with mild HIE (46%) than moderate (25%) or severe (28%). This is a reflection of two factors. Firstly, the fact that, generally, just over 50% of all infants diagnosed with HIE are diagnosed as mild.[110] Secondly, it reflects the possibility that clinics are using a longer follow up time for children with mild HIE following substantial research noting that despite earlier assumptions that children with mild HIE had neurotypical development, these children frequently suffer subtle long-term cognitive dysfunction that often only becomes apparent during school age.[7, 111]

5.4.2 Therapeutic hypothermia

In this study participants were significantly more likely to have received therapeutic hypothermia if they were in the moderate or severe HIE group. The reasons for the number of participants not receiving therapeutic hypothermia being higher in the mild

HIE group may include that they did not meet the facility's criteria, such as presenting to the service more than six hours after birth, difficulties with diagnosing mild HIE before the six hour cut off and as a result of cost vs. benefit decisions.[112]

The reason for the stringent criteria applied by Mowbray Maternity Hospital and all other institutions providing therapeutic hypothermia are for safety and to accurately select those infants who have an encephalopathy diagnosis but also because of limited financial and physical resources that need to be conserved in order for the most benefit to be given to the most infants.[46] For example, the 2008 National Perinatal Morbidity and Mortality Committee report states that 12% of neonatal deaths in South Africa occur as a result of limited neonatal ICU (NICU) facilities or equipment, lack of NICU beds available and/or insufficient nursing staff.[113] In this context it is understandable that resources need to be conserved and that provision of therapeutic hypothermia be given to the children who will benefit the most.

Due to small sample sizes of children who did not receive cooling in the moderate and severe HIE groups it was not possible to split the participants into the HIE severity to compare data from those that received therapeutic hypothermia and those that did not. When the total sample was compared based on therapeutic hypothermia or no hypothermia it was found that therapeutic hypothermia had no significant impact on the participants' PDMS-2 results and for this reason data from participants who both did and did not receive therapeutic hypothermia were analysed together. The reason for the similarity between the groups is most likely due to three reasons. Firstly, the majority of participants who did not receive therapeutic hypothermia were in the mild HIE group and are, in any case, expected to have near normal motor development.[111] Secondly, small sample sizes, particularly in the moderate and severe HIE groups, make the groups difficult to compare. Thirdly, therapeutic hypothermia has been shown to have significant impact on motor development with improved motor outcomes of between sixteen and eighteen percent, though this is less so for those with severe HIE.[29, 41, 46] With the majority of the participants in the moderate (86%) and severe (75%) HIE groups having

received therapeutic hypothermia this may have caused their assessment results to be more similar to the mild HIE group and within normal ranges.

5.4.3 Complications and length of hospitalisation

After a complicated delivery resulting in HIE, many children will suffer with at least one medical complication within the first few days of life.[114] In fact in this study only three participants in total did not suffer any medical complications: none of those were in the severe HIE group (Table 4.3). The most likely complication in the mild group was presumed sepsis whilst in the moderate and severe HIE groups the most likely complication was seizures and prolonged ventilation respectively. While sepsis is not significantly correlated to poor neurodevelopmental outcomes, seizures are.

Rates of seizures in the study overall for all severities was 39%. This is slightly lower than in other HIE studies, which report seizure rates of between 50% – 67% depending on the method of evaluating the seizures.[30, 45, 64, 115] Whilst significantly more participants in the moderate HIE group experienced seizures, approximately a third of participants in the mild and severe HIE groups also experienced seizures. This is unusual as most research shows that infants with mild HIE experience the least seizures while those with moderate HIE are twice as likely to experience seizures and those with severe HIE are three times as likely to experience seizures. Infants diagnosed with neonatal seizures are more likely to have poorer motor and cognitive outcomes. [29, 62]

Data regarding length of hospitalisation are difficult to interpret as information was missing in 71% of the moderate HIE group. The data that was available indicated that the average length of stay was between one and two weeks for the majority of participants. This is in line with other South African studies as well as international studies.[2, 111, 116] Longer stay i.e. greater than three weeks was only noted in the severe HIE group, this is likely due to the severity of HIE as well as the severity of the complications experienced by the severe HIE group. Data regarding outcomes based on length of stay in children with HIE are not available but NICU admissions (which children with HIE will almost certainly have experienced), have been shown to

be significantly correlated with later outcomes with both late preterm and full term neonates who were admitted to the NICU in the neonatal period performing equally poorly on later developmental tests although the nature of the relationship is not well understood.[47]

5.5 Therapy

The only therapy routinely provided at the MMH Neurodevelopmental High-Risk Clinic is physiotherapy. The likelihood of participants receiving physiotherapy was surprisingly high in the mild HIE group being similar to the percentage that received physiotherapy in the severe HIE group. Less than half of the moderate HIE group received physiotherapy but this may just indicate the small group size rather than an intentional selection (n=7). Unfortunately other therapies received, such as occupational therapy and speech therapy, were not documented in the participant's files and the caregivers were not always certain of what therapies the participants were receiving outside of the Mowbray Maternity Clinic. Whilst Physiotherapy is the only service available to the MMH Neurodevelopmental High-Risk Clinic, research has shown that early intervention by a multidisciplinary team (including occupational therapy) in children at high risk of developmental delays, such as those with HIE, has been shown to be effective at improving developmental outcomes.[21, 93] The effects of the therapy that the study participants received may have altered the PDMS-2 findings, particularly for the moderate and severe HIE groups who are more likely to require and benefit from therapy.

5.6 Peabody Developmental Motor Scales-2 scores

The second and third objectives of this study were to determine the gross and fine motor outcomes of children with HIE and compare these to the children's' Thompson HIE scores. Whilst certain factors within the three groups were not comparable, specifically gender, cord prolapse, birth weight, therapeutic hypothermia received, complications in terms of seizures and presumed sepsis, length of stay and therapy received, these factors have been considered and discussed above.

5.6.1 Overall motor development of the mild and moderate hypoxic ischaemic encephalopathy groups

Unsurprisingly the mild HIE group showed average to above average development on all scores of the PDMS-2, showing on par development with their typically developing peers. This is expected as it is well documented in the research that children with mild HIE have typical motor development in their early years.[64, 114, 117] A 2009 systematic review into the neurodevelopmental outcomes of infants with HIE found that infants with mild HIE under the age of 3 years had a nil chance of an adverse neurodevelopmental outcome, a result that was based on the analysis of five separate studies.[64] Some research has shown that these results do not extend into later childhood where it has been shown that even in children who have received therapeutic hypothermia, children with mild HIE scored similarly to those with moderate HIE. A 2017 study assessing the neurodevelopmental outcomes of children with HIE found that children older than 42 months of age had comparable motor problems, specifically in timed activities, in both the mild and moderate HIE groups.[118] This finding replicated earlier research that found that children between the age of nine and ten years previously diagnosed with mild or moderate HIE had comparable motor development according to the Movement-ABC (M-ABC).[75] Two points must be noted however. Firstly, the M-ABC does not measure motor development in isolation but that tasks, especially at this age, often include aspects of attention and planning which reflect the cognitive difficulties, which have been identified in up to 80% of older children with HIE regardless of severity.[53, 75] Secondly neither of these studies included children who had undergone therapeutic hypothermia which has been shown to improve long-term outcomes. Therapeutic hypothermia for children with mild HIE remains somewhat controversial because the risk versus the benefit is not particularly clear in children with mild HIE. It is also because of the great cost it involves to provide therapeutic hypothermia to children it is reserved for those i.e. moderate and severe HIE that will gain the most benefit and lastly it is difficult to identify children with mild HIE before the six hour cut off.[112] However, a very recent 2019 controlled trial published in the American Journal of

Perinatology using MRI and investigating neurodevelopmental outcomes of infants with mild HIE treated with therapeutic hypothermia found that their development was comparable to that of healthy term controls.[111]

The moderate HIE group also showed development in the average range on all of the PDMS-2 subtests. This is unusual amongst similar studies into the developmental outcomes of children with moderate HIE where a percentage of the participants are generally identified as having major neurodevelopmental delays. Van Schie et. al. found that 48% of children assessed with the Alberta Infant Motor Scale (AIMS) had poor motor outcome. These findings were mirrored by West et. al. and Dilenge et. al. who found poor motor outcomes in 40% and 30-60% of children with moderate HIE respectively.[7, 8] Reasons for the lack of identification of any motor problems in this group of children with HIE may be as a result of numerous factors.

Firstly, the sample size may not have been large enough to demonstrate significant findings. Secondly, infant motor assessments are notoriously unreliable in consistent identification of motor difficulties in infants under two years of age.[119] Connolly et. al. proposes this to be as a result of the rapid development of motor skills at this age, which is likely, but there may be another potential reason for this.[120] A study, published in 2012, followed 17 individuals in Switzerland from birth until the age of 20 years with repeated neurodevelopmental assessments. Results indicated that although most development was linear there were also “highly discontinuous developmental trajectories” where progress would plateau for a period and then a large jump in function would be made over a relatively short period of time, potentially affecting the reliability of assessments that expect linear development.[121]

Lastly, while every attempt was made to choose the most appropriate assessment measure, there are some issues with the PDMS-2 that may have affected these results. The PDMS-2 has been shown to have low sensitivity for identification of infants with minor motor delay.[101] [102]These results were applicable to both the gross and the fine motor scales of the PDMS-2.[102] At the outset of this study that was not expected to pose a problem as previous research indicated that gross and fine motor

delays in this population were marked but that was not found in this study and therefore may have been a contributing factor to not finding significant delay in the moderate HIE group.

In addition to this, the PDMS-2 has not been standardised to the South African population. In fact, at the time of beginning this study, none of the most popular, globally recognised standardised motor assessments had been standardised on the South African population. This may have had an effect on the results in three ways: if more demonstration was used to facilitate understanding it may have altered the findings, if a lack of familiarity with the objects affected the child's engagement with it and if the norm-referenced scores are not applicable to the children in the study.[104] Despite the researchers best efforts to control for these factors, they may have played a role in the somewhat unexpected results.

Noting the similarities between the mild and moderate HIE groups a Mann-Whitney U Test (with continuity correction) was performed with effect size determined by Cohen's r to determine if the groups were sufficiently similar so that they could be combined to form one group which then could be compared against the severe group. These calculations showed that the differences between the group were statistically insignificant and thus the groups were combined to form one group; the mild/moderate group.

5.6.2. Gross and fine motor development of the mild/moderate and severe groups

Considering the above it is then unsurprising that the mild/moderate HIE group scores within the average range on all subtests of the PDMS-2 as well as on the gross, fine and total motor quotient which showed percentile scores of 55; 53 and 55 respectively. This is, however, not the case in the severe HIE group. While all scores for the PDMS-2 subtests in severe HIE group were within the normal range, the scores for all subtests were markedly poorer than in the mild/moderate HIE group with small to large effect sizes (Table 4.9). Small effect sizes were noted for Reflexes, Locomotion, Object Manipulation, despite the small effect size for

Locomotion it is important to note that it was the second poorest performing subtest. Moderate effect sizes were noted for Stationary, Grasping, VMI and Gross Motor Quotient scores. Large effect sizes and significant p-values were noted for Fine Motor and Total Motor Quotient scores.

Delayed motor development, specifically those noted in fine motor development has been correlated to a number of different limitations. Firstly it is associated with poorer ADL performance and a flatter trajectory of ADL milestone achievement.[77] It has also been associated with reduced cognitive capabilities and poorer social skills and therefore reduced self-esteem.[62] In this study both Grasping and VMI subtests were found to have moderate effect sizes when the mild/moderate HIE group was compared to the severe HIE group. The grasping subtest showed a moderate effect size due to the above average performance of the mild/moderate group rather than below average performance of the severe HIE group. On the other hand when considering VMI this trend is reversed with a poorer performance by the severe HIE group.

There are very few studies that measure VMI specifically in the HIE population but those that have been done have generally found VMI to score amongst the lowest as compared to other developmental measures.[66, 122, 123] This was first noted by Finer and Robertson in 1981 in their seminal work into outcomes following HIE which highlighted, for the first time, the long term cognitive and behavioural difficulties experienced by the HIE population.[122]

Such VMI difficulties have been strongly correlated to later school performance even in typically developing children, specifically in terms of maths and literacy skills, which are the basis of scholastic achievement.[68-70] These findings have been reproduced in the South African population as well. In 2009 a study investigating VMI and its relationship to letter formation in eight different schools in the Kwa-Zulu Natal area of South Africa it was found that there was a significant correlation between the two.[71]

In 2017 this was taken a step further with a study into the VMI function of 92 preschool children that found that, while cognition and VMI most likely develop reciprocally, VMI tasks may lay the foundation for later cognitive development.[68] This may be as a result of VMI tasks requiring the use of the basic building blocks of later executive functioning such as attention to the task, working memory and the use of inhibitory control.[68] Poor VMI function in HIE children then could be an early indication of the cognitive dysfunction experienced by so many survivors of HIE at school age.

Numerous studies in the past two decades have highlighted the significant cognitive deficits experienced by survivors of HIE. Particularly those who were diagnosed with moderate or severe HIE. These studies have shown that up to 80% of children with moderate HIE suffer from cognitive deficits and that typical assessment results in young children do not necessarily indicate typical cognitive development in later childhood and into the teenage years as these children tend to "grow into their deficits".[4, 25, 39, 44, 73]

Although not quite as evident in this study, gross motor function is equally important. Whilst the Stationary subtest showed a moderate effect size this was, similar to the Grasping subtest, as a result of above average results for the mild/moderate HIE group with average results for the severe HIE group. However, the severe HIE group showed a median percentile score of 31 for Locomotion. Whilst this is still within the normal range of PDMS-2 scores it was amongst the participants' worst performing subtests. It is important to note that lack of sensitivity of the PDMS-2 overall for determining neuromotor deficits, may mean that Locomotion function in these children may be poorer than has been demonstrated by these results.

The definition of locomotion is the child's ability to transport his or her body from one place to another.[5] The reason for their poor performance in the Locomotion subtest is likely due to the gross motor difficulties, which much research has shown are likely for this group. A New Zealand study into the demographics and outcome of 70 infants with moderate and severe neonatal encephalopathy, determined a 100%

chance of death or neurodevelopmental delay for infants in the severe HIE group.[8] The 2013 Cochrane systematic, which included the three largest randomised controlled trials on HIE in the last decade as well as eight others, determined that, overall, 75% of children with severe HIE were diagnosed as having poor outcomes including major neurodevelopmental delays or death. This outcome was not found to be ameliorated by the administration of therapeutic hypothermia.[41]

Locomotion is a vital aspect of childhood development. Not only is it important in the development of motor skill proficiency, it also has important repercussions for cognition and scholastic ability.[62, 63] This link is presumed to be as a result of two processes. The first is embodied cognition which suggests that when motor skills are impaired the child has less opportunity to explore and engage with their environment resulting in reduced learning and further limiting development.[63] The second is automaticity theory, which suggests that when motor skills are impaired the child requires more cognitive resources to perform the task. This means that those resources are unavailable for the child to use for other learning opportunities.[62] Research has shown that poor gross motor skills, including locomotion, result in reduced cognitive abilities. This was particularly evident in terms of attention, visuo-spatial processing, memory, and inhibition.[62] In addition to this it has been found that poor gross motor skills are also implicated in poor self-worth and reduced perceived and actual scholastic ability.[63]

With the effects of poor motor performance extending from physical and scholastic abilities to psychological and cognitive aspects of the child, these are important considerations to occupational therapists trying to facilitate optimal functioning for the child.

5.6.3 The role of the occupational therapist

Considering the types of difficulties experienced by children with HIE such as reduced ADL performance, difficulties in specific cognitive skills and difficulties with school performance, occupational therapy is in a prime position to assist these children.

Occupational therapy for children with neurodevelopmental difficulties harnesses recent neuroplasticity research and theories of motor learning and cognitive development to tailor-make activity-focused and goal-oriented interventions to improve independence and participation in everyday life.[89-91] Research has shown that starting this intervention early has positive effects that persist well into the child's school years.[48, 94] It may also be able to ameliorate the massive costs associated with HIE, estimated at between $800 000 and $900 000 per child.[35]

Whilst the children studied here may not have shown significant disability according to the PDMS-2 it is clear that the children with severe HIE performed significantly worse than those with mild or moderate HIE. This was particularly evident in the Locomotion and VMI subtests. Poor performance in these areas has been shown to have a negative effect on a range of functions including cognition, school performance, performance of ADLs, social competency, IQ and earning potential.[66, 77, 122, 123] These are all areas in which an occupational therapist works to improve independence and quality of life but it is important that intervention is started early in order to give these children the best chance at using early neuroplasticity and family-centred approaches to overcome these difficulties.[15, 20, 83, 93]

Also important to note is that despite therapeutic hypothermia being administered and showing improved neurodevelopmental outcomes in the neonatal and early childhood periods, these gains are not necessarily visible in later childhood when underlying cognitive dysfunction makes it difficult for the child to participate fully in school.[4, 27] It is vitally important then that despite typical results on developmental assessments children with moderate HIE should receive follow up into their school going years and those with severe HIE should be receiving early intervention services from, not just physiotherapists to address obvious motor problems but also occupational therapists who can address the possible motor, cognitive and ADL dysfunction seen in children with HIE.

5.7 Summary

The three groups were not comparable in a number of factors including gender, cord prolapse, birth weight, hypothermia, complications, seizures, therapy received and length of stay. Many of these factors are expected in the population, based on severity and were discussed. When the mild and moderate HIE groups were combined and compared to the severe HIE group it was found that the severe HIE group performed significantly worse on fine motor scores and total motor scores and performed poorer on all subtests with small to large effect sizes.

Poorer Locomotion test results in children with severe HIE is supported by previous literature with most studies finding poor gross motor performance in up to 80% of children with severe HIE.[118] The low VMI scores are also supported by current research that has found that children with HIE routinely perform worse in VMI results than other outcomes measured.[66, 122, 123] Poor VMI performance in early childhood has been shown to have negative consequences later on in childhood, particularly in areas involving cognition. These deficits have been shown to affect school performance, particularly in literacy and maths skills, performance of ADLs, behaviour and social competency, and IQ and may affect their potential to perform well as an adult in the job market. [66, 122, 123]

These limitations in areas of school function, behavioural and social function and work are areas in which occupational therapists have particular competence and early intervention by occupational therapists to ameliorate the effects of HIE on gross and fine motor skills may improve the long-term function of children with HIE.

Chapter 6: Conclusion

6.1 Introduction

This was a quantitative study into the gross and fine motor function of children with HIE based on the Thompson score between the ages of nine and twenty-four months. The sample consisted of 28 participants attending the Neurodevelopmental High-Risk Clinic at Mowbray Maternity Hospital. The sample consisted of thirteen participants with mild HIE, seven participants with moderate HIE and eight participants with severe HIE as staged by the Thompson HIE score. Data were collected with regards to the participant's demographics and medical history. Gross and fine motor outcomes were assessed using the PDMS-2.

6.2. Main Findings

This study's results were slightly unusual in that gross and fine motor outcomes in the severe HIE group were within the normal range, albeit at the very low end of the range. Despite this, performance of the severe HIE group was significantly poorer than that of the mild and moderate HIE group with small to large effect sizes found for all subtests and significantly poorer Fine Motor and Total Motor Quotient scores.

This finding is in line with current research that has found that children with severe HIE consistently perform poorly on gross motor items such as that of the Locomotion subtest of the PDMS-2 as well as on fine motor and cognitive tasks such as VMI.[66, 123, 124] For occupational therapists the finding of poor VMI scores is of particular importance. Poor performance in VMI has been correlated with poor scholastic performance, difficulties with behaviour and social skills, ADL, and IQ.[65, 69, 71, 81] Early intervention in these areas by occupational therapists may improve outcomes in these areas in later years. A severe HIE grade according to the Thomspon HIE score appears to be a good indicator of children that require occupational therapy. Specific focus of that therapy should include VMI and cognition. Further research is needed to investigate this potential benefit.

6.3 Limitations

There were a number of limitations in this study. Despite extending the original data collection period the sample size of 28 is not large enough to make generalisations about the population. The groups were not comparable in a number of factors, which may have affected the results of the PDMS-2.

The PDMS-2 has not been standardised on the South African population and may have led to increased demonstration by the researcher, which may have skewed results in favour of more normal scores that may not reflect an accurate level of disability across the three groups. The norm-referenced values in the PDMS-2 may also lack applicability to the South African population.

The PDMS-2 has been shown to have low sensitivity in younger children as well as those with minor motor dysfunction.[101, 102, 125] This may have led to underestimated levels of disability across the groups.

Inability to access information relating to the use of other therapeutic services such as occupational therapy and speech therapy means that those variables could not be accounted for in the results of the PDMS-2. This may explain why the participants in the severe HIE group did not have results in the disabled range. If they were accessing regular therapy their outcomes may be better than those generally found in the literature.

Physiotherapy and other therapies, particularly with the severe HIE group may have improved the outcomes according to the PDMS-2. Data regarding the frequency and type of physiotherapy was not accessed as part of the study and may also have played a significant role in the acceptable PDMS-2 scores seen in the severe HIE group.

6.4 Recommendations for future studies

The data presented in this study may indicate the fact that early intervention combined with therapeutic hypothermia in all severities of HIE may have significant positive outcomes in children with HIE. Further studies need to be done that control for the variables of therapeutic hypothermia and what therapy is received by the participants as well as using a sample size that is more likely to show statistically significant results.

Future studies in South Africa would greatly benefit from using an outcome measure that has been standardised on the South African population. Due to the uncertainties around how therapeutic hypothermia and the provision of therapy services may affect the outcomes of these children it is important to find an outcome measure that is more sensitive to mild motor delays than the PDMS-2.

While the body of research into the long-term outcomes of children with all severities of HIE is mounting more studies need to be done in children with HIE who have received therapeutic hypothermia, particularly those with mild HIE to determine if the cognitive and fine motor dysfunction seen in those who did not receive therapeutic hypothermia is still present in these children.

The data presented in this study suggests that children with severe HIE perform significantly worse than those with mild or moderate HIE. It is recommended that all children with severe HIE are tested specifically for VMI limitations and the relationship between the limitations seen in VMI and later cognitive dysfunction clarified.

Lastly considering the significantly poorer performance of participants with severe HIE on tests of fine motor, particularly VMI, there is a clear case for the referral of children diagnosed with severe HIE to occupational therapy services. These referrals should be made as soon as possible as early intervention has been shown to be of most benefit to infants at high risk of developmental delay.

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Appendices

Appendix A: Medical records information sheet

Subject Code: _____ Child's age: _____

Gestational age:

	□	
36 weeks		1.1
37 weeks		1.2
38 weeks		1.3
39 weeks		1.4
40 weeks		1.5
41 weeks		1.6
≥42 weeks		1.7

Apgar scores at 10 min:

	□	
1		2.1
2		2.2
3		2.3
4		2.4
5		2.5
6		2.6
7		2.7
8		2.8

9		2.9
10		2.10

Therapeutic Hypothermia:

	□	
Yes: Whole body		
Yes: Head therapeutic hypothermia		3.1
No		3.2

HIE Score:

	□			P				
Day 1 score ≤ 5		4.1	Day 7 score ≤ 5		4.19	Peak score ≤5		4.37
Day 1 score 6		4.2	Day 7 score 6		4.20	Peak score 6		4.38
Day 1 score 7		4.3	Day 7 score 7		4.21	Peak score 7		4.39
Day 1 score 8		4.4	Day 7 score 8		4.22	Peak score 8		4.40
Day 1 score 9		4.5	Day 7 score 9		4.23	Peak score 9		4.41
Day 1 score 10		4.6	Day 7 score 10		4.24	Peak score 10		4.42
Day 1 score 11		4.7	Day 7 score 11		4.25	Peak score 11		4.43
Day 1 score 12		4.8	Day 7 score 12		4.26	Peak score 12		4.44
Day 1 score 13		4.9	Day 7 score 13		4.27	Peak score 13		4.45
Day 1 score 14		4.10	Day 7 score 14		4.28	Peak score 14		4.46
Day 1 score 15		4.11	Day 7 score 15		4.29	Peak score 15		4.47
Day 1 score 16		4.12	Day 7 score 16		4.30	Peak score 16		4.48
Day 1 score 17		4.13	Day 7 score 17		4.31	Peak score 17		4.49
Day 1 score 18		4.14	Day 7 score 18		4.32	Peak score 18		4.50
Day 1 score 19		4.15	Day 7 score 19		4.33	Peak score 19		4.51

Day 1 score 20		4.16	Day 7 score 20		4.34	Peak score 20		4.52
Day 1 score 21		4.17	Day 7 score 21		4.36	Peak score 21		4.53
Day 1 score 22		4.18	Day 7 score 22		4.37	Peak score 22		4.54

Complications at birth (as per medical records)

	□	
Seizures		5.1
Intracranial haemorrhage		5.2
Visual impairment		5.3
Ventilation required		5.4
Other: Specify		5.6

Therapy received:

	□	
Occupational Therapy		6.1
Physiotherapy		6.2
Speech therapy		6.3
Other: specify		6.4

7. Length of intervention received

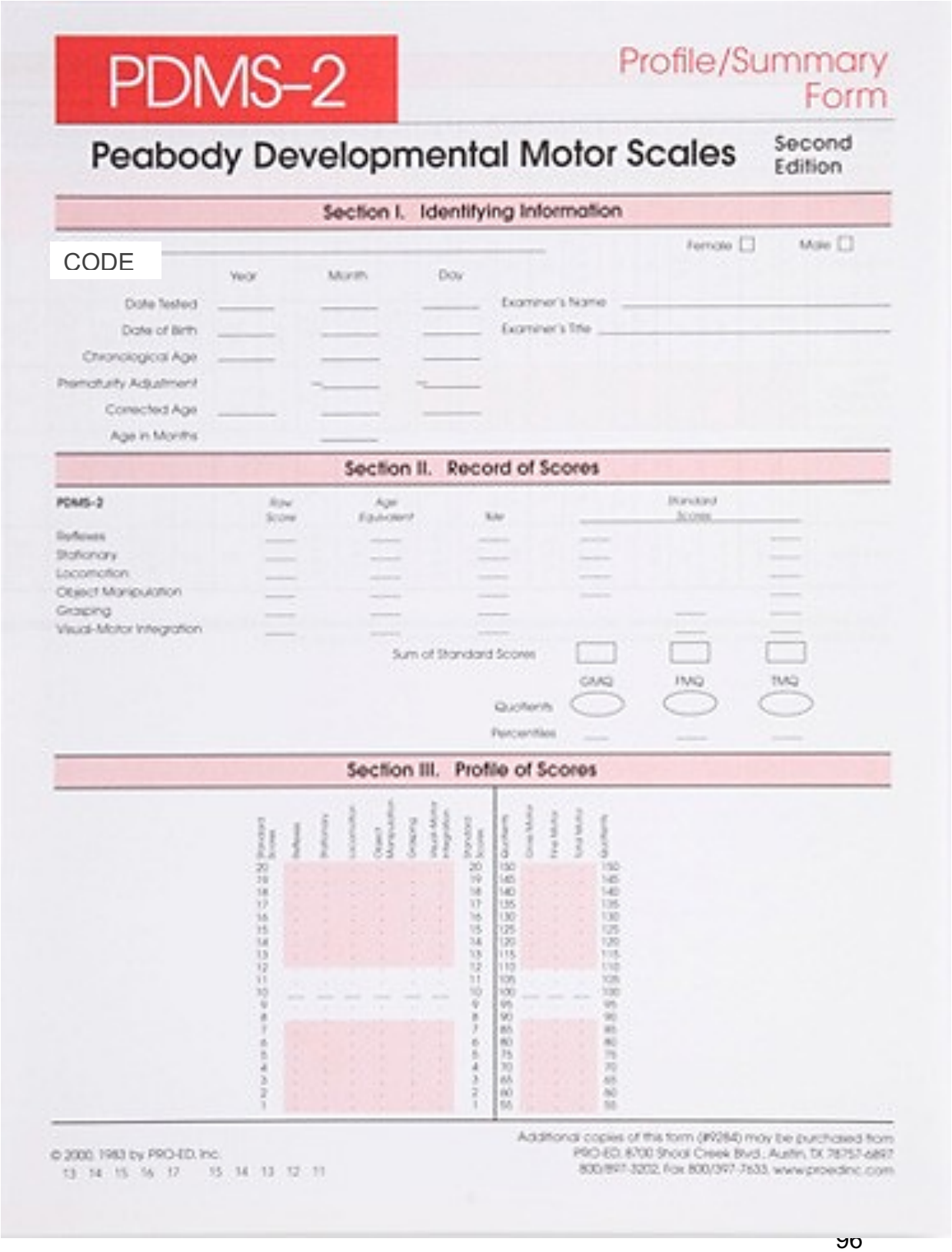
Intervention	Length	□	
Occupational Therapy	0-2 weeks		7.1
	2 weeks-3 months		7.2
	3-6 months		7.3
	6-9 months		7.4
	9-12 months		7.5
Physiotherapy	0-2 weeks		7.6

	2 weeks-3 months		7.7
	3-6 months		7.8
	6-9 months		7.9
	9-12 months		7.10
Speech therapy	0-2 weeks		7.11
	2 weeks-3 months		7.12
	3-6 months		7.13
	6-9 months		7.14
	9-12 months		7.15
Other: specify	0-2 weeks		7.16
	2 weeks-3 months		7.17
	3-6 months		7.18
	6-9 months		7.19
	9-12 months		7.20

Length of stay in hospital

< 1 week		8.1
1-2 weeks		8.2
2-3 weeks		8.3
3-4 weeks		8.4
>4 weeks		8.5

APPENDIX B: Peabody Developmental Motor Scales – Second Edition (PDMS-II) Profile Summary Form



PDMS–2

Profile/Summary Form

Peabody Developmental Motor Scales Second Edition

Section I. Identifying Information

CODE

Female ☐ Male ☐

Year Month Day

Date Tested _____ _____ _____ Examiner's Name _____

Date of Birth _____ _____ _____ Examiner's Title _____

Chronological Age _____ _____ _____

Prematurity Adjustment – _____ – _____

Corrected Age _____ _____ _____

Age in Months _____

Section II. Record of Scores

PDMS-2	Raw Score	Age Equivalent	%ile	Standard Score		
Reflexes						
Stationary						
Locomotion						
Object Manipulation						
Grasping						
Visual-Motor Integration						
Sum of Standard Scores						
				GMQ	FMQ	TMQ
Quotients						
Percentiles						

Section III. Profile of Scores

© 2000, 1983 by PRO-ED, Inc.

13 14 15 16 17 15 14 13 12 11

Additional copies of this form (#9284) may be purchased from PRO-ED, 8700 Shoal Creek Blvd., Austin, TX 78757-6897 800/897-3202, Fax 800/397-7633, www.proedinc.com

APPENDIX C: Study information sheet

Good Day,

My name is Tasha Nicolson from the Occupational Therapy Department at the University of the Witwatersrand Medical School. I am undertaking a research project that is looking into the muscle and movement development of babies who had difficulties with breathing during their delivery. Sometimes this breathing difficulty causes problems, which can be identified by an assessment done in the first week of your child's life, which was probably done while your child was in hospital, called the Thompson score. The Thompson score measures what effect the difficulty in breathing had on the brain of the child and is done whilst the child is in hospital. If your child had this assessment then I would be very grateful if you and your child would consider participating in this study. The title of my research is: 'the Thompson score and motor outcomes of children with hypoxic ischaemic encephalopathy, aged nine to twenty-four months'.

Why are we doing this? Some children who have problems with breathing at birth have slowed motor development as a result of the brain not getting enough oxygen. Therapy, such as occupational therapy, has been shown to improve children's muscle and movement development. I would like to see if the Thompson score can tell us at a very early age which children are most likely to have slowed motor development. This would tell us when to best refer children to occupational therapy in order to help improve their overall development.

What do we expect from the participants in the study? As a participant in this study, I will assess your child using an assessment called the Peabody Developmental Motor Scales Second Edition (PDMS-II). The assessment will only take around 30 minutes of your time. I will also look at your child's medical folder to get information such as what your child's Thompson score was in hospital, what your child's Apgar score was, if there were any complications, such as seizures, what treatment your child received in hospital and if your child is receiving any therapy now. If I find that your child could benefit from therapy you will be informed and referred to an occupational therapist at your nearest Community Health Centre (Day Hospital). All the information that you provide in the interview will be kept confidential.

Are there benefits to the participants? If your child is having problems in certain areas of their muscle and movement development this study may be able to pick up on this and we can then refer your child to an occupational therapist to assist them with this.

May I withdraw my child from the study? You may take your child out of the study at any time and you don't have to give a reason. The study is completely voluntary and not taking part (withdrawing from it) carries no penalty of any kind. Your child's care will not be influenced in any way.

What about confidentiality? Confidentiality will be maintained by using numbers instead of names in all results. The researcher will be the only person to know which name matches each number. This list will be kept locked in a safe.

If you have any questions you can contact me on 0848262288. Any ethical queries or reporting of study-related adverse (negative) events should be made to the chairperson of the Wits Human Research Ethics Committee, Prof. P. Cleaton-Jones at 011 717 1234.

If you are happy to allow your child to take part in the study, please read and sign the attached consent form.

Thank you

Tasha Nicolson

APPENDIX D: Informed consent sheet - participation

I agree to allow _____ (child's name) to participate in the study: The Thompson score and motor outcomes of children with hypoxic ischaemic encephalopathy, aged nine to twenty-four months, as outlined in the information sheet.

Caregiver's name: _____

Signature: _____

Date: _____

I DO NOT agree to allow _____ (child's name) to participate in the study: The Thompson score and motor outcomes of children with hypoxic ischaemic encephalopathy, aged nine to twenty-four months, as outlined in the information sheet.

Caregiver's name:

Signature:

Date: _____

APPENDIX E: Informed consent sheet – medical records

I agree to allow Tasha Nicolson to have access to the medical records of

_____ (Child's name) as part of her research study: *The Thompson score and motor outcomes of children with hypoxic ischaemic encephalopathy, aged nine to twenty-four months*, as outlined in the information sheet.

Caregiver's name: _____

Signature: _____

Date: _____

APPENDIX F: Approval from University of the Witwatersrand Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130442

NAME: (Principal Investigator)	Ms Tasha Nicolson
DEPARTMENT:	Department of Occupational Therapy Medical School
PROJECT TITLE:	The Association between the Thompson Score and Motor Outcomes of Infants with Hypoxic Ischaemic Encephalopathy: Aged Nine Months
DATE CONSIDERED:	26/04/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Ms L Jacobs
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 30/08/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature M130442Date

APPENDIX G: Approval from National Health Research Database

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_2014RP45_683
ENQUIRIES: Ms Charlene Roderick

University of the Witwatersrand
Private Bag 3
Wits
2050
South Africa

For attention: **Ms Tasha Nicolson**

Re: THE ASSOCIATION BETWEEN THE THOMPSON SCORE AND MOTOR OUTCOMES OF INFANTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY, AGED NINE MONTHS

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Mowbray Maternity Hospital **S Fawcus** **Contact No. 021 659 5579**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR J EVANS
ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 22/12/2014

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857; fax: +27 21 483 9895
5th Floor, Norton Rose House., 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_2014RP45_683
ENQUIRIES: Ms Charlene Roderick

University of the Witwatersrand
Private Bag 3
Wits
2050
South Africa

For attention: **Ms Tasha Nicolson**

Re: THE ASSOCIATION BETWEEN THE THOMPSON SCORE AND MOTOR OUTCOMES OF INFANTS WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY, AGED NINE MONTHS

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Mowbray Maternity Hospital **S Fawcus** **Contact No. 021 659 5579**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR J EVANS
ACTING DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 22/12/2014

APPENDIX H: Approval from University of Cape Town Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 June 2015

HREC REF: 275/2015

Dr H Buchanan
Occupational Therapy
F-Floor
OMB

Dear Dr Buchanan

PROJECT TITLE: THE ASSOCIATION BETWEEN THE THOMPSON SCORE AND MOTOR OUTCOMES OF INFANTS DIAGNOSED WITH HYPOXIC ISCHAEMIC ENCEPHALOPATHY, AGED NINE TO TWELVE MONTHS (MSc candidate – Ms T Nicolson)

Thank you for your response letter dated 09 June 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th June 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Tasha Nicolson is also involved in this project

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:275/2015

APPENDIX I: Extension of UCT HREC approval

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN
12 JAN 2017

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.1.2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	12/1/17

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11 January 2017		
HREC REF Number	275/2015	Current Ethics Approval was granted until	30 June 2016
Protocol title	The association between the Thompson score and motor outcomes of infants diagnosed with hypoxic ischaemic encephalopathy, aged nine to twenty-four months		
Protocol number (if applicable)	M130422 (University of Witwatersrand protocol number)		
Are there any sub-studies linked to this study?	☐ Yes * No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Helen Buchanan		
Department / Office Internal Mail Address	Health & Rehab Sciences / Room F45, F45 OMB		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN
12 JAN 2017

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30.1.2018
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	12/1/17

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11 January 2017		
HREC REF Number	275/2015	Current Ethics Approval was granted until	30 June 2016
Protocol title	The association between the Thompson score and motor outcomes of infants diagnosed with hypoxic ischaemic encephalopathy, aged nine to twenty-four months		
Protocol number (if applicable)	M130422 (University of Witwatersrand protocol number)		
Are there any sub-studies linked to this study?	☐ Yes × No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Helen Buchanan		
Department / Office Internal Mail Address	Health & Rehab Sciences / Room F45, F45 OMB		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓☐ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX J: Permission letter to Mowbray Maternity Hospital medical superintendent

Tasha Nicolson

University of the Witwatersrand

Occupational Therapy Department

7 York Rd, Parktown, 2193

Mowbray Maternity Hospital

12 Hornsey Rd, Mowbray, 7700

To whom it may concern,

Re: Permission to carry out research

As a postgraduate occupational therapy student at the University of the Witwatersrand I am required to complete a research report, which I would like to perform using patients and medical records from Mowbray Maternity Hospital (MMH). As such I request your permission to conduct the following study:

Title

The Thompson score and motor outcomes of children with hypoxic ischaemic encephalopathy aged nine to twenty-four months

Description of the study

The study will investigate the gross and fine motor outcomes of children with HIE, aged nine to twenty-four months based on their Thompson hypoxic ischaemic encephalopathy (HIE) scores. The study will be carried out at the paediatric outpatients clinic at Mowbray Maternity Hospital (MMH) which follows up children diagnosed with HIE who were born at both Mowbray Maternity and Groote Schuur Hospitals. The once off, 30-minute assessment will be carried out on the day of the child's booked clinic appointment, should informed consent be granted. The researcher will collect medical information from the patient file.

Ethical considerations

The child's caregiver will sign informed consent after a verbal and written explanation of the study, its requirements and benefits or risks.

Confidentiality will be maintained at all times through the use of subject codes which will be used instead of names or other identifying information. The source list for the subject codes will be kept separate from all data collected.

There are no benefits, nor are there any risks for the child or their caregivers for participating in the study. The caregiver may terminate participation in the study at any time without any negative consequence or effect on their level of care. This will be made clear to the caregivers during the informed consent process. Should the child score a -2 standard deviation below the mean the parent/caregiver will be informed, will be referred to their nearest community occupational therapy department and will be provided with an information pamphlet. In-depth results will be made available on request from the family.

Please feel free to contact my supervisor or myself at the details below for any further queries. Any ethical queries or reporting of study-related adverse events should be made to the chairperson of the Wits Human Research Ethics Committee, Prof. P. Cleaton-Jones at 011 717 1234.

Supervisor:

Name: Lizelle Jacobs

Phone: 011 717 3701

Email: lizelle.jacobs@wits.ac.za

Researcher:

Name: Tasha Nicolson

Phone: 084 826 2288

Email: tashanicolson@gmail.com

Regards,

Tasha Nicolson

APPENDIX K: Approval from Mowbray Maternity Hospital

Western Cape Government
Health

Mowbray Maternity Hospital
Obstetrics and Gynaecology
Reference: letters
Enquiries: Prof Fawcus
Date: 27 August 2015

To: H. Buchanan

Cc: Dr. L. Linley

Dear H. Buchanan

Re: Research Proposal: Association between Thompson score and Motor outcomes of infants diagnosed with HIE, aged 9-12 months

The MMH research committee discussed your research proposal at its meeting on 25 August 2015.

Permission is granted for you to perform the research at MMH.

Please liaise with **Dr. L. Linley** at **MMH** about the logistical arrangements before commencing.

Kind Regards

SR Fawcus

Professor S.R. Fawcus (MBBS FRCOG)
Head Obstetric MMH
Associate/Professor
Department: Obstetrics/ Gynaecology
University of Cape Town

Appendix L: Information pamphlet for parents

Thank you for allowing your child to participate in this study. If your child is found to be having difficulty with some of their muscle and movement development you will be referred to see an Occupational Therapist at your nearest community health centre. This information pamphlet will give you some information about developmental delay, occupational therapy and what you can do to assist your child whilst awaiting your appointment.

What is developmental delay?

Babies learn important skills as they develop. These skills include being able to lift and move their heads, making noises, being able to eat solid food, playing with toys and being able to roll over and sit. These skills are known as “developmental milestones” and usually happen at around the same age in most children.

A child with developmental delay might be slow to learn one or more of these skills than expected. There are different types of developmental delay. Some children may be slower to learn in communication and social skills such as speaking and interacting with others; some may have difficulties with thinking skills; some with motor skills such as rolling, sitting, walking and holding/using objects; and some may struggle with all of these areas. This delay can occur for a number of reasons and may be as a result of the difficulties that they experienced at birth.

It is important to remember that all children develop differently and some may have strengths in one area but be slower in others. Children with developmental delay

might need a bit of extra support to reach their developmental milestones and that is why you have been referred to occupational therapy.

What is occupational therapy?

Occupational therapy professionals work with children and families to help the child to use their hands, minds and bodies to interact with the world around them and that helps them to develop abilities such as play skills which allow them to learn, self care skills such as feeding, toileting and dressing. An occupational therapist can also help the family learn how best to support their child at home and assist with special equipment to make certain tasks easier.

What can we do as a family?

While you wait for your appointment to see the occupational therapist there are many things that can be done at home to help guide your child's development. These are a few ideas:

A child with delayed development in one or more area has exactly the same needs as any other child. They all benefit from a warm, secure and loving environment.

Early stimulation can help your child develop some of the skills we have discussed. Stimulation means giving a child a variety of opportunities to experience, explore, and play with things around her. It involves body movement and the use of all the senses-especially seeing, hearing, and touching. You can do this by giving your child different objects to touch and play with (just remember nothing too small that they might choke on). You can also talk a lot to your child, even though they will not be able to understand you this is very important for their ability to develop speech later on.

Remember that caring for your child means caring for yourself too. Get in touch with other families that are experiencing the same things or find someone that you can talk to if you need.

Below are some of the skills you can help your child develop by the end of their first year of life:

Sitting without needing any support from you or pillows etc.

Rolling from their backs onto their tummy's and back again

Babble, making a wide variety of sounds like ba, da, ma, ga etc.

Look around for toys that are dropped or sounds

Be able to pick up toys and bring them to their mouths

Enjoy games like peek-a-boo

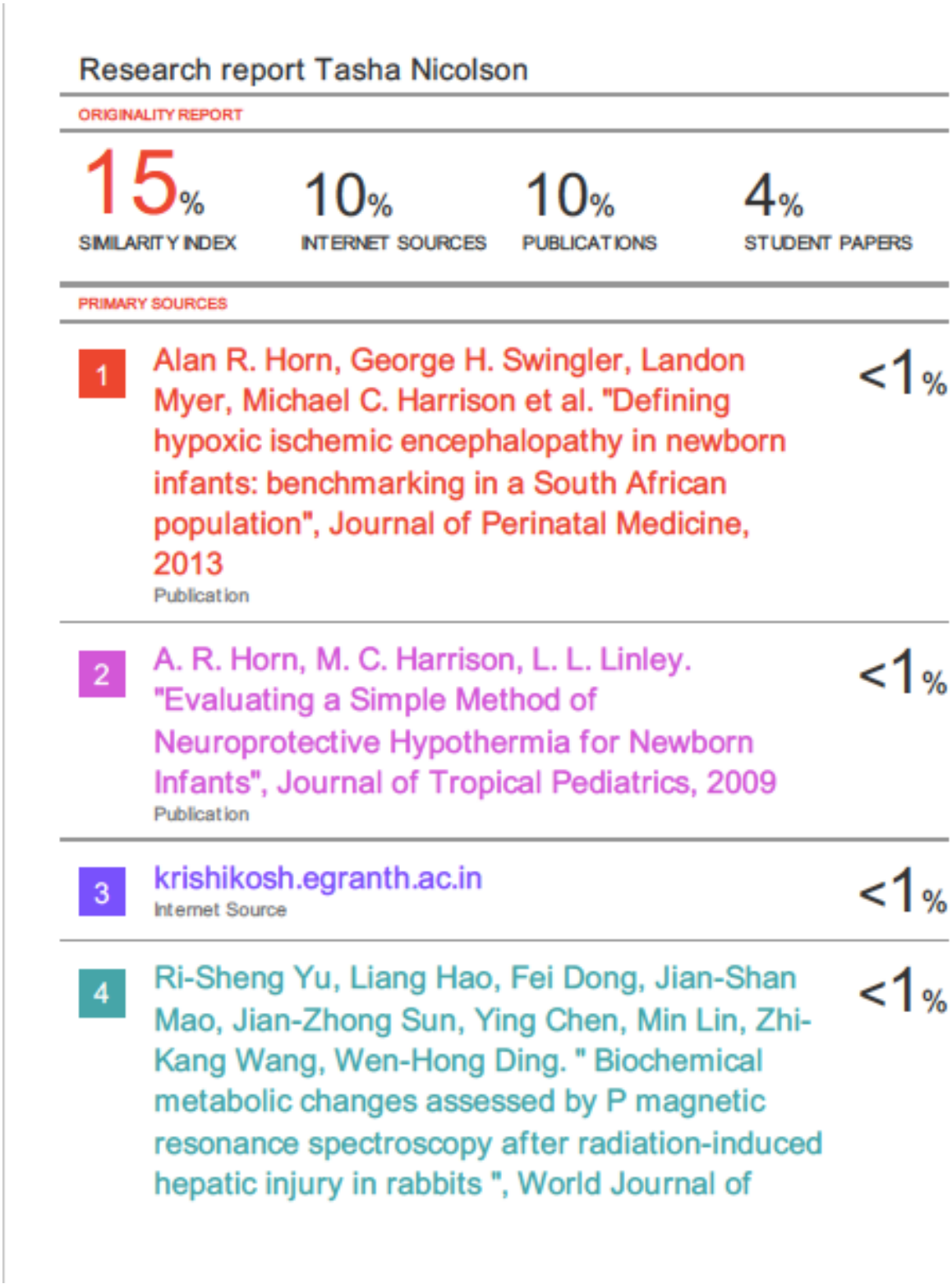
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