Outcomes and Risk Factors of Very Low Birth Weight Infants with Intraventricular Haemorrhage who received Respiratory Support in a Middle Income Country Neonatal Unit

by

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DECLARATION

I, …………*Deepika Goolab*…………, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background

Prematurity is a major risk factor for intraventricular haemorrhage (IVH). Premature infants often require respiratory support. There is little information on neonates with IVH who require respiratory support in low and middle income countries.

Objective

To describe the characteristics and short-term outcomes of very low birth weight (VLBW) infants with IVH who required respiratory support in a tertiary neonatal unit with resource limitations.

Methods

This was a matched retrospective observational study. The population included VLBW infants with IVH, who received positive pressure respiratory support between January 2014 and December 2016. Outcomes of infants with severe IVH was compared to those with mild IVH. Outcomes were further analysed according to mode of ventilation.

Results

150 infants were included in the study, 56 (37%) received continuous positive airway pressure (CPAP) only and 94 (63%) mechanical ventilation. Severe IVH was associated with surfactant therapy across both ventilation groups (p=0.03). Oxygen requirement at 28 days was more frequent in infants with severe IVH compared to mild IVH (79% vs 38%, p=0.01) (OR 6.11 (95% CI 1.19-31.34), p=0.03). Severe IVH and the presence of coagulopathy were the strongest predictors of death in both ventilation groups (p <0.0001). Pulmonary haemorrhage was the commonest cause of death in those with severe IVH and blood culture confirmed sepsis in those with mild IVH. Periventricular leukomalacia (PVL) was associated with severe IVH in those receiving invasive ventilation (OR 6.67 (95% CI 1.11-40.17)).

Conclusion

Mechanical ventilation, coagulopathy and pulmonary haemorrhage were strongly associated with death in VLBW infants with severe IVH in a resource-limited setting. These prognostic factors may have a role in end of life decisions.

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ABBREVIATIONS

IVH	intraventricular haemorrhage
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
NEC	necrotizing enterocolitis
FFP	fresh frozen plasma
PDA	patent ductus arteriosus
ELBW	extremely low birth weight
IVH-PVH	intraventricular-periventricular haemorrhage
CPAP	continuous positive airway pressure
MRI	magnetic resonance imaging
CSF	cerebrospinal fluid
PHH	post haemorrhagic hydrocephalus
VP	ventriculoperitoneal shunt
EVD	external ventricular drainage
LP	lumbar puncture
ROP	retinopathy of prematurity
VLBW	very low birth weight
GSH	Groote Schuur Hospital
VON	Vermont Oxford Network

INTRODUCTION AND LITERATURE REVIEW

INTRODUCTION

Intraventricular haemorrhage (IVH) is a common complication in preterm infants. The relationship has been well described with the incidence increasing with decreasing gestational age.[1-3] This differs to IVH in term infants, which is due to a different pathophysiology with bleeding in areas other than the germinal matrix.[4]

The periventricular germinal matrix is a highly vascularized region which is vulnerable to bleeding in the preterm infant.[1,2] Involution begins at 28 weeks gestation and is usually complete by 36 weeks, after which the risk of bleeding is minimal.[5] Multiple factors can injure this fragile area of the brain leading to IVH.[3] These factors lead to injury by causing disturbances in the cerebral blood flow.[1,2] Fluctuations in cerebral blood flow alters the brain's ability to maintain cerebral autoregulation, a process likely already compromised based on the severity of the prematurity and the stability of the infant.[1,2]

Cranial ultrasonography allows for rapid diagnosis and grading of IVH.[3] Volpe adapted Papile's original grading system to create the following widely used classification [6,7]:

Grade 1 – Germinal matrix haemorrhage and/or IVH <10% of ventricle

Grade 2 – Germinal matrix haemorrhage and IVH 10-50% of ventricle

Grade 3 – Germinal matrix haemorrhage and IVH involving more than 50% of ventricle (often with distended lateral ventricles)

Grade 4 – Periventricular haemorrhagic infarction, cystic periventricular leukomalacia (PVL)

Grading IVH is important in determining prognosis. Mild IVH refers to grade 1 and 2, severe IVH grade 3 and 4.[6,7]

OBJECTIVES

1. To assess the common risk factors associated with intraventricular haemorrhage in preterm infants
2. To assess the complications and outcomes associated with intraventricular haemorrhage in preterm infants

LITERATURE SEARCH

An online search was done on Pubmed to review the literature from the year 2000 onwards. The literature review was conducted during 2016 with the intention of researching evidence over the last 15 years.

Search terms:

1. (("Infant, Premature"[Mesh]) OR "Infant, Premature, Diseases"[Mesh]) AND ((("Intracranial Hemorrhages/etiology"[Mesh] OR "Intracranial Hemorrhages/prevention and control"[Mesh])) OR ("Cerebral Hemorrhage/etiology"[Mesh] OR "Cerebral Hemorrhage/prevention and control"[Mesh]))

   Restrictions included:

   - Humans
   - English

   This search yielded 625 results, of which 72 articles were relevant to the objectives of this study. 57 clinical trials were available and comprise the risk factors analysis for this literature review.

2. (("Infant, Premature"[Mesh]) OR "Infant, Premature, Diseases"[Mesh]) AND (("Intracranial Hemorrhages/complications"[Mesh]) OR "Cerebral Hemorrhage/complications"[Mesh])

   Restrictions included:

   - Humans

- English

This search yielded 220 results of which 29 articles were relevant to the objectives of this study. 18 clinical trials were available and comprise the outcomes analysis for this literature review.

RESULTS

Risk Factors

IVH has been extensively studied to determine potential means of either preventing the incidence or worsening of this condition. 57 studies were reviewed with a summary of the findings presented in table 1.

Prematurity is the most important risk factor for developing IVH.[1-2] The best way to prevent IVH is to prevent factors that lead to preterm labour and delivery.

Multiple trials have confirmed the recognised benefits of antenatal corticosteroids in reducing the incidence of IVH.[8-13] This is achieved by stabilizing blood vessels in the germinal matrix and maintaining cerebral blood flow. In addition, antenatal steroids reduce respiratory distress syndrome (RDS), a disease process which contributes to cerebral blood flow fluctuations.[1]

Partial or complete treatment with steroids showed improved mortality outcomes and lower rates of severe IVH compared to no treatment.[13] A single dose in preterm rupture of membranes was shown to decrease the incidence of severe IVH.[13] Both betamethasone and dexamethasone reduce the risk of IVH and severe IVH.[8,9]

Chorioamnionitis is a risk factor for preterm delivery and the associated complications thereafter. It has been well described as a risk factor for IVH, even when adjusting for gestational age.[14-17] Steroids have been shown to be beneficial in decreasing IVH in the presence of chorioamnionitis.[18]

More evidence is emerging showing a strong association between transportation of extreme preterm infants and IVH.[19,20] High risk mothers should ideally be delivered in a tertiary neonatal unit where early stabilisation of the infant may prevent IVH.

While a multicentre prospective cohort showed caesarean section delivery as protective against IVH,[21] further studies found no difference in outcome depending on mode of delivery and IVH.[22,23]

Maternal HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) was associated with an increased incidence of severe IVH in preterm infants.[24] Antenatal magnesium sulphate showed improved long term neurological outcomes but has had no effect on IVH.[25]

Delayed cord clamping (along with the benefits of improved mortality, reduced anaemia and reduced incidence of necrotizing enterocolitis (NEC)) has shown to be protective against IVH across all grades and is generally recommended for vigorous preterm infants not requiring resuscitation.[25-28]

Reducing blood transfusions in the first week of life may be associated with a decreased incidence of IVH.[29.30] The association is unclear given that the clinical factors that lead to early blood transfusions may be relevant to the cause of IVH in these infants.[29]

The role of coagulopathy in the pathogenesis of IVH is not clearly demonstrated. However it does influence the risk and severity of the condition. Several treatment strategies have been reviewed.[31-37]

The use of anticoagulants to prevent the formation of thrombi (implicated as a possible cause of IVH) does not show any clear benefit.[31] Systematic reviews done by Bruschettini et al. found insufficient evidence to recommend treatment with heparin or antithrombin.[32,33] Fresh frozen plasma (FFP) transfusions are not recommended prophylactically.[34,35] Dani et al.

demonstrated that coagulopathy screening and empiric treatment with FFPs reduced the risk of IVH only in 23-26 week gestation infants.[34] Tran et al. was able to identify preterm infants at risk for coagulopathy and severe IVH but FFPs were not beneficial in preventing IVH or decreasing mortality.[35] Prophylactic administration of Factor VII did not demonstrate any clear benefits in reducing IVH in a small prospective study.[36] Antenatal vitamin K did not reduce the incidence of IVH in preterm infants.[37]

The incidence and severity of IVH was not influenced by platelet transfusions. Thrombocytopaenia can be found in IVH, but the severity of the thrombocytopaenia does not compare with the grade of IVH.[38] Platelet transfusions did not influence the incidence of IVH.[39] Ethamsylate was considered due to its ability to promote platelet adhesiveness. A systematic review showed a decrease in severe IVH in infants <35weeks but did not affect infants <32 weeks. It does not reduce mortality or affect neurodevelopment and is not recommended for routine use.[40]

Patent ductus arteriosus (PDA) causes variations in cerebral blood flow and is a risk factor for IVH.[1] The role of indomethacin and ibuprofen has been reviewed in preventing this phenomenon. Indomethacin has a role in treating infants with symptomatic PDAs. It reduces severe IVH in the short term by creating vascular stability.[1-3] This has been demonstrated in several studies.[41-44] However, it does not provide any long term protection against neurodevelopmental outcomes and has no effect on mortality.[41,42] Ibuprofen does not influence cerebral blood flow and therefore has no effect on IVH.[1] This was demonstrated in several randomised controlled trials in infants who received prophylactic ibuprofen.[45-46]

The mechanism of action of phenobarbital in stabilisation of blood pressure was postulated to potentially prevent IVH. A meta-analysis of twelve randomised control trials showed no effect of postnatal phenobarbital on prevention of IVH with an increased requirement for mechanical ventilation due to the sedative effects of phenobarbital.[47] Antenatal phenobarbital has also been reviewed with no benefits demonstrated.[48]

Hypothermia failed to show a strong association with IVH in the studies reviewed.[49,50]

Hypernatraemia, a complication of extremely low birth weight (ELBW), leads to vascular rupture and is associated with IVH.[51]

A large randomized control trial by Fauchère, showed no difference in IVH in infants given erythropoietin.[52]

Respiratory distress, acidosis, asphyxia and hypoxia all affect cerebral blood flow and are associated with an increased incidence of IVH.[53-55] Both hypercapnia and hypocapnia are associated with severe IVH.[56-58] Pneumothorax increases cerebral venous pressure and can influence the progression of IVH.[59]

Prophylactic surfactant was an independent protective factor in reducing IVH overall compared to rescue treatment when analysed across three randomized controlled trials.[60] A 2012 meta-analysis showed an overall marginal decrease in IVH in patients receiving prophylactic surfactant in comparison to selective surfactant treatment.[61]

Mechanical ventilation has significant hemodynamic effects on the infant which could affect cerebral blood flow.[1] Prolonged positive pressure ventilation also increases the blood brain barrier permeability and contributes to the development of IVH.[1] The SUPPORT study compared infants who received CPAP versus intubation with surfactant in the delivery room. There was no difference in IVH between the two groups.[62] Early and prolonged mechanical ventilation are important predictors for severe IVH.[54,63] Pancuronium use in infants to achieve better control of mechanical ventilation, has shown a decrease in the incidence of IVH; regular use cannot be recommended due to possible associated long-term complications.[64]

Table 1: Summary of Risk factors of IVH

No	Author	Title	Type of Study	Subjects	Objective/ Intervention	Findings
Antenatal Steroids						
1	Elmian et al [8]	Antenatal Betamethasone Compared With Dexamethasone (Betacode Trial)	Randomized Double Blind Controlled Trial	Preterm neonates 23-34 weeks	Comparison of betamethasone to dexamethasone and the effects on neonatal morbidity and mortality	Reduction in IVH with both agents, but more so with dexamethasone
2	Lee et al [9]	Adverse neonatal outcomes associated with antenatal dexamethasone versus antenatal betamethasone	Retrospective Cohort Study	Preterm neonates <1500g	Comparison of betamethasone to dexamethasone and the effects on neonatal morbidity and mortality	Reduction in severe IVH in both groups, with a lower mortality with betamethasone

3	Chawla et al [10]	Association of neurodevelopmental outcomes and neonatal morbidities of extremely premature infants with differential exposure to antenatal steroids	Observation-al Cohort Study	Preterm neonates, 401-1000g, 22-27 weeks	Comparison of outcomes of no, partial or complete antenatal steroids in preterm infants	Both partial and complete antenatal steroids was associated with a decrease in severe IVH compared to no antenatal steroids
4	Maksić et al [11]	The effects of antenatal corticosteroid treatment on intraventricular-periventricular haemorrhage (IVH-PVH) of premature infants.	Randomized Controlled Trial	Preterm neonates, 26-34 weeks	The effects of antenatal corticosteroids on the incidence of IVH	Decreased incidence of IVH in infants who received antenatal steroids
5	Wei et al [12]	Impact of antenatal steroids on intraventricular hemorrhage in very-low-birth weight infants.	Retrospective cohort	Preterm neonates, 401g-1500g/ 22-32 weeks	The effects of antenatal steroids in preventing IVH	Antenatal steroids are strongly associated with a lower risk of IVH

6	Vermillion et al [13]	Effectiveness of antenatal corticosteroid administration after preterm premature rupture of the membranes	Prospective cohort	Preterm neonates, 24-32 weeks	The effect of antenatal betamethasone on preterm morbidities in preterm premature rupture of membranes	Antenatal betamethasone given in preterm premature rupture of membranes is associated with a reduced risk of severe IVH
Chorioamnionitis						
1	Ahn et al [14]	The association of histological chorioamnionitis and antenatal steroids on neonatal outcome in preterm infants born at less than thirty-four weeks' gestation	Prospective cohort	Preterm neonates, <34 weeks	Assess the effects of chorioamnionitis on neonatal morbidities	Higher incidence of severe IVH with chorioamnionitis
2	De Felice et al [15]	Early neonatal brain injury in histologic chorioamnionitis	Prospective cohort	Neonates, 24-42 weeks, 500g-3850g	Determine neonatal outcomes in clinical and histological chorioamnionitis	Significant association with IVH in histological chorioamnionitis, independent of gestational age

3	Mehta et al [16]	Neonatal morbidity and placental pathology	Retrospective cohort	Preterm neonates, ≤34 weeks	Determine neonatal outcomes in preterm infants with placental pathology and its association with gestational age	Placental pathology is associated with an increased risk of IVH independent of gestational age
4	Tauscher et al [17]	Association of histologic chorioamnionitis, increased levels of cord blood cytokines, and intracerebral hemorrhage in preterm neonates	Prospective cohort	Preterm neonates, ≤32 weeks	The association of histological chorioamnionitis with IVH	Histological chorioamnionitis is a risk factor for IVH
5	Miyazaki et al [18]	The effects of antenatal corticosteroids therapy on very preterm infants after chorioamnionitis	Retrospective cohort	Preterm neonates, <34-22 and <1500g	Assess neonatal outcomes following antenatal steroids in histological chorioamnionitis	Antenatal steroids was associated with reduced incidence of IVH
Transport						
1	Köksal et al [19]	Risk factors for intraventricular haemorrhage in very low birth weight infants	Prospective cohort	Preterm neonates, ≤1500g	To assess the risk factors associated with IVH in preterm infants	Postnatal transport of infants to tertiary hospitals was associated with an increased risk of IVH

2	Mohamed et al [20]	Transport of premature infants is associated with increased risk for intraventricular haemorrhage	Retrospective cohort	Preterm neonates, ≤1500g	The association of neonatal inter-hospital transport on the incidence and severity of IVH.	Inter-hospital transport of neonates is associated with an increased incidence and increased severity of IVH
Mode of delivery						
1	Helwich et al [21]	Intraventricular hemorrhage in premature infants with Respiratory Distress Syndrome treated with surfactant: incidence and risk factors in the prospective cohort study	Prospective cohort	Preterm neonates, <32 weeks	Assess risk factors for IVH in preterm infants with respiratory distress syndrome treated with surfactant	Caesarean section was protective against IVH in preterm infants
2	Ljuština et al [22]	Analysis of intracranial hemorrhage grade in preterm singleton pregnancies delivered vaginally or by cesarean section	Retrospective cohort	Preterm neonates, 750-1500g	To compare mode of delivery with IVH	No significant difference demonstrated between mode of delivery and IVH

3	Werner et al [23]	Mode of delivery and neonatal outcomes in preterm, small-for-gestational-age newborns	Retrospective cohort	Preterm neonates, 25-34 weeks	To assess mode of delivery on preterm neonatal outcomes	No difference in IVH between mode of delivery
HELLP syndrome						
1	Kim et al [24]	Neonatal outcome after preterm delivery in HELLP syndrome	Retrospective cohort	Preterm neonates, <37 weeks	Assess outcomes of preterm neonates in HELLP syndrome and severe preeclampsia	Increased incidence of severe IVH in HELLP syndrome
Magnesium Sulphate						
1	Crowther et al [25]	Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis	Meta-analysis, 5 randomized controlled trials	Preterm neonates, <37 weeks	Determine effects and outcomes of antenatal magnesium sulphate on preterm neonates	• Neuroprotective effect with decreased incidence of cerebral palsy • No effect on IVH

Delayed cord clamping						
1	Chiruvolu et al [26]	Effect of delayed cord clamping on very preterm infants	Retrospective and prospective cohort	Preterm neonates, <32 weeks	The assess the effects of delayed cord clamping on IVH in preterm infants	Delayed cord clamping decreases the incidence of IVH in preterm infants
2	Mercer et al [27]	Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial	Randomized controlled trial	Preterm neonates, <32 weeks	Comparison of neonatal outcomes between immediate and delayed cord clamping in preterm infants	Delayed cord clamping decreases the incidence of IVH in preterm infants
3	Rabe et al [28]	Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes	Meta-analysis, 48 randomized controlled trials	Preterm neonates, <37 weeks	Comparison of neonatal outcomes with delayed cord clamping compared to early cord clamping	Reduced incidence of IVH with delayed cord clamping compared to early cord clamping

Blood Transfusion						
1	Christensen et al [29]	Association, among very-low-birthweight neonates, between red blood cell transfusions in the week after birth and severe intraventricular haemorrhage	Retrospective cross sectional	Preterm neonates, <1500g	The effects of reduced early red blood cell transfusions on the incidence of IVH	• Decreased incidence of severe IVH since reducing early RBC transfusions in a neonatal intensive care unit (NICU). • Association is unclear
2	Hasanbegovic et al [30]	Evaluation and treatment of anemia in premature infants	Retrospective observational	Preterm neonates, ≤37 weeks	Assess the frequency of anaemia in preterm infants in a neonatal unit and the need for blood transfusions	Anaemia was more frequent in infants < 32 weeks' gestational age, who required blood transfusions more often
Coagulopathy						
1	Fulia et al [31]	Can the Administration of Antithrombin III Decrease the Risk of Cerebral Hemorrhage in Premature Infants?	Randomized controlled trial	Preterm neonates, <30 weeks	To assess if antithrombin given prophylactically to preterm infants decreases the risk of IVH	Antithrombin did not decrease the incidence of IVH

2	Bruschettini et al [32]	Heparin for the prevention of intraventricular haemorrhage in preterm infants	Systematic review, 2 randomized controlled trials	Preterm neonates <32 weeks	To assess if heparin given prophylactically to preterm infants decreases the risk of IVH	Heparin did not decrease the incidence of IVH
3	Bruschettini et al [33]	Antithrombin for the prevention of intraventricular hemorrhage in very preterm infants	Systematic review, 2 randomized controlled trials	Preterm neonates <32 weeks	To assess if antithrombin given prophylactically to preterm infants decreases the risk of IVH	Antithrombin did not decrease the incidence of IVH
4	Dani et al [34]	Coagulopathy screening and early plasma treatment for the prevention of intraventricular hemorrhage in preterm infants	Prospective cohort	Preterm neonates, 23-29 weeks	To assess the effects of early FFP treatment, in preterm infants with coagulopathy, on IVH	Coagulopathy screening and early FFPs were beneficial in reducing IVH in infants < 23-26 weeks' gestational age

5	Tran et al [35]	Does risk-based coagulation screening predict intraventricular haemorrhage in extreme premature infants?	Retrospective cohort	Preterm neonates, 23-26 weeks	To assess the effects of early FFP treatment on IVH, in preterm infants with abnormal coagulation screens	• Screening identified high risk neonates at risk for IVH • FFPs to correct coagulopathy did not decrease the incidence of IVH
6	Veldman et al [36]	A prospective pilot study of prophylactic treatment of preterm neonates with recombinant activated factor VII during the first 72 hours of life	Prospective cohort	Preterm neonates, 23-28 weeks	To assess the effects of prophylactic factor VII on preterm infants	• Small sample size • Did not show any clear benefit
7	Crowther et al [37]	Vitamin K prior to preterm birth for preventing neonatal periventricular haemorrhage	Systematic review, 7 randomised controlled trials	Preterm neonates, <37 weeks	To assess the effects of antenatal vitamin K on neonatal morbidity and mortality	No difference noted in the incidence of IVH with antenatal vitamin K

8	Von Lindern et al [38]	Thrombocytopaenia and intraventricular haemorrhage in very premature infants: a tale of two cities	Retrospective cohort	Preterm neonates, <32 weeks	To assess the effects of platelet transfusions on IVH in preterm neonates with thrombocytopaenia	Platelet transfusions in asymptomatic neonates with a count of <30 x 10^9/l did not reduce the incidence of IVH
9	Sparger et al [39]	Platelet transfusion practices among very-low-birth-weight infants	Retrospective cohort	Preterm neonates, <1500g	To assess platelet transfusions in preterm neonates with thrombocytopaenia and its risk on IVH	• Transfusion depended on severity of illness • Thrombocytopaenia did have a higher risk of IVH, but was not dependant on the actual platelet count • Platelet transfusions did not reduce the incidence of IVH

10	Hunt et al [40]	Ethamsylate for the prevention of morbidity and mortality in preterm or very low birth weight infants	Systematic review, 8 randomized controlled trials	Preterm neonates, <35 weeks or <2000g	Prophylactic ethamsylate in preterm infants and its effects on neonatal outcomes	• Reduced severe IVH in infants < 35 weeks' gestational age, but not in infants < 32 weeks' gestational age • No difference in mortality or neurodevelopmental outcome
Indomethacin and Ibuprofen						
1	Fowlie et al [41]	Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants	Systematic review, 19 randomized controlled trials	Preterm neonates, <37 weeks	To assess the effects of prophylactic indomethacin in preterm infants, on morbidity and mortality	• Decreased incidence in IVH and PDAs • No difference in mortality or long term neurodevelopmental outcome

2	Schmidt et al [42]	Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants	Randomized controlled trial	Preterm neonates, <1000g	To assess the effects of prophylactic indomethacin in preterm infants, on morbidity and mortality	• Decreased incidence in IVH • No difference in mortality or long term neurodevelopmental outcome
3	Al-Shawaf et al [43]	The use of indomethacin for the prevention of intraventricular brain hemorrhage in high-risk neonates	Retrospective cohort	Preterm neonates, ≤1250g	To assess the effects of prophylactic indomethacin on the incidence of IVH	Decreased incidence in IVH with prophylactic indomethacin
4	Yanowitz et al [44]	Prophylactic indomethacin reduces grades III and IV intraventricular hemorrhages when compared to early indomethacin treatment of a patent ductus arteriosus	Retrospective cohort	Preterm neonates, <29 weeks and <1350g	To assess the effects of prophylactic indomethacin on the incidence of severe IVH	Decreased incidence in severe IVH with prophylactic indomethacin

5	Dani et al [45]	Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study	Randomized controlled trial	Preterm neonates, <28weeks	To assess the effects of prophylactic ibuprofen on the incidence of IVH grade 2-4	There was no difference in the incidence of grade 2-4 IVH
6	Van Overmeire et al [46]	Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial	Randomized controlled trial	Preterm neonates, <31 weeks	To assess the effects of prophylactic ibuprofen on the incidence of severe IVH	• No effect on severe IVH • Decreased incidence of PDA

Phenobarbital						
1	Smit et al [47]	Postnatal phenobarbital for the prevention of intraventricular haemorrhage in preterm infants	Meta-analysis, 12 randomized controlled trials	Preterm neonates, <34 weeks or <1500g	Prophylactic phenobarbital in preterm infants and its effects on neonatal outcomes	• Does not reduce the incidence of IVH • Increased mechanical ventilation
2	Crowther et al [48]	Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage	Meta-analysis, 9 randomized controlled trials	Preterm neonates, <34 weeks	Antenatal prophylactic phenobarbital and its effects on preterm IVH	• Does not reduce the incidence of IVH • Increased maternal sedation
Hypothermia						
1	Audeh et al [49]	Does admission hypothermia predispose to intraventricular hemorrhage in very-low-birth-weight infants?	Retrospective observational	Preterm neonates, ≤32 weeks and <1500g	To assess admission hypothermia as a risk factor for IVH in preterm infants	Admission hypothermia was not significantly associated with IVH

2	Miller et al [50]	Hypothermia in very low birth weight infants: distribution, risk factors and outcomes	Retrospective cohort	Preterm neonates, <1500g	To assess the outcomes of preterm neonatal hypothermia	Babies with moderate hypothermia had an increased odds of developing IVH
Hypernatraemia						
1	Dalton et al [51]	Assessment of association between rapid fluctuations in serum sodium and intraventricular hemorrhage in hypernatremic preterm infants	Retrospective observational	Preterm neonates, <29 weeks and <1000g	To determine the association between serum fluctuations in sodium and IVH	Hypernatraemia in preterm infants is associated with IVH
Erythropoeitin						
1	Fauchère et al [52]	Safety of early high-dose recombinant erythropoietin for neuroprotection in very preterm infants	Randomized controlled trial	Preterm neonates, 26-32 weeks	To assess the neuroprotective effects of prophylactic erythropoietin	There was no difference in the incidence of IVH

Respiratory Complications						
1	Ertan et al [53]	Perinatal risk factors for neonatal intracerebral hemorrhage in preterm infants	Retrospective observational	Preterm neonates, 24-34 weeks	To assess the risk factors associated with IVH in preterm infants	Acidosis, low APGARS and thrombocytopaenia was associated with IVH
2	Helwich et al [54]	Intraventricular hemorrhage in premature infants with Respiratory Distress Syndrome treated with surfactant: incidence and risk factors in the prospective cohort study	Prospective cohort	Preterm neonates, <32 weeks	To assess IVH in preterm infants with RDS treated with surfactant	• Significant incidence of IVH in RDS • Mechanical ventilation was the strongest risk factor for IVH

3	Krediet et al [55]	Respiratory distress syndrome-associated inflammation is related to early but not late peri/intraventricular hemorrhage in preterm infants	Prospective cohort	Preterm neonates, <32 weeks	To determine if cytokine levels in infants with RDS are associated with the development of early IVH-PVH within the first 12 hours of life in contrast to IVH-PVH developing after 12 hours of life	Association between RDS and developing IVH demonstrated by raised cytokine levels
4	Fabres et al [56]	Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants	Retrospective cohort	Preterm neonates, 401g-1250g	To assess hypocapnia and hypercapnia in preterm infants in the first 4 days of life and its association with severe IVH	Hypocapnia and hypercapnia is associated with severe IVH in preterm infants

5	Erickson et al [57]	Hypocarbia in the ventilated preterm infant and its effect on intraventricular haemorrhage and bronchopulmonary dysplasia	Retrospective cohort	Preterm neonates, <29 weeks	To assess CO2 levels in ventilated preterm infants and severe IVH	Hypocapnia is associated with severe IVH in ventilated preterm infants
6	Kaiser et al [58]	Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants	Retrospective cohort	Preterm neonates, <1500g	To assess hypercapnia as a risk factor for severe IVH in preterm infants during first 3 days of life	Hypercapnia is associated with an increased risk of severe IVH in preterm infants
7	Pishva et al [59]	Intraventricular hemorrhage in premature infants and its association with pneumothorax	Prospective cross-sectional	Preterm neonates, 24-36 weeks	To assess pneumothorax as a risk factor for IVH	• Pneumothorax aggravates IVH in preterm infants • Pneumothorax is a risk factor in < 28 week infants

Surfactant						
1	Walti et al [60]	Prophylactic administration of porcine-derived lung surfactant is a significant factor in reducing the odds for peri-intraventricular haemorrhage in premature infants	Meta-analysis, 3 randomized controlled trials	Preterm neonates at risk of RDS	Comparison of prophylactic surfactant to rescue surfactant in reducing the rate of IVH	Prophylactic surfactant in preterm infants with RDS is an independent protective factor against IVH
2	Rojas-Reyes et al [61]	Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants	Meta-analysis, 11 randomized controlled trials	Preterm infants with or without RDS	Comparison of outcomes of prophylactic surfactant to selective surfactant in RDS preterm infants	• Decreased risk of IVH with prophylactic surfactant compared with early CPAP and selective surfactant • Trend towards decreased risk of severe IVH with prophylactic surfactant compared with selective surfactant

Ventilation						
1	SUPPORT study group [62]	Early CPAP versus surfactant in extremely preterm infants	Randomized controlled trial	Preterm neonates, 28-24 weeks	Comparison of CPAP to surfactant and ventilation in preterm infants	No difference in IVH between the two groups
2	Aly et al [63]	Is mechanical ventilation associated with intraventricular hemorrhage in preterm infants?	Retrospective cohort	Preterm neonates, <1500g	The association between mechanical ventilation and IVH in preterm infants	Early and prolonged mechanical ventilation is associated with severe IVH
3	Cools et al [64]	Neuromuscular paralysis for newborn infants receiving mechanical ventilation	Meta-analysis, 6 randomized controlled trials	Preterm neonates	Determine the effects of neuromuscular paralysis in mechanical ventilation	• Decreased risk of IVH noted • Adverse effects of pancuronium prohibits routine use

Outcomes

IVH is associated with multiple significant short and long term complications. 18 studies were reviewed with a summary of the findings presented in table 2.

IVH causes brain injury through both primary and secondary mechanisms. The mass effect of blood in the ventricles leads to stretching of the ventricles and cellular damage (although the level of damage is unclear). Raised intracranial pressure may occur as a late complication due to the skull flexibility of the neonate. Finally, impaired reabsorption of the cerebrospinal fluid (CSF) due to inflammation of the subarachnoid villi, may cause a communicating hydrocephalus. [65,66]

Secondary damage occurs from the effects of red blood cell lysis causing toxic effects on the cells of the brain and choroid plexus. Activation of the coagulation system leads to an inflammatory response and thrombus formation. Thrombus formation causes obstruction of the ventricular system leading to a non-communicating hydrocephalus.[65,66]

Mortality increases as the severity of IVH progresses, with grade 4 IVH having the worst prognosis.[67,68]

Several studies have supported the notion that mild IVH is associated with normal neurological outcomes.[69.70] This is being continually studied. Magnetic resonance imaging (MRI) scans on preterm infants with mild IVH found a reduction in cerebral volume in this referenced prospective cohort analysis.[71] A meta-analysis comprising 9 studies, assessing the long term outcomes of IVH found mild IVH was associated with some neurological impairment, but not cerebral palsy, compared to no IVH.[68] The impact of severe IVH has been clear; neurodevelopmental outcomes are worse with increasing severity.[72]

Post haemorrhagic hydrocephalus (PHH) is a severe complication of IVH with important complications. Hydrocephalus affects the white matter of the brain and impairs brain growth.[73] It has a direct link with the severity of the grade of IVH.[74] It also has a strong association with poor neurological outcomes.[75]

Increasing severity of IVH is a risk factor for ventriculoperitoneal (VP) shunts in PHH.[76] Infants who require VP shunts have poorer neurological outcomes and higher mortality rates than infants who don't require shunts.[75-77]

Removal of CSF by repeat lumbar punctures does not improve outcomes in comparison to conservative treatment, or reduce the need for surgical shunts.[78,79] Thrombolytics, acetazolamine and furosemide also do not reduce the need for surgical shunts to treat hydrocephalus.[79,80]

If there is progressive dilatation, surgical management of PHH includes external ventricular drainage (EVD) as a temporary measure. Early placement with stabilization of intracranial pressure is associated with better outcomes.[79] Ventricular access devices/reservoirs is another temporizing measure which allows for easier withdrawal of CSF than serial lumbar punctures (LP), although have a higher incidence of needing a permanent VP shunt compared to EVD.[79]

White matter injury and the formation of cystic PVL are complications from severe IVH. [81] White matter injury can occur from ventricular enlargement and compression on surrounding brain tissue. The resulting effect is inflammation and further injury.[81] The immaturity of the vascular system of the brain also predisposes it to ischaemic injury. [3] Brain parenchyma is also vulnerable to oxygen free radicals which occur during ischemia. This leads to periventricular focal necrosis and cyst formation, which usually occurs 2-3 weeks post injury.[81]

Cystic PVL is associated with significant outcomes of severe neurological impairment and cerebral palsy. The risk of cystic PVL increases in grade 3 and 4 IVH.[82]

There is no clear relationship between retinopathy of prematurity (ROP) and IVH. A small cross sectional study looking at ocular outcomes, found severe IVH to be associated with worse ROP than mild IVH.[83] A study by Watts et al. showed no association between severe IVH and severe ROP; the majority of infants with stage 3 ROP had grade 1 IVH.[84] Optic atrophy was another possible complication associated with severe IVH.[85]

Table 2: Summary of Outcomes of IVH

No	Author	Title	Type of Study	Subjects	Objective/ Intervention	Findings
Mortality						
1	Radic et al [67]	Outcomes of intraventricular haemorrhage and post haemorrhagic hydrocephalus in a population-based cohort of very preterm infants born to residents of Nova Scotia from 1993 to 2010	Retrospective Cohort	Preterm neonates	Analyse outcomes of IVH in preterm infants	• Mortality increased with severity of IVH • Grade 4 IVH associated with cerebral palsy
2	Mukerji et al [68]	Periventricular/Intra-ventricular Hemorrhage and Neurodevelopmental Outcomes	Meta-Analysis, 9 observational studies	Preterm neonates, <34 weeks	To describe neurodevelopmental outcomes in preterm infants with IVH	• Severe IVH is associated with poorer outcomes compared to mild and no IVH • Mild IVH associated with neurological impairment compared to no IVH

Neurological Outcomes						
1	Reubsaet et al [69]	The impact of low-grade germinal matrix-intraventricular hemorrhage on neurodevelopmental outcome of very preterm infants	Retrospective case control	Preterm neonates, 24-32 weeks	Compare neurodevelopmental outcomes in preterm infants with mild IVH compared to no IVH	Outcomes were similar in both groups
2	Wy et al [70]	Impact of intraventricular hemorrhage on cognitive and behavioral outcomes at 18 years of age in low birth weight preterm infants	Retrospective case control	Preterm neonates, low birth weight	To determine the effect of mild IVH on intellectual and behavioural function	Mild IVH was not a risk factor for neurological impairment
3	Vasileiadis et al [71]	Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age	Prospective cohort	Preterm neonate, <1500g	To assess cortical development following uncomplicated IVH	MRI scans demonstrated a reduction in cerebral cortical grey matter in infants with uncomplicated IVH as they approached term

4	Klebermass-Schrehof et al [72]	Impact of low-grade intraventricular hemorrhage on long-term neurodevelopmental outcome in preterm infants	Retrospective cohort	Preterm neonates < 32 weeks	To determine neurodevelopmental outcomes in different grades of IVH in preterm infants	• Neurological impairment occurred in all grades of IVH • Worse outcomes with increased severity of IVH
Post haemorrhagic hydrocephalus						
1	Jary et al [73]	Impaired brain growth and neurodevelopment in preterm infants with posthaemorrhagic ventricular dilatation	Prospective cohort	Preterm neonates, <37 weeks	To correlate MRI scans in preterm infants closer to term with neurodevelopmental outcomes at 2 years	• Preterm infants with post haemorrhagic ventricular dilatation had reduced brain volumes on MRI • Decreased brain volumes was strongly associated with motor impairment

2	Sajjadian et al [74]	Incidence of intraventricular hemorrhage and post haemorrhagic hydrocephalus in preterm infants	Prospective descriptive	Preterm neonates, ≤37 weeks and ≤1500g	To determine the incidence of IVH and post haemorrhagic hydrocephalus	Hydrocephalus correlates with severity of IVH
3	Srinivasakumar et al [75]	Post haemorrhagic ventricular dilatation-impact on early neurodevelopmental outcome	Retrospective cohort	Preterm neonates, ≤34 weeks	To assess neurodevelopmental outcomes of severe IVH with post haemorrhagic ventricular dilatation	• Severe IVH with post haemorrhagic ventricular dilatation is associated with worse outcomes than severe IVH without post haemorrhagic ventricular dilatation • Outcomes were worse in infants who required a neurosurgical procedure

4	Kazan et al [76]	Hydrocephalus after intraventricular hemorrhage in preterm and low-birth weight infants: analysis of associated risk factors for ventriculoperitoneal shunting	Retrospective cohort	Preterm neonates	To assess risk factors for VP shunts in posthaemorrhagic hydrocephalus	Severity of IVH is a risk factor for VP shunts
5	Christian et al [77]	Trends in hospitalization of preterm infants with intraventricular hemorrhage and hydrocephalus in the United States, 2000-2010	Retrospective cohort	Preterm neonates	To describe post haemorrhagic hydrocephalus in preterm infants	Severity of IVH correlates with hydrocephalus and mortality

6	Whitelaw et al [78]	Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage	Meta-analysis, 4 randomized controlled trials	Infants <3 months	To assess if repeated CSF removal in infants at risk of post haemorrhagic hydrocephalus, reduces the risk of permanent shunt, disability or death compared to conservative management	Does not reduce placement of permanent shunt, risk of disability or mortality rates
7	Mazzola et al [79]	Paediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: management of post haemorrhagic hydrocephalus in premature infants	Systematic review, 68 articles	Preterm neonates	To assess the optimal treatment strategies for post haemorrhagic hydrocephalus	Serial lumbar punctures, acetazolamide, furosemide and thrombolytics do not reduce the need for shunt placement Surgical temporizing measures are treatment options

8	Yapicioğlu et al [80]	Intraventricular streptokinase for the treatment of post haemorrhagic hydrocephalus of preterm	Randomized controlled trial	Preterm neonates	The effects of streptokinase in treating post haemorrhagic hydrocephalus	Streptokinase was not effective in reducing the need for shunt surgery
Periventricular leukomalacia						
1	Kusters et al [81]	"Intraventricular" hemorrhage and cystic periventricular leukomalacia in preterm infants: how are they related?	Retrospective cohort	Preterm neonates, <30 weeks	To assess the association between grades of IVH and cystic PVL	Increased incidence of cystic PVL in severe IVH

Ocular complications						
1	Christiansen et al [83]	Ocular outcomes in low birth weight premature infants with intraventricular haemorrhage	Retrospective cross-sectional	Preterm neonates, <1500g	To assess ocular outcomes in preterm infants with IVH	Infants with severe IVH were more likely to have stage 3 retinopathy or higher
2	Watts et al [84]	Intraventricular haemorrhage and stage 3 retinopathy of prematurity	Retrospective cohort	Preterm neonates, 24-28 weeks and 540g-1010g	To assess association between IVH and stage 3 ROP	• IVH was associated with stage 3 ROP • ROP was not dependent on severity of IVH
3	O'keefe et al [85]	Ocular significance of intraventricular haemorrhage in premature infants	Retrospective cohort	Preterm neonates, 24-35 weeks and 630g-2240g	Comparison of ocular pathology in mild and severe IVH	• All grades of IVH associated with reduced visual acuity • Optic atrophy is more common in severe IVH

CONCLUSION

Very low birth weight (VLBW) infants are vulnerable to complications associated with prematurity. There is on-going research to help develop strategies to improve these risks, especially for developing countries.

The increased use of non-invasive ventilation and the practice of INSURE (intubation-surfactant-extubation) has helped to improve respiratory complications and reduced the need for invasive ventilation, a scarce resource in developing countries.

IVH is another significant complication in preterm infants. Severe IVH is strongly associated with increased mortality. It also leads to neurodevelopmental impairment, post haemorrhagic hydrocephalus and prolonged hospital admissions, which carry further risks and complications. Lifelong medical support is often needed comprising multidisciplinary teams. This places an additional strain on an already burdened healthcare system.

Applying preventative measures such as antenatal steroids and delayed cord clamping are valuable in protecting against IVH. Identifying which risk factors are more common will assist in the management of high risk infants and resource allocations. Risk factors such as ventilation, blood transfusions, coagulopathy and hypothermia can be identified in a unit and targeted for improvement strategies.

The majority of articles in this literature review are from developed settings. More research is needed applying to resource limited settings. In this study the risk factors and outcomes of IVH will be analysed in VLBW infants in a developing setting. Given the close association with respiratory complications in VLBW infant as well as its relation as a risk factor in IVH, infants requiring respiratory support will be part of the studied population. This comparison could provide important information on reduction strategies and appropriate application of distributive justice in our hospital and similar settings.

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PUBLICATION READY MANUSCRIPT

Outcomes and Risk Factors of Very Low Birth Weight Infants with Intraventricular Haemorrhage who received Respiratory Support in a Middle Income Country Neonatal Unit

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ABSTRACT

Background

Prematurity is a major risk factor for intraventricular haemorrhage (IVH). Premature infants often require respiratory support. There is little information on neonates with IVH who require respiratory support in low and middle income countries.

Objective

To describe the characteristics and short-term outcomes of very low birth weight (VLBW) infants with IVH who required respiratory support in a tertiary neonatal unit with resource limitations.

Methods

This was a matched retrospective observational study. The population included VLBW infants with IVH, who received positive pressure respiratory support between January 2014 and December 2016. Outcomes of infants with severe IVH was compared to those with mild IVH. Outcomes were further analysed according to mode of ventilation.

Results

150 infants were included in the study, 56 (37%) received continuous positive airway pressure (CPAP) only and 94 (63%) mechanical ventilation. Severe IVH was associated with surfactant therapy across both ventilation groups (p=0.03). Oxygen requirement at 28 days was more frequent in infants with severe IVH compared to mild IVH (79% vs 38%, p=0.01) (OR 6.11 (95% CI 1.19-31.34), p=0.03). Severe IVH and the presence of coagulopathy were the strongest predictors of death in both ventilation groups (p <0.0001). Pulmonary haemorrhage was the commonest cause of death in those with severe IVH and blood culture confirmed sepsis in those with mild IVH. Periventricular leukomalacia (PVL) was associated with severe IVH in those receiving invasive ventilation (OR 6.67 (95% CI 1.11-40.17)).

Conclusion

Mechanical ventilation, coagulopathy and pulmonary haemorrhage were strongly associated with death in VLBW infants with severe IVH in a resource-limited setting. These prognostic factors may have a role in end of life decisions.

INTRODUCTION

Intraventricular haemorrhage (IVH) is a frequent complication in preterm infants.[1,2] Severe IVH (characterized as grade III and grade IV) is associated with a high incidence of mortality, significant morbidities and long-term neurological impairment.[3] The rate of IVH increases with decreasing gestational age, with prematurity being the most important risk factor as evidenced by multiple studies.[1,2,4]

Respiratory support as a risk factor for IVH has shown conflicting reports. Randomised controlled trials have showed that the use of prophylactic continuous positive airway pressure (CPAP) in preterm infants at birth does not demonstrate a significant difference in the incidence of IVH compared to low flow nasal cannula/oxyhood[5,6] or mechanical ventilation at birth.[7-9] However, observational research suggests that mechanical ventilation is associated with an increase in IVH, with early and prolonged ventilation being important determinants for severe IVH.[10]

Respiratory support is frequently required in preterm infants.[11] Published literature on the subject is mainly from resource rich settings, limiting the applicability in middle income and developing countries where a high burden of preterm births exists.[12] These settings would benefit from studies in similar resource contexts and assist with appropriate application of distributive justice.

OBJECTIVES

To describe the occurrence of IVH and short-term outcomes in very low birth weight (VLBW) infants receiving positive pressure respiratory support in a single tertiary centre in a middle income African country.

METHODS

This was a matched retrospective observational study. Groote Schuur Hospital (GSH) has an incidence of approximately 500 VLBW infants born per annum. The source population included VLBW neonates with IVH, requiring either CPAP (non-invasive) or mechanical ventilation (invasive) admitted to GSH between January 2014 and December 2016. Neonates with major congenital abnormalities or other severe comorbidities, such as congenital syphilis or congenital cytomegalovirus infection, were excluded from the study. From the eligible infants all those with a diagnosis of severe IVH were chosen as cases. The remaining infants, all comprising of mild IVH (Grade 1 and 2), were allocated as comparative controls. Controls were individually matched to each case (1:1) within the following strata: (1) Birth weight category (750 g or less; >750 g to 1000 g; >1000 g to 1250 g; or >1250 g), (2) Type of respiratory support (non-invasive versus invasive) and (3) year of birth. The matching process therefore yielded two groups for comparison: (A) all infants with severe IVH and (B) matched infants with mild IVH.

Data Collection

Since mid-2013 details of all VLBW infants admitted to GSH have been retrospectively entered into the Vermont Oxford Network (VON) database. The database consists of clinical details from birth until discharge/death and was utilised as a source for patient characteristics and outcomes. Data were extracted from patients' folders for additional information not available from the database.

Clinical care in the neonatal unit

Clinical decision making for VLBW infants was guided by evidence based standardized protocols, in keeping with the resource limited setting of this study.

Mechanical ventilation was considered for infants with a birth weight of ≥ 800 g. Those with severe IVH were ineligible for starting mechanical ventilation. Surfactant use was limited to those on CPAP or mechanical ventilation with persistent fraction of inspired oxygen (FiO2) requirements above 30%. Cranial sonography was performed on all VLBW infants before day 3 of life, again at age 3-5 weeks and at discharge or corrected term gestation (depending on which came first). Scan frequency would be increased according to clinical condition. Cranial ultrasounds are done by medical staff trained in this skill and reviewed by certified neonatologists.

Analytic Approach

Descriptive statistics were used to summarize all relevant characteristics, using standard comparative methods. Data were analyzed for the full cohort and within strata of ventilation strategy, using Stata 14.0 (Statacorp, College Station TX).

Potential risk factors for the outcomes of severe compared to mild IVH were evaluated, using a case-control approach. Data were analysed using crude and adjusted conditional logistic regression, controlling for matched pairs.

Outcomes following IVH were evaluated using a matched cohort approach with severe IVH being the main exposure. Survival analysis was used to assess risk of mortality, overall and within strata of (1) ventilation strategy and (2) eligibility for treatment escalation. Exposure time (expressed as child-years) was measured from birth to death/ discharge from the neonatal unit. Between-group comparisons were made using Kaplan-Meier curves (log-rank test), incidence rate ratios and Cox proportional hazards regression (robust standard errors to account for clustering; proportional hazards assumption checked with Schoenfeld residuals). Morbidity outcomes were compared between severe and mild IVH using logistic regression (robust standard errors).

We estimated that a sample size of 150 (1:1) would have 80% power to detect a 1.6-fold or greater mortality hazard ratio among severe versus mild IVH (α=0.05, two-sided).

Ethical Considerations

Data collection was done by the primary author and all records were kept anonymous. Patients' records on the VON database are structured on number allocations ensuring confidentiality. Furthermore, the database is password protected and only accessible to designated users involved in data capturing.

The study was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town. (HREC REF: 725/2017)

RESULTS

Study Demographics

The study population comprised 150 infants (75:75, severe versus mild IVH), of whom 56 (37%) received non-invasive and 94 (63%), invasive ventilation.

Maternal and Infant Characteristics

The median/interquartile range (IQR) gestation at birth was 28 (27-29) weeks. In the non-invasive ventilation group 28 (50%) of the infants were not considered eligible for escalation based on gestation and birth weight, Table 1. Infants who received non-invasive ventilation had a lower mean birth weight (880 g versus 1081 g, p<0.0001) and lower median gestation at birth (27.9 vs 28.6 weeks, p=0.001) compared to infants who received invasive ventilation.

A greater proportion of infants with severe (compared to mild) IVH received surfactant therapy during their admission (81% vs 61%, p=0.007). This result extended across both ventilation groups (p=0.03). Other study population characteristics are shown by ventilation strategy, in Table 1.

Predictors for severe IVH included gestation at birth (per week increase, OR 0.79 (95% 0.61-1.03), p=0.08), antenatal steroid use (versus none, OR 0.60 (95% CI 0.32-1.14), p=0.12) and, after adjusting for the above, coagulopathy (versus none, aOR 2.36 (95% CI 0.82-6.81), p=0.11). The strength of these associations differed within strata of ventilation strategy but precision was limited. After adjustment, the strongest predictor for severe IVH was antenatal steroid use among non-invasively ventilated patients; and coagulopathy among invasively ventilated patients.

Outcomes

Overall, 61 (41%) of 150 infants died (table 2). Severe IVH was associated with substantially increased mortality risk. Figure 1 demonstrates this association within the non-invasive ventilation (IRR 5.88, 95% CI 1.85-24.53) and invasive ventilation (IRR 3.96, 95% CI 2.00-8.26) strata. These results were further reflected in crude and adjusted Cox regression models (Table 3). After adjusting for antenatal steroid use, birth weight, coagulopathy and ventilation type, the relative hazard for death comparing severe to mild IVH was 4.32 (95% CI 1.99-9.37, p<0.0001) in non-invasive ventilation and 2.82 (1.47-5.40, p=0.002) in invasive ventilation.

In the sub-group of infants not for mechanical ventilation, 11/22 (50%) died: 9/12 (75%) infants with severe IVH compared to 2/10 (20%) infants with mild IVH, with an IRR 9.74 (95% CI 2.02-92.64), as shown in supplemental table 1. Mortality rates and IRR for severe versus mild IVH for the sub-group of infants who were eligible for mechanical ventilation are summarised in Supplemental Table 2.

Overall, the age of death was lower among infants with severe IVH than mild IVH; 68% (30/44) of deaths in the severe IVH group demised within the first seven days. Similar associations were seen in strata of ventilation strategy (table 2). However, none of these results were significant.

Although severity of IVH and presence of coagulopathy during admission were consistently the strongest predictors of death (table 3), the effects of birth weight, resuscitation at birth and sepsis varied. The protective effects of increasing birth weight were most evident in the non-invasive ventilation group (aHR 0.64 (95% CI 0.45-0.91), p=0.01). CPR was protective against death in the invasive ventilation group (aHR 0.44 (95% CI 0.20-0.98), p=0.04). Sepsis was a significant risk factor for mortality in the non-invasive ventilation group (HR 4.55 (95% CI 2.25-9.23), p<0.0001).

The commonest primary cause of death overall was blood culture confirmed sepsis (22/61, 36%). This was followed by pulmonary haemorrhage (16/61, 26%), hyaline membrane disease (11/61, 18%), necrotizing enterocolitis (6/61, 10%), extreme prematurity (5/61, 8%) and severe hypoxic ischaemic encephalopathy (1/61, 2%). Pulmonary haemorrhage was the commonest cause of death in those with severe IVH and blood culture confirmed sepsis in those with mild IVH.

Necrotizing enterocolitis (NEC) developed in 16/150 (11%) patients overall. Patients with severe IVH and NEC were more likely to have an early death (less than 7 days) close to the time of diagnosis of NEC. Mild IVH with NEC was less likely to demise from this.

Morbidity is presented in Table 2. Median length of hospital stay was 62 days (IQR 50-76) among survivors overall, with no significant difference by IVH severity. This differed compared to time to death/discharge which was considerably shorter in infants with severe IVH in each ventilation group.

Periventricular leukomalacia (PVL) was associated with severe IVH in invasive ventilation (OR 6.67 (95% CI 1.11-40.17)) in infants who survived through to discharge. Post haemorrhagic hydrocephalus (PHH) was not specifically associated with severe or mild IVH. Data for ROP were only consistently available for 2016, with one case of clinically significant ROP recorded (non-invasive ventilated infant with mild IVH). Among survivors, a higher proportion of infants with severe IVH had prolonged oxygen requirements at 28 days (79% vs 38%, p=0.01) (OR 6.11 (95% CI 1.19-31.34), p=0.03) than those with mild IVH.

DISCUSSION

Preterm birth represents a significant burden in low and middle income countries.[12] The study highlighted the role of mechanical ventilation and severe IVH as predictors of mortality. Coagulopathy and pulmonary haemorrhage were important contributors to this group.

Severely premature infants receive restricted care based on a standardised protocol, in order to maintain distributive justice in our setting. The majority of infants received invasive ventilation due to reasons other than extreme prematurity. This explains the association between a lower mean birth weight and gestation with non-invasive ventilation in our study. It also explains why prematurity is an uncommon primary cause of death in the invasive ventilation group.

The restriction of invasive ventilation to more mature infants may have influenced certain predictors of mortality. Infants receiving invasive ventilation were not protected by an increasing birth weight due to resource limitations.[1] In addition, the poor outcomes associated with CPR in preterm infants births was not demonstrated.[13] This protective effect of CPR in the invasive ventilation group could be explained by the fact that extremely preterm infants may not have been offered CPR at birth; hence CPR was associated with the provision of invasive ventilation.

Expectedly, overall mortality showed a significant association with severe IVH with no difference across ventilation groups.[14] Aly *et al.*[10] found mechanical ventilation to be an important predictor of severe IVH. Our study demonstrated that mechanical ventilation and severe IVH (when analysed in the subgroup of infants eligible for escalation) was an important predictor of mortality with higher mortality rates per child years and IRR compared to non-invasive ventilation.

In patients receiving invasive ventilation with severe IVH, pulmonary haemorrhage was the commonest cause of death, with nine out of eleven instances having associated coagulation abnormalities. Coagulopathy was shown to be a poor prognostic factor for mortality overall and within ventilation categories. This highlights a vulnerable group in our neonatal unit which may benefit from closer monitoring and ICU admission. Current studies suggest that coagulopathy screening and correction benefit only a small population of extreme premature infants.[15,16]

There was a higher incidence of NEC in mild IVH with the majority surviving, while those with severe IVH had a lower incidence of NEC but higher mortality. This can be explained by the shorter lifespan and increased mortality rates in infants with severe IVH. Despite the temporal relationship between NEC and death, our study did not find it to be predictor of mortality. In other studies NEC has not been recognized as an independent risk factor for IVH.[3]

Premature infants who survived to discharge had similar lengths of stay in both the invasive and non-invasive ventilation groups. Oxygen requirement at 28 days of life was more common in infants who received non-invasive ventilation and had severe IVH than those who received non-invasive ventilation with mild IVH. This is likely due to the lower birth weight and gestational age of infants in this group and their associated comorbidities. However, there was no difference in bronchopulmonary dysplasia (assessed at 36 weeks corrected gestational age) in either ventilation group in infants with severe or mild IVH.

PHH and PVL are known complications of IVH.[17] This could not be demonstrated in our study due to the low numbers with this diagnosis.

Incomplete ROP records could not allow for accurate analysis. Current evidence does not show an association between severity of IVH and ROP.[18]

Prophylactic surfactant compared to selective surfactant, in patients with routine CPAP, has been researched. The SUPPORT study showed a reduction in severe IVH in patients who have received prophylactic surfactant but was not significant.[9] A 2012 Cochrane review demonstrated an overall marginal decrease in IVH in patients receiving prophylactic surfactant, with or without routine CPAP.[19]

Our results reflect the neonatal policy at GSH where surfactant is administered as rescue therapy only. Unstable infants are more likely to receive surfactant which may explain the high rate of severe IVH and mortality in this group. The timing of surfactant was not recorded in relation to the timing of the bleed, so infants may have developed IVH prior to surfactant administration. Further studies on surfactant rescue therapy in resource-limited settings are needed.

Study limitations and strengths

The study was limited by its retrospective design, which may increase the risk of bias. The use of matched controls resulted in exclusion of some data; the smaller sample size resulted in imprecision for some estimates. The effects of mechanical ventilation on severe IVH could not be determined for extremely preterm infants because these infants were not offered invasive ventilation. Limited data on ROP precluded analysis for this critical outcome. Finally, the study was completed in a single tertiary neonatal population, which may limit generalizability. However, a major strength of the study is its "real world" setting, which provides greater generalizability than data from clinical trials.

CONCLUSION

Our study demonstrated that mechanical ventilation and severe IVH were important predictors of mortality. The commonest cause of death in severe IVH was pulmonary haemorrhage with an associated coagulopathy in this group. This provides a useful clinical adjunct when determining prognostication and counselling of these patients.

Infants receiving surfactant had a high rate of severe IVH. The high incidence was attributed to their instability qualifying them for surfactant therapy. Future studies can focus on the relationship between severe IVH and respiratory support, following the administration of surfactant.

Understanding outcomes of preterm infants in low and middle income settings may be improved by the development and maintenance of quality improvement databases in order to facilitate patient management protocols and research in this context.

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TABLES AND FIGURES

Table 1: Characteristics of study population by ventilation strategy

	Total (n=150)	**Non-invasive ventilation (N=56)**			**Invasive ventilation (N=94)**		
		Severe IVH (n=28)	**Mild IVH (n=28)**	***p***	**Severe IVH (n=47)**	**Mild IVH (n=47)**	***p***
Maternal characteristics							
Chorio-amnionitis	5 (3%)	1 (4%)	1 (4%)	1.00	2 (4%)	1 (2%)	0.56
Antenatal steroids	66 (44%)	12 (43%)	19 (68%)	0.06	16 (34%)	19 (40%)	0.52
Hypertension							
No maternal hypertension	112 (75%)	20 (71%)	20 (71%)	1.00	40 (85%)	32 (68%)	0.05
Maternal hypertension	38 (25%)	8 (29%)	8 (29%)		7 (15%)	15 (32%)	
Birth characteristics							
Delivery mode							
Vaginal	83 (55%)	16 (57%)	17 (61%)	0.79	28 (60%)	22 (47%)	0.21
Caesarian section	67 (45%)	12 (43%)	11 (39%)		19 (40%)	25 (53%)	
APGAR score 5 minutes	7 (6-9)	8 (6-9)	8 (7-9)	0.48	7 (6-9)	7 (5-8)	0.84
Required CPR at birth	32 (21%)	5 (18%)	3 (11%)	0.44	12 (26%)	12 (26%)	1.00
Hypothermia (<36.5°C) within 1st hour of birth	116 (77%)	23 (82%)	22 (79%)	0.74	34 (72%)	37 (79%)	0.47
Male sex	83 (55%)	11 (39%)	14 (50%)	0.42	33 (70%)	25 (53%)	0.09

	Total (n=150)	Non-invasive ventilation (N=56)			Invasive ventilation (N=94)		
		Severe IVH (n=28)	**Mild IVH (n=28)**	***p***	**Severe IVH (n=47)**	**Mild IVH (n=47)**	***p***
Gestation (weeks)	28 (27-29)	27 (27-29)	28 (27-29)	0.14	28 (27-29)	29 (28-30)	0.22
< 27 weeks	17 (11%)	6 (21%)	6 (21%)	1.00	2 (4%)	3 (6%)	0.65
Birth weight (grams)	1007 (182)	882 (151)	880 (160)	0.96	1078 (158)	1085 (153)	0.82
< 800g	16 (11%)	8 (29%)	8 (29%)	1.00	0	0	n/a
Admission characteristics							
Timing of ventilation							
Early (< 48 hours of life)	129 (86%)	27 (96%)	28 (100%)	0.31	39 (83%)	35 (74%)	0.31
Late	21 (14%)	1 (4%)	0		8 (17%)	12 (26%)	
Ever received surfactant	107 (71%)	16 (57%)	8 (29%)	0.03	45 (96%)	38 (81%)	0.03
Age at IVH diagnosis (days)	4 (2-7)	4 (3-7)	7 (3-13)	0.04	3 (2-5)	4 (2-8)	0.36
Any sepsis during admission	17 (11%)	3 (11%)	0	0.07	4 (9%)	10 (21%)	0.08
Coagulopathy	21 (14%)	1 (4%)	1 (4%)	1.00	12 (26%)	7 (15%)	0.20
Necrotizing enterocolitis (NEC)	16 (11%)	2 (7%)	3 (11%)	0.64	2 (4%)	9 (19%)	0.02
Age at NEC diagnosis (days)	6 (5-21)	3 (1-6)	6 (4-11)	0.37	4 (4-4)	15 (6-30)	0.03

Numbers are n (column %) except where otherwise indicated; or median (interquartile range, IQR) for non-normally distributed and mean (standard deviation, SD) for normally distributed variables. Comparisons (p-values) from Chi2 for categorical, Kruskal-Wallis for non-normally distributed and t-tests for normally distributed continuous variables

Abbreviations: IVH, intraventricular haemorrhage; CPR, cardiopulmonary resuscitation

Table 2: Outcomes of study population by ventilation strategy

	Total (n=150)	Non-invasive ventilation (N=56)			Invasive ventilation (N=94)		
		Severe IVH (n=28)	Mild IVH (n=28)	*p*	Severe IVH (n=47)	Mild IVH (n=47)	*p*
Outcomes							
Time to death or discharge (overall days in hospital)	48 (6-69)	38 (7-61)	63 (46-78)	0.002	7 (4-57)	48 (24-73)	0.002
Combined >27 weeks and > 800 g	128 (85%)	16 (57%)	18 (64%)	0.58	47 (100%)	47 (100%)	n/a
Deaths	61 (41%)	14 (50%)	4 (14%)	0.004	30 (64%)	13 (28%)	<0.0001
Died, >27 weeks and >800 g	50/128 (39%)	5/16 (31%)	2/18 (11%)	0.15	30/47 (64%)	13/47 (28%)	<0.0001
Age at death (days)	5 (3-15)	7 (3-15)	16 (9-17)	0.31	4 (3-7)	5 (4-19)	0.28
Early death (≤7 days)	38/61 (62%)	7/14 (50%)	1/4 (25%)	0.38	23/30 (77%)	7/13 (54%)	0.14
Survived through to discharge	89 (59%)	14 (50%)	24 (86%)	0.004	17 (36%)	34 (72%)	<0.0001
Length of hospital stay (days)	62 (50-76)	61 (56-64)	70 (55-78)	0.30	59 (50-75)	63 (48-76)	0.75
PVL	8/89 (9%)	1/14 (7%)	0	0.19	5/17 (29%)	2/34 (6%)	0.02
PHH	3/89 (3%)	1/14 (7%)	1/24 (4%)	0.69	1/17 (6%)	0	0.15
Clinically significant ROP*	1/89 (1%)	0	0	n/a	0	1/34 (3%)	0.48
Oxygen dependent at 28	45/85 (53%)	11/14 (79%)	9/24 (38%)	0.01	9/15 (60%)	16/32 (50%)	0.52

	Total (n=150)	Non-invasive ventilation (N=56)			Invasive ventilation (N=94)		
		Severe IVH (n=28)	Mild IVH (n=28)	*p*	Severe IVH (n=47)	Mild IVH (n=47)	*p*
days of age†							
Oxygen dependent at 36 weeks of age‡	10/73 (14%)	0/10	2/22 (9%)	0.32	4/13 (31%)	4/28 (14%)	0.22
Combined end-point: death and/or disability§	110 (73%)	25 (89%)	13 (46%)	0.001	41 (87%)	31 (66%)	0.01

Numbers are n (column %) except where otherwise indicated; or median (interquartile range, IQR) for non-normally distributed and mean (standard deviation, SD) for normally distributed variables. Comparisons (p-values) from Chi2 for categorical, Kruskal-Wallis for non-normally distributed and t-tests for normally distributed continuous variables

Abbreviations: PVL, peri-ventricular leukomalacia; PHH, post-haemorrhagic hydrocephalus; ROP, retinopathy of prematurity

*Defined as Grade 3 or greater

†among those alive and in hospital at 28 days (total N=90; non-invasive, n=39; invasive, n=51)

‡among those alive and in hospital at 36 weeks' corrected gestation (total N=76; non-invasive, n=32; invasive, n=44)

§Defined as death and/or at least one of PVL, PHH, ROP, chronic oxygen requirements

Table 3: Adjusted hazard ratios for mortality, comparing severe to mild intraventricular haemorrhage: stratified by ventilation strategy

	Non-invasive ventilation (n=56)				Invasive ventilation (n=94)			
	HR (95% CI)	*p*	aHR (95% CI)	*p*	HR (95% CI)	*P*	aHR (95% CI)	*p*
Severe vs. mild IVH	4.58 (1.73-12.14)	0.002	4.32 (1.99-9.37)	<0.0001	3.14 (1.67-5.88)	<0.0001	2.82 (1.47-5.40)	0.002
Antenatal steroids	0.48 (0.21-1.08)	0.08	0.71 (0.27-1.85)	0.49	0.76 (0.43-1.35)	0.35	0.70 (0.35-1.39)	0.31
Required CPR at birth	2.42 (0.72-8.10)	0.15	-	-	0.40 (0.18-0.92)	0.03	0.44 (0.20-0.98)	0.04
Birth weight (per 100 g increment)	0.65 (0.51-0.83)	0.001	0.64 (0.45-0.91)	0.01	0.87 (0.73-1.03)	0.12	0.88 (0.74-1.04)	0.14
Sepsis during admission	4.55 (2.25-9.23)	<0.0001	1.37 (0.37-5.06)	0.64	0.96 (0.50-1.83)	0.89	-	-
Coagulopathy during admission	11.29 (4.70-27.11)	<0.0001	14.68 (3.68-58.46)	<0.0001	2.95 (1.79-4.86)	<0.0001	2.51 (1.46-4.31)	0.001

Abbreviations: aHR, adjusted hazards ratio; CI, confidence interval; IVH, intraventricular haemorrhage; CPR, cardio-pulmonary resuscitation; NEC, necrotizing enterocolitis

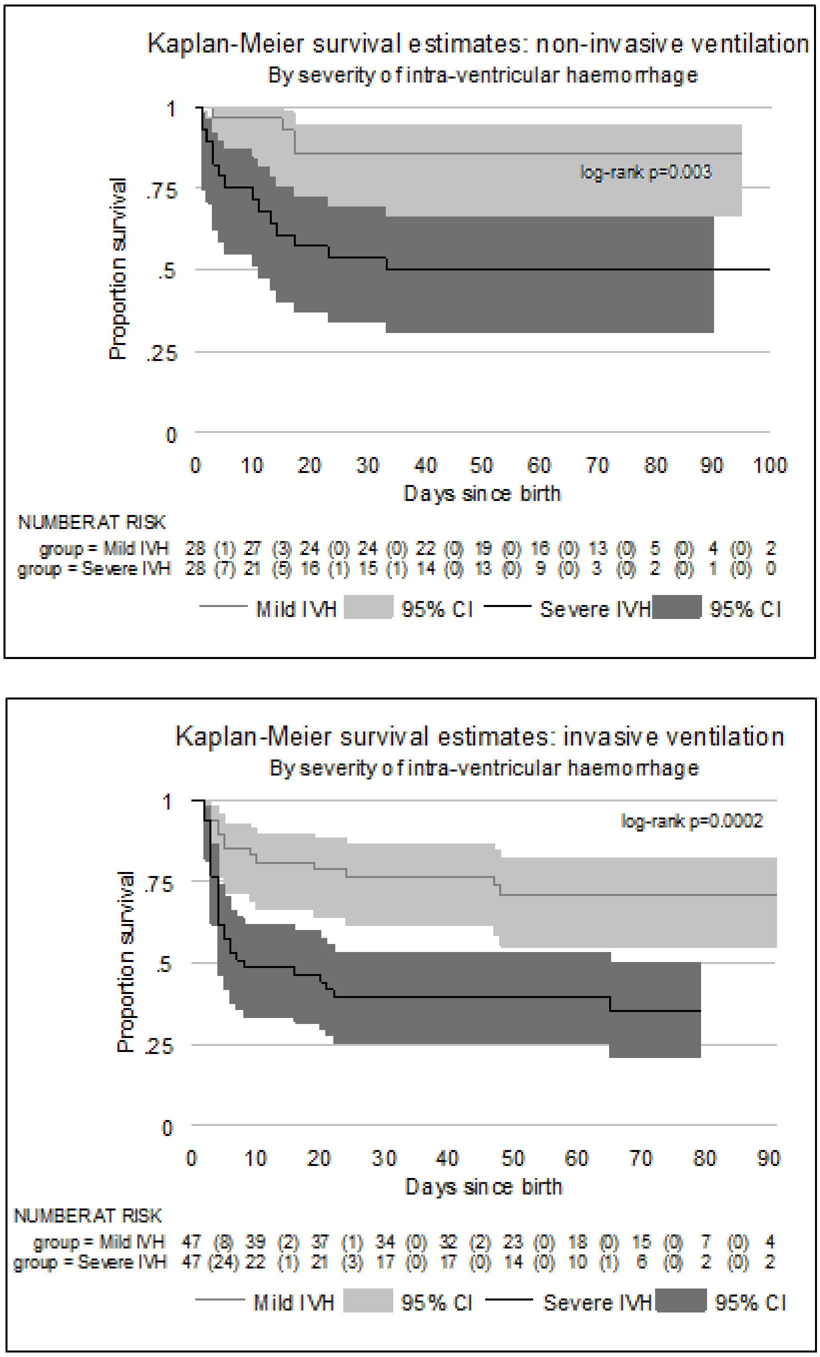
SUPPLEMENTAL TABLE 1: Mortality rates and rate ratios comparing severe to mild intraventricular haemorrhage

	≥800 g and ≥27 weeks' gestation		**<800 g and/or <27 weeks' gestation**	
	Severe IVH	Mild IVH	Severe IVH	Mild IVH
Mortality rate per child-year (95% CI)	6.21/cy (4.46-8.64)	1.63/cy (0.98-2.71)	10.40/cy (5.41-20.00)	1.07/cy (0.27-4.27)
Incidence rate ratio (95% CI)	***3.80 (2.02-7.49)***		***9.74 (2.02-92.64)***	

SUPPLEMENTAL TABLE 2: Mortality rates and rate ratios among infants ≥800 g and ≥27 weeks' gestation: comparing severe to mild intraventricular haemorrhage

	Non-invasive ventilation		**Invasive ventilation**	
	Severe IVH	Mild IVH	Severe IVH	Mild IVH
Mortality rate per child-year (95% CI)	2.61/cy (1.09-6.27)	0.71/cy (0.18-2.85)	8.06/cy (5.63-11.52)	2.04/cy (1.18-3.51)
Incidence rate ratio (95% CI)	***3.65(0.60-38.37)***		***3.96 (2.00-8.26)***	

Figure 1: Kaplan-Meier survival curves of infants with severe compared to mild intra-ventricular haemorrhage by ventilation strategy



APPENDICES

ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
HEALTH SCIENCES FACULTY

FHS017: Annual Progress Report/Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

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	30.04.2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	13/5/2020

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

- Currently completing write-up of research paper, should not be impacted by lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	06/05/2020		
HREC REF Number	725/2017	Current Ethics Approval was granted until	30/04/2020
Protocol title	Outcomes and Risk Factors of Very Low Birth Weight Infants with Intraventricular Haemorrhage who received Respiratory Support in a Middle Income Country Neonatal Unit		
Principal Investigator	Dr. Yaseen Joolay		
Department / Office Internal Mail Address	yaseen.joolay@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☑ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☑	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	N/A
Total number of records or specimens collected, reviewed or stored since last progress report	N/A

25 March 2020 Page 1 of 4 FHS011

Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature signature removed to avoid exposure online

Signature of PI		Date	06 May 2020

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