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Early mean systemic blood pressure as a risk factor in neurodevelopmental outcome of ELBW preterm infants

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Early Mean Systemic Blood Pressure as a Risk Factor in Neurodevelopmental Outcome of ELBW Preterm Infants

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Ethics Approval: M090808

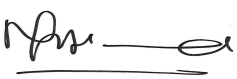
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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Child Health (Neurodevelopmental Option).

Candidates Declaration:

I, Richard John Alexander declare that this research report is my own work. It is being submitted for the degree of Master of Science, in Neurodevelopment 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 this the 3rd day of October, 2010.

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Abstract:

Background:

ELBW preterm infants are at extremely high risk for adverse neurodevelopmental (ND) outcome. Systemic hypotension is an important peri-natal risk factor in neurodevelopmental outcome. Numerous other risk factors exist for adverse neurodevelopmental outcome.

Aim:

To assess whether early mean systemic blood pressure and other risk factors contribute to poor ND outcome in ELBW preterm infants managed at Panorama Medi-Clinic.

Methods:

A retrospective, analytical study using data obtained from 2003 to 2008. Data from the Vermont Oxford Network database of which Panorama Medi-Clinic is a member was used to select a cohort of inborn, surviving infants weighing ≤ 1000g or ≤ 30 weeks gestational age. Early mean systemic BP records were obtained from nursing records. ND data was obtained from the neurodevelopmental clinic or routine follow up clinics notes. Infants with major defects at birth were excluded. The cohort was classified according to their general developmental quotient and whether or not they had signs of cerebral palsy into a normal or abnormal neurodevelopmental group. All patients remained completely anonymous and ethical clearance was obtained from the ethics committee at Panorama Medi-Clinic.

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Results:

82 infants were eligible. 78 were entered the study. 4 were lost to follow up. Average birth weight was 782.1g ± 148.23. Average gestational age was 27.06w ± 1.32. Normal neurodevelopmental outcome was found in 64(82%). An abnormal neurodevelopmental outcome was found in 14(18%).

No statistically significant difference was found by logistical regression when mean systemic blood was compared between normal and abnormal neurodevelopmental groups.

If a cut off BP of <30 mm Hg, or inotropic agents were administered, no statistical difference was found between the normal and abnormal groups.

Severe grades of IVH, ROP, post-natal steroids, and chronic lung disease, and gastro-intestinal perforation, were identified as risk factor of adverse outcome.

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Conclusion:

Early mean systemic blood pressure could not be identified as a risk factor in neurodevelopmental outcome, nor could we show that a cut off in mean systemic blood pressure < 30 mmHg (our definition of systemic hypotension) is associated with adverse neurodevelopmental outcome.

Inotropic usage to improve early mean systolic blood pressure is not associated with adverse neurodevelopmental outcome.

We confirmed that, severe grades of IVH and ROP, postnatal steroids, chronic lung disease, and gastrointestinal perforation are important risk factors for adverse neurodevelopmental outcome.

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Abbreviations Key:

NICU= Neonatal intensive care unit

VON= Vermont Oxford Network

ELBW= Extremely Low Birth weight

CLD= Chronic Lung Disease

CP= Cerebral palsy

MDI= Mean developmental Index

PDA= Patent ductus arteriosus

NEC= Necrotizing enterocolitis

IVH= Intraventricular Haemorrhage

ROP= Retinopathy of Prematurity

PVL=Periventricular leucomalacia

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1. Introduction:

Over the last two decades the survival of extremely low birth weight infants has been steadily increasing due to improved neonatal intensive care[1,2]. However, morbidity free survival, has not kept pace with the improved survival of the ELBW preterm infant. Morbidity in these ELBW premature infants often involves neurodevelopmental disabilities which may be present despite normal brain ultrasounds[3]. The classical lesions seen in the very premature infant occur in the white matter at vascular border zones where the poorly developed ventriculo-pedal and ventriculo-fugal arteries feed deep white matter. Other more subtle damage, as well as damage to the deep grey matter particularly the thalami, is now being described due to modern MRI imaging and PET scanning techniques as well as neuropathological studies[4,5,6]. Hypotension is present in up to 45% of ELBW infants and its incidence is inversely proportional to the gestational age of the infant[7]. Poor cerebral perfusion due to hypotension aggravated by an inability to auto-regulate and maintain adequate cerebral perfusion, as well as inflammation of the white matter due to chorioamnionitis, ultimately results in damage of the white and grey matter[4,8,9].

Khwaja and Volpe eloquently explain how hypoxia and ischaemia together with inflammation result in microglial cell activation and ultimately oligodendrocyte death due to cytokine, oxidative free radical (ROS), free nitrogen species (RNS) and glutamate release[10]. See Fig. 1 below

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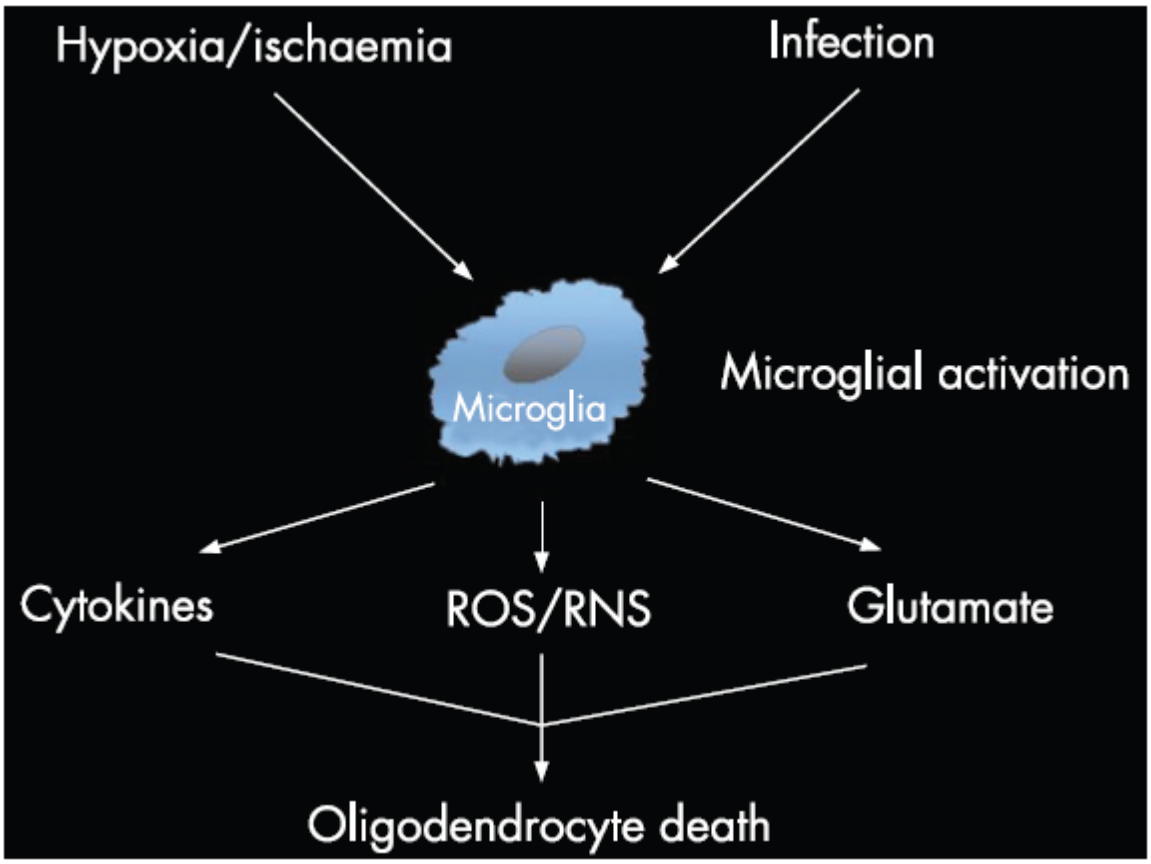


Figure 1. Pathogenesis of cerebral white matter injury of prematurity

(Khwaja O, Volpe JJ: ***Pathogenesis of Cerebral White matter Injury of Prematurity***. Arch Dis Child Fetal Neonatal Ed. 2008 Mar;93(2):F153-61 Review, Figure 3, page F155, *Microglia as a convergence point for upstream and downstream mechanisms in pathogensis*)[10]

The perfusion of the very immature infant`s brain, particularly the watershed areas described above, has been thought to be pressure dependent and therefore dependent on systemic blood pressure for adequate perfusion of the deep white and grey matter. Unfortunately, scientifically proven normal values

for early systemic mean blood pressures do not exist for this group of preterm infants as most of these infants are not born healthy and most require ventilatory and other intensive care support in order for them to survive. Clinicians therefore have to rely on unsubstantiated normal values such as a mean systemic blood pressure equivalent to the gestational age of the infant and other assumed values to evaluate normal systemic blood pressure. Values derived using the gestational age and mean blood pressure are the most commonly cited in various articles and have no research proven validity. They also do not take into account whether other vital organs are being adequately perfused or not, and are at best simplistic. It is up to the clinician to make correct judgments regarding the latter and to assess other parameters of the infant's wellbeing which might maintain or improve cerebral blood flow and therefore limit prolonged hypoperfusion and prevent white matter ischaemia and damage.

Systemic mean blood pressure, or hypotension, might therefore be an important risk factor (by no means the only one) in the neurodevelopmental outcome of extremely low birth weight infants.

This study investigates the early mean blood pressure of a group of ELBW preterm infants as a possible risk factor in early neurodevelopmental outcome. In our NICU we aim at maintaining the early mean systemic blood pressure above 30mmHg and do not accept the definition of hypotension as being a mean BP below the gestational age of the infant. Hence we define hypotension as a mean systemic arterial blood pressure less than 30mmHg.

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2. Literature Review:

Improved neonatal care of extremely low birth weight (ELBW) preterm infants over the last two decades has resulted in vastly improved survival of ELBW infants. Despite improved survival, numerous studies have shown that many of these survivors are left with major long term developmental deficits[1,2].

Poor neurodevelopmental outcome has been proven to be associated with a number of peri- and post-natal risk factors[11]. Laptook A.R. et al showed that nearly 30% of ELBW infants with a normal head ultrasound (HUS) either had CP or a low MDI[3].

It was suggested that risk factors associated with this high rate of adverse outcomes include pneumothorax, prolonged exposure to mechanical ventilation, and educational and economic disadvantage. Many questions remain with regards to other risk factors that possibly underlie abnormal neurodevelopmental outcome in ELBW preterm infants. Systemic hypotension has been shown to be associated with poor neurodevelopmental outcome in ELBW preterm infants[12].

The cerebral perfusion of the ELBW infant is extremely vulnerable to even minor systemic blood pressure changes because of immature auto-regulation[10,12]. ELBW preterm infants rely on perfusion pressure for cerebral perfusion as normal auto-regulation mechanisms for the maintenance of adequate cerebral perfusion, particularly watershed areas, has been shown to be inadequate when there is associated systemic hypotension[13,14]. Systemic

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hypotension and subsequent ischaemia of deep white matter, along with inflammation, has been shown to be one of the most important causes of white matter injury in ELBW infants[10,15]. Hence, the effect of systemic blood pressure levels / changes during the first 12 hours of life might be an important risk factor for the development of periventricular leucomalacia (PVL) as well as intraventricular haemorrhages as well as more subtle damage to the immature brain, ultimately leading to adverse neurodevelopmental outcome.

Another dilemma is the lack of normal systemic blood pressures values for ELBW preterm infants in the first hours to days of life and hence there is no clear definition of hypotension in the extremely low birth weight preterm infant[16]. Normal and more importantly adequate mean systemic blood pressure values have thus far not been firmly established in the scientific literature for these infants and still remains controversial. A common but unproven definition (rule of thumb) of normal blood pressure, assumed in many studies, is that the mean systemic blood pressure should not fall below the gestational age of the infant. Unfortunately, because there are no seminal scientific studies which define normal blood pressure in ELBW infants, we have to rely on extrapolations from studies done in more mature infants, which might be inappropriate in the setting of ELBW infants[17,18]. Our definition of hypotension is a mean systemic BP < 30mmHg and is independent of the gestational age of the infant.

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3.Null Hypothesis

3.1 Primary Hypothesis

Early Mean Systemic Arterial Blood pressure is not associated with poor Neurodevelopmental Outcome in Extremely Low Birth Weight Preterm Infants

3.2 Alternative Hypothesis

Early mean systemic arterial blood pressure is associated with poor Neurodevelopmental Outcome in Extremely Low Birth weight Preterm Infants

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4.Objectives:

4.1 Primary Objectives:

To determine the effect of mean systemic blood pressure during the first 12 hours of life birth on neurodevelopmental outcome of a cohort of ELBW preterm infants.

4.2 Secondary Objectives:

1. To report on the effect of early inotropic administration to support systemic blood pressure on the neurodevelopmental outcomes of ELBW preterm infants.
2. To report on the incidence and assess the statistical significance of the following risk factors in neurodevelopmental outcomes in ELBW preterm infants
   - 2.1 Severe IVH (grades 3 and 4)
   - 2.2 Periventricular Leucomalacia
   - 2.3 Severe ROP (Grades 3 and 4)
   - 2.4 CLD (Oxygen dependency at 36 weeks post conceptual age)
   - 2.5 NEC
   - 2.6 NEC requiring surgery
   - 2.7 Patent ductus arteriosus
   - 2.8 Pneumothorax
   - 2.9 Late onset sepsis
   - 2.10 Duration of oxygen dependency
   - 2.11 Length of Hospitalization

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5. Methods:

A cohort of extremely low birth weight and gestational age preterm infants treated at the Panorama Medi-Clinic Neonatal Intensive Care Unit were selected using the Vermont Oxford database. The NICU at Panorama Medi-Clinic is a member of the **Vermont Oxford Network Database (VON)**. The VON is a non-profit collaborative of health care professionals interested in promoting and improving the quality and safety of medical care of newborn infants and their families[19]. The Panorama Medi-Clinic submits all of its data into the VON database. The cohort used in this research report was selected from the VON Database.

6. Inclusion Criteria:

All infants' ≤1000g and ≤ 30 weeks gestation consecutively inborn at Panorama Medi-Clinic and admitted to the Panorama Medi-Clinic NICU were selected from the VON database from 2003 till 2008.

A cohort of 78 infants was studied.

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7. Exclusion Criteria:

The following patients were excluded:

1. Outborn infants- infants born at other hospitals and transferred to Panorama Medi-Clinic for further management.
2. Infants ≤1000g but > 30 weeks gestational age at delivery.
3. Patients with severe or fatal congenital abnormalities.
4. Patients who were completely lost to follow up.
5. Infants who died before discharge.
6. Patients in whom no clinical notes were available.

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8. Data Collection:

Information was retrieved retrospectively from neonatal charts, nursing records and the electronically compiled Vermont Oxford Network database.

Apart from the relevant demographic data for each of the cohort the following additional information was collected for each of the cohort:

1. **Mean systemic blood pressure** was obtained from nursing observation charts. All these readings were obtained from indwelling peripheral arterial cannulae or central umbilical arterial lines. The first recordings were noted once the infant`s line had been inserted in the NICU. The next recordings were made at 6 and 12 hours of age.

2. **Inotropic** use during the first 24 hours was obtained from Nursing records or clinical notes and included the use of Dopamine (Intropin®), Dobutamine (Dobutrex®) and adrenalin / epinephrine.

3. **Neurodevelopmental data** was obtained in the following manner:

   From the Neurodevelopmental Follow up clinic:

   An established high risk neurodevelopmental clinic exists at Panorama Medi-Clinic. High risk preterm infants are followed up a 4½ months, 8 months and 12 months, 18 months and 2 yrs corrected age. The follow up team consists of an experienced neurodevelopmental paediatrician, as well as an experienced neurodevelopmentally trained (NDT)

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Physiotherapist. The same paediatrician and physiotherapist were used in all the follow up visits at this clinic. During each follow up session a complete neurological examination was performed looking specifically for signs of cerebral palsy.

An **Infant Neuromotor Assessment** (INA) (up to 12months) was carried out on each patient under 1 year of age and any deviations from the norm noted[20].

A **Molteno Adapted Scale** assessment was performed at each visit up to 2 years of age. The Molteno Adapted Scale allows for a developmental quotient to be obtained for gross motor, fine motor, communication and personal-social categories. A general developmental quotient can then be derived for the specific patient by deriving the average of the 4 developmental quotients from the above 4 developmental domains assessed. This developmental screening tool has been shown in an MSc thesis submitted to the University of Witwatersrand by Dr. B. Laughton to have a close correlation with the Griffiths Mental Developmental Scales performed at 2 yrs of age[21].

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A **Griffiths Mental Development Scales** assessment was performed at approximately 24months corrected age by the same Neurodevelopmental Paediatrician. This is a formal standardized developmental screening tool and a developmental quotient is obtained for Gross motor, Fine Motor, Speech and Language, Personal-Social and Performance scales. A general developmental quotient is then derived for each patient as an average of the 5 developmental quotients in the 5 domains examined in the Griffiths Mental Developmental Scale.

Follow up Visits to Paediatrician – Developmental information was also reviewed in clinical records of patients who had not had any or only incomplete formal assessments, or where no formal assessments were performed.

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The survivors' Neurodevelopmental Outcome was then classified into the following categories:

Normal- If the patient has no clinical signs of cerebral palsy and general developmental quotient was ≥ 90.

Abnormal – If the patient had either a clinical diagnosis of cerebral palsy and/or

general developmental quotient of <90

9. Time Frame:

Inborn infants weighing ≤1000g and ≤30 weeks gestational age born from 1 January 2003 till 31 December 2008 were included in the study cohort.

10. Study Limitations:

This study has the following limitations:

Retrospective data and analysis has been used in this study

A relatively small sample size of infants has been used.

Blood pressure readings were only taken at 3 specific times after birth and not continuously, as this was not possible given the retrospective nature of the study

The study uses information over a relatively long period, namely 5 years, during which there might have been policy changes in the management of the cohort defined above. For example the delivery room resuscitation and early

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management of these infants with in/out surfactant and Nasal CPAP.

The neurodevelopmental follow up of these infants was assessed up until approximately two years of age. Many studies by a number of authors have cast doubt on the accuracy of follow up only until this age as more subtle deficits might become manifest only later in these survivors life[22].

Infants who died before discharge were excluded from the study cohort and might have had complications due to hypotension early in life.

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11. Statistical Analysis:

Characteristics, treatments and outcomes were compared between survivors with abnormal and/or suspected abnormal neurodevelopmental outcome and those surviving without any handicap by using univariate analysis. Continuous variables were compared with Student's t test, whereas dichotomous variables were assessed with the chi-square statistic with correction for multiple comparisons. Logistic regression adjusted for birth weight, gestational age, gender, antenatal steroid treatment, small for gestational age and severe IVH were used to test the relationship between neurodevelopmental outcome and hypotension and a separate logistic regression was used to test the effect modification by hypotension.

12. Human Subject Protection:

This Study uses retrospective data that has already been captured and no patient names and other identifying information will be published.

13. Funding:

This study was privately funded, including the statistical analysis.

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14. Results:

Demographic:

82 ELBW infants were found to be eligible for the study between 1 January 2003 and 31 December 2008.

Of these infants 4 infants were excluded because of insufficient data or loss to follow up. Data pertaining to the remaining 78(95.1%) infants was used for the study. See **table 1** below.

Table 1: Cohort Demographics:

Infants	**Numbers(%)**
Study Cohort	82(100)
Year	2003-2008
Lost to Follow Up	4(4.9)
Follow up N(%)	78(95.1)

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Table 2: Cohort Demographic and Risk Factor data pertaining to selected cohort:

DEMOGRAPHIC/ RISK FACTOR	Overall Value N(%)	Normal Neurodevelopmental Outcome N(%)	Abnormal Neurodevelopmental Outcome N(%)
Inborn	78(100)	64(82)	14(18)
Birth weight (g)± SD	782.1 ± 148.23	787.42 ± 142.39	757.86 ± 176.38
Gestational Age(w)± SD	27.06 ± 1.32	27.09 ± 1.28	26.92 ± 1.54
Sex (M:F)(M%)	31:47(40)	23:41(36)	8:6(57)
1' Apgar Score ± SD	5.94 ± 2.17	5.97 ± 2.16	5.79 ± 2.29
5' Apgar Score ± SD	8.03 ± 1.26	7.98 ± 1.33	8.21 ± 0.89
Antenatal Steroid	72(92.3)	60(93.8)	12(85.7)
Mode Delivery C/S	73(93.6)	61(95.3)	12(85.7)
Multiples	27(34.6)	23(35.9)	4(28.6)
Respiratory Distress Syndrome	78(100)	64(100)	14(100)

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Of the eligible 78 infants 64(82%) were found to have a normal neurodevelopmental outcome according to our definition, i.e., a General Quotient of ≥90 and no signs of any cerebral palsy. 14(18%) infants had abnormal developmental outcomes defined as either a General Developmental Quotient <90 and / or signs of cerebral palsy.

The mean gestational age was 27.06 weeks and there was no statistical significant difference between those with normal or abnormal neurodevelopment.

No statistically significant difference could be found between the sex distribution, Apgar scores at 1` or 5`, antenatal steroid usage, mode of delivery, or multiple pregnancy.

100% of the cohort in both normal and abnormal neurodevelopmental outcome groups developed respiratory distress, however not all required intubation and active ventilation.

In **Table 3** below, 18 different risk factors which were included as part of the secondary objectives were statistically analysed between the normal and abnormal neurodevelopmental outcome groups. No statistical significant difference was noted between the two groups for the following:

1. Pneumothorax,
2. Exogenous surfactant,
3. Patent ductus arteriosus (confirmed by echocardiography),
4. Indomethacin usage for PDA,
5. Surgical ligation of PDA,
6. Necrotizing enterocolitis,
7. Late onset sepsis,
8. Retinopathy of Prematurity, ROP (grade 1&2),
9. Intraventricular Haemorrhage, IVH(grade 1&2),

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10. Discharge weight,
11. Oxygen dependency on discharge and,
12. Length of stay in hospital.

Statistical significant differences ($p<0.05$) were found for the following:

1. Severe grades of Intraventricular Haemorrhage IVH(grade3&4),
2. Retinopathy of Prematurity, ROP(grade 3&4),
3. Postnatal steroid usage,
4. Chronic lung disease defined as oxygen dependency at 36 weeks post-conceptual age, as well as for,
5. Gastrointestinal perforation

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Table 3: Analysis of Various Risk factors for Normal and Abnormal Neurodevelopmental Outcome and Statistical Significance:

RISK FACTORS	Overall Value	Normal Neurodevelopmental outcome N(%)	Abnormal Neurodevelopmental outcome N(%) * p< 0.05
Pneumothorax	1(1.3)	0(0)	1(7.1)
Exogenous Surfactant	71(91.0)	58(90.6)	13(92.9)
PDA(Echo)	50(64.1)	39(60.9)	11(78.6)
Indomethacin	44(56.4)	33(51.6)	11(78.6)
PDA Ligation	3(3.8)	3(4.7)	0(0)
G-I perforation	2(2.6)	0(0)	2(14.3)*
NEC	3(3.8)	1(1.6)	2(14.3)
Late Onset Sepsis	18(23.1)	13(20.3)	5(35.7)
ROP(Grade1&2)	27(34.6)	21(32.8)	6(42.9)
ROP(grade3&4)	2(2.6)	0(0)	2(14.3)*
Post Natal Steroids	38(48.7)	27(42.2)	11(78.6)*
Oxygen at 36 weeks PCA	27(34.6)	18(28.1)	9(64.3)*
IVH(Grade 1&2)	10(12.8)	9(14.1)	1(7.1)
IVH(Grade 3&4)	1(1.3)	0(0)	1(7.1)*
PVL	2(2.6)	1(1.5)	1(7.1)
Discharge Weight(grams)	2266.85±551.14	2263.73±439.16	2281.07±929.68
Oxygen at Discharge	8(10.3)	6(9.4)	2(14.2)
Length of Stay(d)	86.22±39.60	87.80±41.32	95.71±31.02

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In **Table 4** below, the mean systemic BP was compared in the normal and abnormal neurodevelopmental groups at three intervals beginning with the first recorded BP in the NICU and subsequently at 6 and 12 hours postnatal age with a generalised linear regression model. No statistical significant difference was found between the two groups.

Table 4: Results of Normal versus Abnormal Neurodevelopment Where No Cut Off in Mean Systemic Blood Pressure Used:

Measurement **No Cut Off**	**Normal Neurodevelopment**	**Abnormal Neurodevelopment**	**p-value**
	Mean BP ± SD (mmHg)	**Mean BP ± SD (mmHg)**	**Significance**
1St Mean BP	30.33 ± 6.23	29.93 ± 7.17	NS
6 Hours	36.38 ± 6.33	37.50 ± 4.86	NS
12 Hours	36.00 ± 4.99	36.57 ± 6.68	NS

In **table 5** below, a comparison was performed between the normal and abnormal neurodevelopmental groups where the mean systemic blood pressure was less than 30 mmHg at the three periods defined above. No statistical difference could be found using a linear regression model between those with normal or abnormal neurodevelopmental outcomes.

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Table 5: Results of Statistical Comparison of Normal versus Abnormal Neurodevelopment where Cut Off Applied of Mean Systemic BP Below 30 mmHg:

Measurement Cut Off <30 mmHg	**Normal Neurodevelopmental Outcome**	**Abnormal Neurodevelopmental Outcome**	**p-Value**
	N(%)	**N(%)**	**Significance**
1St Mean BP	30(46.9)	7(50.0)	NS
6 Hours	6(9.4)	1(7.1)	NS
12 Hours	4(6.3)	1(7.1)	NS

Table 6: Statistical Comparison of Normal and Abnormal Neurodevelopmental Outcomes where Inotropic Support where used Within first 24 Hours life:

Risk Factor	**Normal Neurodevelopmental Outcome N=64**	**Abnormal Neurodevelopmental Outcome N=14**	**Pearsons Chi 2 Test**
	N(%)	**N(%)**	
Inotropes First 24 Hours	27(42.2)	5(35.7)	NS

In **table 6** above the developmental outcomes of all the infants who were given inotropic support during the first 24 hours are compared statistically using the Pearson`s Chi^2 test. No statistical difference was found between the normal and abnormal neurodevelopmental groups.

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15. Discussion:

The aim of this study was to assess if mean systemic blood pressure is a risk factor for poor neurodevelopmental outcome in a cohort of ELBW infants managed at Panorama Medi-Clinic. The secondary objectives were to identify whether inotropic usage, a marker of cardiovascular instability as well as other risk factors contributed to poor neurodevelopmental outcome in ELBW infants.

ELBW premature infants are at a high risk for neurodevelopmental disabilities. The incidence of neurodevelopmental disability has not improved over the last two decades despite the great strides made with regards to improved survival. A variety of risk factors have been implicated in determining neurodevelopmental outcome in survivors.

Cerebral hypoperfusion owing to systemic hypotension in ELBW infants has been cited as a risk factor that might be responsible for damage to both white and grey matter structure hence leading to neurodevelopmental disabilities in these immature infants[9,10]. It is assumed from a number of animal studies that the intrinsic vaso-regulatory mechanisms found in more mature infant humans are not functional in these very immature infants, particularly ill ELBW infants. These infants who might be hypotensive are therefore at risk of cerebral hypoperfusion as they are unable to maintained adequate cerebral perfusion particularly in vulnerable watershed zones owing to perfusion being a pressure passive phenomenon. A recent article by Lightburn et al has shown that perhaps this is not the case and that perfusion as measured by cerebral blood flow velocities is maintained despite hypotension in these ELBW infants[17].

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Nevertheless, prolonged, severe episodes of hypotension in these infants might be the cause of later neurodevelopmental disabilities due to ischaemic damage to deep white and grey matter in the developing brains of ELBW infants[5].

In our study cohort we were unable to demonstrate using a logistical regression analysis correcting for birth weight, gestational age, gender, antenatal steroid treatment, small for gestational age and severe IVH, a statistically significant effect of mean systemic blood pressure and adverse neurodevelopmental outcome.

Normal values for systemic blood pressure according to the gestational age and chronological age of the ELBW infant is at present controversial and poorly defined in the literature. In most studies looking at systemic blood pressure in the ELBW infant, non-validated generalized values are used where hypotension is defined as a mean systemic blood pressure lower than a value equivalent to the gestational age of the infants, for example, in a 26 week gestational age infant, infant is hypotensive if its mean systemic blood pressure is below 26 mm Hg, etc[23]. However, other definitions such as < 10^{th} percentile of gestational age and postnatal age according to published norms, and <30 mmHg can also be used and are perhaps more accurate[17].

In our NICU we aim at maintaining a mean systemic BP above 30 mmHg particularly when there is no spontaneous increase in mean systemic blood pressure over time. Our definition of systemic hypotension is therefore a mean systemic BP of <30mmHg. This is achieved by firstly giving fluid challenges in the form of stabilized human serum or normal saline and if there is a poor

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response then inotropic medication is commenced. It is also well described that infants who remain hypotensive for prolonged periods of time are at risk for developing intraventricular bleeds[18,24,25]. Unfortunately this study being a retrospective one assesses systemic blood pressure only at three specific post natal ages. It does not assess continuous blood pressure or more specifically cerebral perfusion.

We were unable to confirm the poorer neurodevelopmental outcome and an increase in sensorineural deafness in these infants if they were treated for hypotension as previously reported by Fanaroff and co-workers[26].

Management policies in our NICU have changed over the last couple of years and more of these ELBW infants are receiving in-out surfactant in the ICU and fewer infants are being actively intubated and ventilated in the delivery room. This may have had an impact on survival as well as stabilizing the infant from a hemodynamic point of view. Delayed cord clamping has also been shown to improve blood volume and this intervention has been introduced in the last approximately 2 years of this study period[27]. Both the above new interventions might have had an impact on systemic blood pressure in these ELBW infants and resulted in improved mean systemic blood pressure and therefore improved cerebral perfusion and neurodevelopmental outcome.

A cut off value for mean systemic blood pressure of < 30 mmHg was used to assess if we could demonstrate a particular minimum threshold mean systemic blood pressure below which one could prove a statistical difference between the normal and abnormal neurodevelopmental outcome groups (see table 5

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results). Again we were unable to find a statistically significant difference between the normal and abnormal outcome groups. This could be because the small number of infants who fell into this category or because of our policy of attempting to maintain a mean systolic pressure above 30mmHg and therefore although there might have been a brief period where the mean systemic blood pressure was recorded below 30 mm Hg this was never prolonged enough so as to have an adverse neurodevelopmental effect.

Fanaroff et al in his study showed a poorer neurodevelopmental outcome in ELBW infants who were treated for hypotension with inotropic agents[26]. In our study the normal and abnormal groups who received inotropic support in the first 24 hours were compared and again no statistical difference in neurodevelopmental outcome could be demonstrated (see table 6).

Other risk factors (see table 3 and 4) for abnormal neurodevelopmental outcome identified as secondary variables to explain significant differences between the normal and abnormal neurodevelopmental outcome groups. Of these risk factors the following were found to have statistical significance:

1. Severe grades of Intraventricular Haemorrhage IVH(grade3&4),
2. Retinopathy of Prematurity, ROP(grade 3&4),
3. Postnatal steroid usage,
4. Chronic lung disease defined as oxygen dependency at 36 weeks post conceptual age, as well as for,
5. Gastrointestinal perforation.

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16. Conclusion:

This study was unable to prove that early mean systemic blood pressure is a risk factor for poor neurodevelopmental outcome in extremely low birth weight infants even if a cut off level of <30 mm Hg is used to define hypotension. We were able to show that severe grades of intraventricular haemorrhage and retinopathy of prematurity, postnatal steroid usage, chronic lung disease and gastrointestinal perforation are associated with adverse neurodevelopmental outcome in extremely low birth weight infants treated at out institution.

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