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A cross-sectional descriptive study of symptomatic patent ductus arteriosus in very low birth weight neonates at Charlotte Maxeke Johannesburg Academic Hospital 2013-2016

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

M MED RESEARCH PROJECT

A CROSS-SECTIONAL DESCRIPTIVE STUDY OF SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN VERY LOW BIRTHWEIGHT NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, 2013-2016

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DECLARATION

I Nokukhanya A. N Ngubane-Mwandla declare that this research report submitted for the degree of Master of Medicine in Paediatrics at the University of Witwatersrand, is a presentation of my original research work. It contains no material previously published or written by another person, except where due reference is made. It has not been submitted before for any other degree, part degree or examination at this or any other university.

The work was done under the guidance of Professor Daynia E. Ballot and Dr Firoza Motara, at Charlotte Maxeke Johannesburg Academic Hospital, Gauteng.

_____ _____day of _____2019

Nokukhanya Ngubane-Mwandla

DEDICATION

“And whatever you do, in word or deed, do everything in the name of the Lord Jesus, giving thanks to God the Father through him.” Colossians 3:17

I dedicate this work to my husband, Sibusiso Mwandla and my son, Mangaliso Mwandla. Thank you for your love, guidance and unsympathetic driving force to be the best I can be.

With love
Khanyo

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ABBREVIATIONS

HMD	Hyaline membrane disease
CLD	Chronic lung disease
IVH	Intraventricular haemorrhage
NEC	Necrotizing enterocolitis
LOS	Late onset sepsis
NCPAP	Nasal Continuous Positive Airways Pressure
PDA	Patent ductus arteriosus
VLBW	Very low birth weight
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
PVL	Periventricular Leukomalacia
ROP	Retinopathy of prematurity
g	Grams
hrs.	Hours
mm	Millimetres
g/dl	Grams per decilitre
REDCap	Research Electronic Data Capture
SA	South Africa

A cross-sectional descriptive study of symptomatic Patent Ductus Arteriosus in very low birthweight neonates at Charlotte Maxeke Johannesburg Academic Hospital, 2013-2016

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ABSTRACT

Background: Very low birth weight neonates (VLBW) with symptomatic patent ductus arteriosus (PDA) are at increased risk of complications of prematurity.

Objective: To describe the incidence and clinical conditions associated with a symptomatic PDA in VLBW neonates.

Methods: This was a cross-sectional, retrospective, descriptive study of VLBW neonates admitted to CMJAH between 1 January 2013 to 30 June 2016. Survival outcome and characteristics between VLBW neonates with PDA and those without PDA were compared and anyalysed using univariate analysis. Binary logistic regression was used to obtain characteristics most significantly associated with a symptomatic PDA.

Results: There were 1844 eligible neonates. There were 308 excluded (24 major birth defects, 34 missing records and 250 discharged or died in the first 72 hours). There was echocardiographic confirmation of symptomatic PDA in 184 remaining neonates (11.9%). Blood transfusion (odd ratio 3.180, 95% confidence interval 1.578-6.405, p = 0.001), surfactant therapy (3.190, 1.215-8.381, p = 0.019), intermittent positive pressure ventilation (IPPV) (2.746, 1.703-4.429, p<0.001) and age on discharge (1.028, 1.017-1.039, p<0.001) were most associated with increased incidence of PDA. Antenatal steroids use (0.459, 0.285-0.738, p = 0.001) was associated with a decreased incidence of PDA. Majority of symptomatic PDAs received oral ibuprofen (n = 110) compared to conservative treatment (n = 60) and oral indomethacin (n = 5). A few had surgical ligation (n = 9). There was no statistical significance in mortality rates.

Conclusion Symptomatic PDA occurred in a minority of VLBW neonates and was not associated with an increased risk of mortality.

Keywords: very low birth weight, patent ductus arteriosus, echocardiography, blood transfusion, surfactant therapy, antenatal steroids, ibuprofen, indomethacin, ligation

Word count: 250

BACKGROUND

A patent ductus arteriosus (PDA) is amongst the most frequently occurring complications of the premature neonate, especially those with accompanying lung disease.[1,2] Studies were conducted examining outcomes of very low birth weight (VLBW) neonates at Charlotte Maxeke Johannesburg Academic hospital (CMJAH)[3]; no study has explored factors associated with a symptomatic PDA in VLBW neonates at CMJAH.

The National Collaborative study reported an incidence of symptomatic PDAs ranging from 11% to 36% in 13 different neonatal units, with a higher incidence in neonates with hyaline membrane disease (HMD), <30 weeks gestation.[4] James E Dice et al. in a review article reports an incidence of 48% in neonates <1000g.[5] Clinical diagnosis of a symptomatic PDA (such as bounding pulses, active precordium, wide pulse pressure, systolic murmur on left sternal border, increase in ventilator requirements despite surfactant therapy, congestive cardiac failure and apnea) lacks accuracy, particularly in the early post-natal days.[5,6] Both false negative and false positive clinical findings are common in the first post-natal week. As a result, echocardiography has become an important non-invasive method for confirming ductal patency and determining its haemodynamic significance.[5]

In addition to prematurity and HMD, there are other risk factors associated with persistent ductal patency in VLBW neonates, these include female gender and sepsis.[7] Complications of prematurity which have been associated with a symptomatic PDA include: Necrotizing enterocolitis (NEC), Intraventricular haemorrhage (IVH), Cystic periventricular leukomalacia (PVL), chronic lung disease (CLD), and retinopathy of prematurity (ROP).[8]

Not all VLBW neonates with PDAs need treatment, and trying to define a target population becomes difficult.[8] Some studies use clinical, echocardiographic, pharmacokinetic and biochemical parameters to identify the target population needing treatment.[8] Time of treatment becomes debatable, whether prophylactically, pre-symptomatically, or when the neonate has symptoms.[8] In addition, individual variability exists as to the drug and dose choice.[8] At CMJAH, VLBW neonates are treated once symptomatic, after confirmation by echocardiography.

Over the past few years the approach to PDA has changed from early diagnosis and medical treatment (using indomethacin or ibuprofen), to conservative treatment.[8] The PDA in

neonates is increasingly not being viewed as a pathological condition but as a physiological bystander.[8] There is further evidence that a PDA has no significant effects on major morbidities and mortalities in VLBW neonates.[8] However, a previous study done at CMJAH reported a significant rise in mortality in VLBW neonates with a PDA compared to those without PDA.[3] This evidence has made the decision to treat a PDA debatable. Treating when the PDA becomes symptomatic seems to be the most reasonable approach.[8]

Our current study, aims to highlight clinical conditions significantly associated with a symptomatic PDA, and analyse current practices in the management of a symptomatic PDA at CMJAH compared to other studies. The overall aim is to improve survival outcome of VLBW neonates with symptomatic PDAs at CMJAH.

METHODS

Study design

This study was a cross-sectional, retrospective, descriptive study of symptomatic PDAs in VLBW neonates weighing between 500 – 1500 grams (g), admitted at CMJAH between 1 January 2013 to 30 June 2016. For this study, symptomatic PDA is defined as showing a clinical impact (respiratory or circulatory) on the neonate. The terminology 'symptomatic' PDA and 'haemodynamically' significant PDA are often used interchangeably.[9, 10] There are no standard definitions.[9, 10] Entry criteria included all VLBW neonates admitted for longer than 72 hours (hrs.) after birth. Exclusion criteria included unobtainable records, major birth defects as per Vermont Oxford Network (VON) (www.vtoxford.org) and neonates with cardiac conditions co-existing with a PDA.

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary hospital in the public sector at the Gauteng province in South Africa. The neonatal unit has 98 beds, including 14 intensive care beds. All neonates are seen by a paediatrician every day. Very low birth weight neonates with a clinically symptomatic PDA confirmed on echocardiogram, were compared to those without PDA. Echocardiography was obtained within 24 to 48 hrs. after clinical suspicion of a symptomatic PDA. Echocardiographic criteria of a symptomatic PDA included: a left atrial/aortic ratio >1.4 and a PDA diameter >1.4 millimeters (mm).

Database

Data was collected from an existing CMJAH neonatal database on the REDCap (Research Electronic Data Capture). REDCap is a web based program where all the neonatal records are verified, collected and then securely stored for quality improvement and clinical audit.[11] Diagnosis of a PDA was substantiated by records captured electronically at the department of Cardiology. Any missing information in both systems was verified through retrieval of patient files at the hospital records department. Data collected from REDCap included (i) Maternal data – antenatal steroids, antenatal care, multiple gestation; (ii) Neonatal data – gender, age on admission, age on discharge, birth weight; (iii) Neonatal ventilator support – resuscitation at birth, nasal continuous positive airway pressure (NCPAP), intermittent positive pressure ventilation (IPPV), surfactant at any point; (iv) Complications of prematurity – HMD, NEC stage 2 and 3 as per modified Bells staging criteria[12], blood transfusion, CLD, steroids for CLD, late onset sepsis (LOS), IVH grade 3 and 4 as per sonographic grading system by Papile et al.[13], pneumothorax, pulmonary haemorrhage, ROP stage 3 and 4 as per Quinn[14] and Cystic PVL. Management of PDA including conservative treatment), indomethacin, ibuprofen and surgical ligation was recorded. Conservative treatment included fluid restriction to 150 ml/kg/day beyond day 5 of life, treatment of cardiac failure with furosemide and optimising haemoglobin levels to 14 grams per deciliter (g/dl). Very low birth weight neonates who were discharged and those who were transferred out were grouped together as survivors for the purpose of analysis.

Statistical Analysis

Data was captured into an MS Excel (Microsoft, USA) spreadsheet and exported into a statistical software program SPSS 23 (IBM, USA) for analysis. Continuous variables were normally distributed and were described using mean and standard deviation. Categorical variables were described using frequencies and percentages. Comparison was made between VLBW neonates with symptomatic PDA vs those without PDA for clinical characteristics and outcome. Continuous variables were normally distributed and compared using unpaired t test. Categorical variables were compares using X^2 tests or Fisher's exact test, as appropriate. A p value <0.05 was considered significant. Variable with a p value <0.1 on univariate analysis were entered into a binary logistic regression model to determine the most significant association with a symptomatic PDA. Only valid data was reported (i.e. missing variables were excluded).

Ethics

This study was approved by the Human Research Ethic Committee at the University of the Witwatersrand Johannesburg (clearance certificate number M160732).

RESULTS

There were 1844 eligible VLBW neonates. Three hundred and eight were excluded, leaving 1536 neonates in the final sample. One hundred and eighty-four (11.9%) had echocardiographically confirmed PDA and the remaining 1352 (88.0%) had no PDA (See Figure 1). The mean birth weight of all eligible neonates was 1157.0g (SD 222.1), the mean age on admission was 1.2 days (SD 7.0) and the mean age at discharge was 34.8 days (SD 21.9).

Figure 1: Flow diagram of patient selection

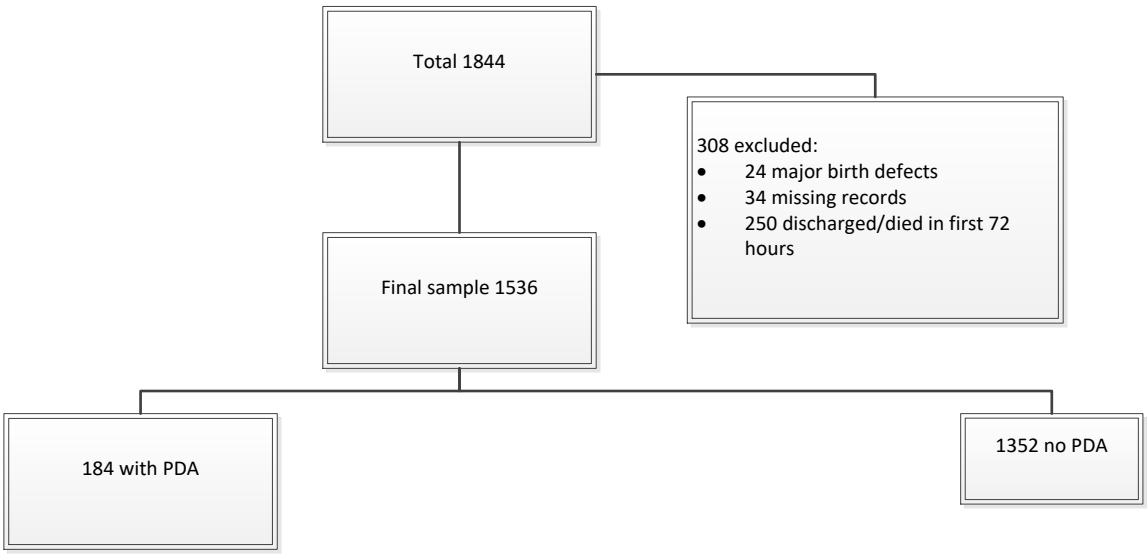


Table 1: Comparison between neonates with PDA and without PDA for continuous variables

Variable	PDA (mean SD)	No PDA (mean SD)	P value
Birth weight (grams)	1062.3 (118.0)	1169.9 (224.1)	<0.001
Age on admission (days)	1.4 (7.2)	1.2 (7.0)	0.76
Age on discharge (days)	54.2 (28.9)	32.2 (19.3)	<0.001

Birth weight and age on discharge were statistically significant (p<0.001). VLBW neonates with PDA demonstrated longer days of admission as shown in Table 1. Clinical and

demographic characteristics in VLBW neonates with a symptomatic PDA as compared to those without a PDA are shown in Table 2. Neonates with a symptomatic PDA were significantly less likely to have received antenatal steroids (p<0.001) or to have a mother who attended antenatal care (p = 0.002) compared to those without a PDA. Resuscitation at birth (p = 0.001), HMD (p<0.001), NCPAP (p<0.001), IPPV (p<0.001), surfactant therapy (p<0.001), NEC (p<0.001) and blood transfusion were significantly more common in VLBW neonates with a symptomatic PDA than those without PDA (155/183 (84.7%) vs 479/1321 (36.3%), p<0.001). Other complications of prematurity such as CLD (p<0.001), LOS (p<0.001), IVH grade 3 and 4 (p<0.001), pneumothorax (p = 0.006) and pulmonary haemorrhage (p = 0.026) were all significantly more common in VLBW neonates with a symptomatic PDA (see Table 2). The overall rate of LOS in these VLBW neonates was 33.2%.

Table 2: Comparison between neonates with PDA and without PDA for clinical and demographic characteristics

Variable	Total sample (1536) n (% of total)	PDA (184) n (%)	No PDA (1352) n (%)	P value
Antenatal steroids	671/1363 (49.2)	54/151 (35.8)	617/1212 (50.9)	<0.001
Antenatal care	1154/1441(80.1)	117/165 (70.9)	1037/276 (81.3)	0.002
Resuscitation at birth	556/1411 (39.4)	82/159 (51.6)	474/1252 (37.9)	0.001
NCPAP	1015/1419 (71.5)	154/171(90.1)	861/1248 (69.0)	<0.001
IPPV	317/1386 (22.9)	101/177 (57.1)	216/1209 (17.9)	<0.001
Surfactant therapy	1054/1491 (70.7)	164/172 (95.3)	890/1319 (67.5)	<0.001
HMD	1352/1518 (89.1)	178/183 (97.3)	1174/1335(87.9)	<0.001
NEC 2 and 3	161/1533 (10.5)	33/183 (18.0)	128/1350 (9.5)	<0.001
Blood transfusion	634/1504 (42.2)	155/182 (84.7)	479/1321 (36.3)	<0.001
CLD	418/1508 (27.7)	119/183 (65.0)	299/1325 (22.6)	<0.001
Steroids for CLD	230/1485 (15.5)	70/174 (40.2)	160/1311 (12.2)	<0.001
LOS	505/1522 (33.2)	106/182 (58.2)	399/1340 (29.8)	<0.001
IVH 3 and 4	67/929 (7.2)	18/158 (11.4)	49/771 (6.4)	<0.001
Pneumothorax	10/1531 (0.7)	4/183 (2.2)	6/1348 (0.4)	0.006
Pulmonary haemorrhage	22/1536 (1.4)	6/184 (3.3)	16/1352 (1.2)	0.026
Multiple gestation	271/1503 (18.0)	20/180 (11.1)	251/1323 (19.0)	0.010
ROP 3 and 4	16/467 (3.4)	4/82 (4.9)	12/385 (3.1)	0.120
Cystic PVL	14/1188 (1.2)	3/167 (1.8)	11/1021 (1.1)	0.425
Gender (Male)	719/1533 (46.9)	85/183 (46.4)	634/1350 (47.0)	0.896
Death	270/1536 (17.6)	41/184 (22.3)	229/1352 (16.9)	0.074

*****Percentages are expressed in columns.

There was no significant difference in multiple gestation, ROP, cystic PVL and gender between VLBW neonates with a symptomatic PDA and those without a PDA (see Table 2).

The overall mortality rate between VLBW neonates with PDA and those without PDA was not statistically significant, 41/184 (22.3%) vs 229/1352 (16.9%) respectively, p = 0.074.

Variables with p<0.1 were entered into binary logistic regression to determine which are most significantly associated with a symptomatic PDA. Blood transfusion (p = 0.001), surfactant therapy (p = 0.019), IPPV (p<0.001), age on discharge (p<0.001) and antenatal steroids (p = 0.001) (see Table 3) were most significantly associated with a symptomatic PDA.

Ibuprofen was given to 110/184 (59.8%) of the VLBW neonates with symptomatic PDA, while indomethacin was given to 5/184 (2.7%). The patent ductus arteriosus was ligated in 9/184 (4.9%) of the VLBW neonates with symptomatic PDA. The remaining VLBW neonates were treated conservatively i.e. 60/184 (32.6%).

Table 3: Binary logistic regression for factors associated with PDA in VLBW neonates at CMJAH

Variable	OR	95%CI	P value
Blood Transfusion	3.180	1.578-6.405	0.001
Surfactant	3.190	1.215-8.381	0.019
IPPV	2.746	1.703-4.429	<0.001
Age on discharge	1.028	1.017-1.039	<0.001
Antenatal steroids	0.459	0.285-0.738	0.001

DISCUSSION

The PDA is a vascular structure allowing a left to right shunt from the proximal descending aorta to the main pulmonary artery.[6,15] It becomes persistent once there is failure of the ductus arteriosus (DA) to close within 72hrs. after birth.[6,15] In our study, the incidence of symptomatic PDAs at CMJAH was 11,9%, which was higher compared to previous studies done at CMJAH where it was reported to be 5,6% in 2006/2007 and 9,6% in 2013.[3] The increase in incidence may be due to increasing survival of extremely low birth weight (ELBW) neonates at CMJAH.[3] The incidence in our study is comparable to the National Collaborative study.[4]

There was a significant association between surfactant therapy and a symptomatic PDA in our study. This finding is in agreement with a study done by Abhay Kumar.[16] Exogenous

surfactant therapy may increase shunting across PDAs following rapid decrease in pulmonary vascular resistance.[17] It is vital that VLBW neonates who received surfactant therapy for HMD, be monitored clinically and by echocardiogram for an appearance of a haemodynamically significant PDA.[16] A study hypothesized that therapies which result in less mechanical ventilation and improvement of lung function (such as surfactant therapy, fluid restriction, NCPAP) could be associated with lower incidence of symptomatic PDAs.[17] Our study supports this finding because a significantly lower number of VLBW neonates with symptomatic PDAs required mechanical ventilation, this may be due to the rise in use of surfactant therapy and NCPAP in ELBW neonates at CMJAH.[3] Our study is in agreement with other studies which found closure of symptomatic PDA to be less likely to occur in neonates who do not receive antenatal steroids.[6,18] Our study demonstrated a decrease incidence of PDA with antenatal steroids use. Despite desperate measures to optimize respiratory function, there is still a strong association between symptomatic PDA and development of CLD.[19] This is further emphasized by a recent study done by Mphaphuli on CLD at CMJAH.[20] The presence of a PDA with sepsis substantially increases the risk of CLD.[19] Previous studies done around VLBW neonates at CMJAH revealed an increasing number of LOS in 2013 (19%) compared to 2006/2007 (12.5%).[3] The rate of sepsis in the current study was even higher – at 33.2%. Therefore, prevention of sepsis should be prioritized so that the adverse effects of ductal patency can be altered.[19]

Blood transfusion was significantly associated with PDA in our current study. This is unsurprising as a lower haematocrit after birth places VLBW neonates at greater risk of PDA.[21] All preterm neonates develop physiological anemia of prematurity and this is aggravated by iatrogenic blood loss.[22] However, PDA and blood transfusion in VLBW neonates may place the neonate at even greater risk of NEC than each of these factors alone.[21] This is further emphasized in our study which found a significantly greater number of VLBW neonates with symptomatic PDA developing NEC compared to those without PDA.

Over the years, the haemodynamic and pulmonary consequences of a persistent PDA justified closing the duct.[23] Neonates <28 weeks gestation or with birth weights ≤1000g are the target group for controversy since only 60% will develop significant debilitating PDA related symptoms but only 30% will spontaneously close their PDA.[18] Observational studies demonstrate that the majority of VLBW neonates with persistent PDA after the third day of life, especially those ≥1000g birth weight, can do well without any treatment.[23] Current

recommendations prefer conservative treatment.[24] It is interesting to note that very few VLBW neonates in our current study received conservative treatment compared to medical treatment. It is unsurprising that in our current study ibuprofen was more popular than indomethacin. Only oral preparations of both drugs are available at CMJAH. Intravenous indomethacin is not registered in South Africa (SA). Oral ibuprofen is available as a syrup and is favoured at CMJAH because of its fewer side effects compared to indomethacin.[24] Intravenous ibuprofen is very expensive. A randomized pilot study by Cherif, et al. states that oral ibuprofen is as good as IV ibuprofen in terms of ductal closure and is associated with fewer side effects.[24]

Only 4.9% of VLBW neonates with symptomatic PDA underwent ligation. Studies show that delaying ligation (by more than 30 days) causes a reduction in several morbidities associated with ligation.[18,25]

The overall mortality rate of VLBW neonates in our study was 17.6%. There was no significant difference in the mortality rates between neonates with symptomatic PDA and those without PDA. This is encouraging because it is in agreement with other studies across the world which show failure of long term benefits of ductal closure from several adverse outcomes that are strongly associated with persistent PDA such as death, HMD, BPD, NEC, IVH etc.[23,25] Tools need to be developed to identify VLBW neonates at risk of detrimental outcomes related to a symptomatic PDA such as those with large left to right shunts.[19,23] This must be followed by intervention trials to conclude whether closing the PDA can avoid such outcomes.[19] Until then, choosing to aim to close a PDA of a VLBW neonate who is ill actually remains subjective.[19]

CONCLUSION

Our study described the incidence and clinical characteristics significantly associated with a symptomatic PDA. It highlighted the most common method of treatment used for symptomatic PDAs in VLBW neonates at CMJAH. Although management of a symptomatic PDA remains highly controversial, there is a move towards a more conservative approach at the CMJAH neonatal unit.

STUDY LIMITATIONS

Our study was limited as this was a secondary analysis of a database. Timing of treatment or whether multiple courses of medication were given could not be established. The dose of medication and timing of complications could not be evaluated.

RECOMMENDATION

A move towards conservative treatment because there is insufficient evidence supporting that medical or surgical closure of the ductus is beneficial in preterm neonates and a more permissive approach does not result in worse outcomes. [23, 25]

Word count: 2755

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APPENDIX 1 – PROTOCOL



University of Witwatersrand, Faculty of Health Sciences

Department of Paediatrics, Mmed Paediatrics

Research Protocol

05 August 2016

A cross-sectional descriptive study of symptomatic Patent Ductus Arteriosus in very low birthweight neonates at Charlotte Maxeke Johannesburg Academic Hospital, 2013-2016

Candidate: Dr Nokukhanya Ngubane-Mwandla

Student number: 1332856

Supervisor: Dr F Motara

MBBCh, FC Paeds, M Med, Cert cardio SA Paeds

Co-supervisor: Prof Daynia Ballot,

MBBCh, FC Paeds, PhD

A. Executive Summary

Patent ductus arteriosus (PDA) is very common congenital clinical condition occurring in neonates.[1] This study aims to describe symptomatic PDA in very low birthweight neonates (VLBW) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This will be achieved by looking at the neonatal and cardiology records of VLBW neonates diagnosed with a symptomatic PDA, confirmed by echocardiography, across a 3year period. Using these records, a cross-sectional descriptive study will be done, comparing demographics and clinical characteristics of VLBW neonates with symptomatic PDA and those without PDA. Choice of treatment will be described. Survival outcome of VLBW neonates with symptomatic PDA and those without PDA will be compared.

1. Introduction

1.1 Incidence

A PDA is amongst the most frequently occurring congenital clinical condition in the neonate.[1] It is a common diagnosis in extremely preterm neonates, especially those with accompanying lung disease.[2]

The reported incidence of PDA in the preterm neonate ranges from 20% to 60% depending on population and diagnostic criteria. In one study done over a four year period at the University of California San Francisco, the incidence of PDA in the premature neonate weighing 1750g or less at birth was 15.3%.[4] In the general population, the incidence of PDA is about 0.04% at sea level however rises to 0.72% at high altitude.[4]

Gestational age and weight are closely linked to PDA in the preterm neonate.[5] In neonates less than 1500g at birth, the incidence is reported as approximately 30% in a literature review by Joseph B Phillips.[5] In neonates weighing less than 1200g at birth, PDA is present in 80% versus 40% in those weighing less than 2000g at birth. [6] Symptomatic PDA is present in 48% of neonates weighing less than 1000g as quoted in a review article in Georgia.[6] Another study by the Paediatric Cardiology unit in France states 70% to 80% of neonates weighing less than 1000g at birth will have PDAs.[1]

1.2 Regulation of Ductal Patency and Closure

Developmental immaturity is the primary cause for ductal patency in the preterm neonate. Responsiveness of the DA to oxygen increases with increasing gestational age. The duct of a

premature neonate has a high threshold response to oxygen. Prostaglandin E2 (PGE2) especially, acts as a vasodilator maintaining ductal patency in the foetal and neonatal life. The immature duct produces more prostaglandin and has greater sensitivity to the vasodilating effect of PGE2. Furthermore, circulating levels of PGE2 are higher because of incomplete metabolism in the immature lungs.[1]

1.3 Risk Factors and Comorbidities associated with PDA

There are several risk factors describe in the literature besides prematurity, contributing to ductal patency. There has been no study conducted at CMJAH exploring common risk factors for ductal patency. These risk factors are described below:

1.3.1 Gender, Maternal factors, and neonatal sepsis

Patent Ductus Arteriosus is more common in females than males with a ratio of 2:1.[1] In congenital rubella syndrome, gender incidence is equal.[2] One investigation however reported 53% of PDA cases to be among males.[8] Rubella infection during the first trimester of pregnancy, particularly in the first four weeks, is associated with a high incidence of PDA.[7] Respiratory illness such as hyaline membrane disease (HMD) is associated with PDA especially in infants less than 30 weeks gestation. As much as 80% of preterm neonates presenting with HMD have been described to having a PDA. Closure of the PDA is less likely to occur in neonates who do not receive antenatal steroids.[5, 6] A study conducted in the CMJAH neonatal unit in 2013 showed antenatal steroids were significantly associated with survival to discharge of very low birth weight (VLBW) neonates. In the same study, the number of PDAs was significantly higher in 2013 compared to the year 2006/2007. This can be attributed to the increasing number of surviving premature neonates in 2013.[9] The DA is functionally closed by the fourth day in nearly all healthy neonates greater than 30 weeks gestation.[5] In ill neonates less than 30 weeks gestation, PDA persists on the fourth day in about 65% and its closure delayed, especially for moderate to large PDAs .[5] Infections cause a release of inflammatory mediators, which increase failure of the DA to close. These mediators are also associated with late patency of the DA. There is a rising number of late onset sepsis in VLBW at CMJAH.[9, 10, 11]

1.3.2 Neonatal complications associated with PDA

In a large prospective multicenter study, PDA in ventilated VLBW infants was associated with increased risk of bronchopulmonary dysplasia (BPD), regardless of the timing of the diagnosis of the PDA (odds ratio of 1.9, 95% CI 1.18-3.09).[12] In a study done over a four year period, BPD was associated with nearly sixty percent of deaths due to PDA.[13] Patent ductus arteriosus is considered as an independent risk factor for development of necrotising enterocolitis (NEC) with an odds ratio of 1.8 (95% CI, 1.24-2.69).[12] Myocardial dysfunction due to left sided volume overload, together with a ductal steal phenomenon compromise systemic perfusion. Patent ductus arteriosus is also found to be an independent risk factor for inotrope-resistant hypotension, impaired renal function, intraventricular haemorrhage (IVH), and periventricular leukomalacia (PVL) in preterm neonates.[14] It is important to note that although these are associations described with a PDA, this does not necessarily mean that the condition is caused by the PDA. A recent retrospective study suggests that PDA has no significant effect on mortality and major morbidities in VLBW infants.[12, 14] It will be of benefit to explore morbidities common to neonates diagnosed with a symptomatic PDA.

1.4 Diagnosing PDA

The method of diagnosing a DA varies. The confirmatory gold standard is by echocardiography.[1] It may not always be possible to get the echocardiography done urgently, this can cause delay in initiating treatment and recovery of the neonate. At CMJAH an echocardiogram is usually done within 24 to 48 hours of a murmur having been diagnosed; if there is suspicion of a symptomatic PDA (based on clinical findings with or without a murmur), an echocardiogram is performed to confirm the PDA. It is unlikely a symptomatic PDA will be missed because the VLBW neonates are in a high care/intensive care environment and are examined by doctors (junior and senior) every day. An echocardiogram requested urgently will be done within a couple of hours of its request.

1.4.1 Clinical Diagnosis

The clinical picture of a PDA depends on the size of the PDA. Small PDAs can be asymptomatic, also termed silent PDAs whereas moderate to severe PDAs can present with congestive cardiac failure. Haemodynamically significant PDA can present with increased ventilator requirement despite surfactant treatment, metabolic acidosis, bounding pulses, prominent left ventricular pulse, wide pulse pressure and other non-cardiovascular findings such as apnoea, increased carbon dioxide, and tachypnoea. However, no single finding is specific for a PDA.[1, 5] Risk of haemodynamically significant PDA increases with decreasing

gestational age and birth weight.[5] Approximately 80% of extremely low birth weight neonates with a murmur progress to large, persistent PDAs.[5] In a few premature neonates, asymptomatic PDA can persist with closure occurring after 10 days of age.[5]

1.4.2 Electrocardiogram & Chest X-Ray Diagnosis

Electrocardiogram (ECG) patterns can range from completely normal to showing left ventricular hypertrophy, left atrial enlargement, atrial fibrillation and non-specific signs such as pulmonary hypertension.[1, 7] In the premature neonate, ECG is not diagnostic and is usually normal, but may show left ventricular hypertrophy.[2] A significant shunt will show enlargement of pulmonary arteries, pulmonary veins, left atrium and left ventricle on chest X-Ray (CXR).[2]

1.4.3 Echocardiogram Diagnosis

The echocardiogram besides confirming the PDA, also determines size and geometry. Echocardiography is used to evaluate haemodynamic significance of the PDA and presence of associated ductal –dependent cardiac lesions. In neonates with moderate to large PDA, the left atrium and left ventricle are enlarged, whereas they are normal in neonates with smaller PDA. The left atrium to aorta ratio of >2 is considered a reliable marker of a haemodynamically significant ductal shunt.[1] The colour Doppler is very sensitive in detecting tiny ducts and can also show presence of elevated pulmonary vascular resistance by looking at the direction of the shunt. However, in neonates with elevated pulmonary vascular resistance the PDA may be difficult to visualize, even if it is large.[1] It is therefore crucial that presence of pulmonary hypertension on echocardiography should prompt the clinician to look for the presence of a patent duct. Contrast with saline and micro bubbles may be helpful.[1]

In one study of mechanically ventilated infants younger than 30 weeks gestation, a ductal diameter of 1.5mm or greater, at 7 to 31 hours of life predicted a significant PDA with 83% sensitivity and 90% specificity for a PDA that was treated.[5] However, using a trans-ductal diameter as the sole method of measuring a significant PDA is increasingly being scrutinized because it has not resulted in a reduction of neonatal morbidity associated with PDA. A proposed staging system to detect clinically significant PDA using both clinical findings and echocardiographic measurements is now recommended.[5] Others have used the PDA to left pulmonary artery (LPA) ratio to define large ≥1, moderate ≤1 and small <0.5 PDAs in the first four days of postnatal life to predict which infants would receive treatment for PDA

closure.[5] Those with large or moderate PDAs are 15 times more likely to receive treatment versus small PDAs who are more likely to have spontaneous resolution.[5] Sensitivity, specificity and positive predictive value of a large or moderate PDA to LPA ratio in the first four days in this study, was 80, 86, and 92% respectively, for infants <27 weeks gestation.[5]

At CMJAH, a haemodynamically significant PDA is defined by the following: Left atrial to Aorta ratio more than 1.4; the internal diameter of the ductus/body surface area ratio >14; PDA diameter more than 1.4mm; a low-velocity pulsatile flow pattern; a diastolic reverse flow in the aorta, mesenteric, cerebral, and renal arteries; and lastly if the neonate is clinically in cardiac failure.[12] If all of the above characteristics are present and the neonate is not weaning off oxygen and not growing, the patient is started on anti-failure treatment. Surgical closure is not commonly done and is reserved for those haemodynamically significant PDAs that are resistant to medical treatment.

1.5 Treatment of PDA

Most neonatologists agree that not all PDAs require treatment but that there is a subgroup that should be closed. There is individual variability among preterm neonate when it comes to who will respond to which drug and at which dose. Several studies have tried to define the target population that should be treated using different clinical, echocardiographic, pharmacokinetic, and biochemical parameters.[13] When to treat becomes debatable, whether prophylactically, pre-symptomatically or when a neonate has symptoms. It will be of benefit to determine the outcome of VLBW neonates treated conservatively versus medical closure or surgical closure, and exploring the common method of treatment. Outcome of VLBW neonates who used ibuprofen vs. indomethacin should also be evaluated.

A study done at the University of Kentucky states most term neonates with PDA are asymptomatic and do not need treatment. Those with symptoms, however, usually improve with diuretics, digoxin and afterload reduction as a temporary measure before surgical closure.[3] Patients with a PDA and pulmonary vascular disease who have contraindication to closure may be managed with pulmonary vasodilating agents, such as chronic oxygen, prostacyclin, nifedipine, bosentan, or sildenafil.[3] A recent article in which the outcomes of 129 preterm neonates (501-1500g birth weight) in 4 different NICUs in the Netherlands were interrogated, demonstrated that the BPD rate and combined outcome of death after day 7 and/or the outcome of BPD is higher in the period where permissive tolerance of PDA was

applied.[12] Permissive tolerance is described as fluid restriction, waiting for PDA closure and limiting medication use or surgical ligation to only those neonates with large PDAs needing significant respiratory support. However, this was not associated with significant changes in other neonatal morbidities.[12] Patent ductus arteriosus is associated with 4 to 8 fold increase in the mortality of preterm neonates.[12]

This study aims to determine survival outcome in VLBW neonates with a symptomatic PDA compared to those without PDA. The study will describe risk factors, complications and therapeutic interventions associated with VLBW neonates with symptomatic PDA. A PDA is one of the complications of prematurity significantly affecting survival of VLBW neonates at CMJAH.[10] There are less VLBW neonates with PDA surviving, compared to VLBW neonates without a PDA.[10] This study will highlight problem areas associated with PDA, and contribute to future research which may be conducted at CMJAH around the topic of symptomatic PDAs. The overall aim is to describe survival outcomes of VLBW neonates with a symptomatic PDA.

2. Protocol

2.1 Aim

To describe symptomatic PDA in the neonatal unit at CMJAH.

2.2 Objectives

1. To determine the incidence of symptomatic PDA in VLBW neonates admitted to CMJAH neonatal unit between 1st of January 2013 and 30th of June 2016.
2. To describe the demographic factors and outcome to discharge of the neonates with symptomatic PDA.
3. To establish risk factors and complications of symptomatic PDA, by comparing VLBW neonates with symptomatic PDA to VLBW neonates without PDA.

2.3 Study Design

This is a retrospective, cross-sectional, descriptive study of symptomatic PDA in VLBW neonates at CMJAH from 1st of January 2013 to the 30th of June 2016, by analysis of existing neonatal and cardiac databases. A data collection sheet will demonstrate all variables.

2.4 Study Population

Very low birth weight neonates admitted to CMJAH neonatal unit.

2.5 Inclusion Criteria

All VLBW neonates admitted to the neonatal unit for longer than 72 hours after birth.

2.6 Exclusion Criteria

1. Neonates with unobtainable records;
2. Major birth defects as defined in the Vermont Oxford Network (VON);
3. PDA associated with persistent pulmonary hypertension of a newborn (PPHN) on echocardiogram.

3. Patients beyond the first

2.7 Sample Size Prediction

There are approximately 200 VLBW neonates with a diagnosis of PDA on the existing neonatal database. A sample of VLBW neonates without PDA will be selected randomly, giving a total sample size of approximately 400 VLBW neonates.

Study Variables

Demography such as age on admission (>72hours), gestational age (≥28 weeks), very low birth weight as per VON (between 500g and 1500g), gender (male/female) and multiple gestation will be recorded in the database sheet. Maternal factors such as access to antenatal care and antenatal steroids will be included.

se of supplemental oxygen and ventilation will be described in terms of resuscitation at birth and use within 28 days of life. Apgar score at 5 minutes (defined as >6 or <6) will be included. Co-morbidities of neonates with and without symptomatic PDAs will be

compared. These co-morbidities and complications include: HMD, BPD (defined as using oxygen at 28 days or at 36 weeks), pulmonary haemorrhage, culture-proven after 3 days of life, blood transfusion, NEC (stage ≥2), and IVH (grade ≥3) through record of cranial sonar findings. Pneumothorax, retinopathy of prematurity (ROP) screening and findings will be included (stage ≥2). Use of surfactant and steroids will be recorded. Outcomes of patient using indomethacin, ibuprofen or surgical ligation will be compared.

Results will be analysed to see if there was any statistical significance between the VLBW neonates with symptomatic PDA and those without PDA. VLBW neonates with symptomatic PDAs confirmed on echocardiogram will be compared to VLBW neonates with no PDA on echocardiogram. VLBW neonates with suspected PDA (based on clinical findings with or without a murmur) with no echocardiographic findings of a PDA or with echocardiographic findings of either peripheral pulmonary stenosis (PPS) or a normal heart, will be included in the group of VLBW neonates with no PDA. Survival outcome between the VLBW neonates with symptomatic PDA and with no PDA will be described. The database will demonstrate statistically significant co-morbidities and complications associated with symptomatic PDA.

T

2.8 Data Analysis

Continuous variables with a normal distribution will be described using mean and standard deviation. Skewed data will be described sing median or interquartile range (IQR). Categorical variables will be described using frequency and percentages. Data will be captured into an Excel spread sheet and exported to IBM SPSS 23 for analysis. Comparisons of outcome (survival) and clinical characteristics between neonates with and without PDA will be done. Continuous variables with a normal distribution will be compared using unpaired t test, whereas continuous variables with skewed distributions will be compared using Mann Whitney U test. Categorical variables will be compared using Chi Square or Fisher's exact test, as appropriate. A p value less than 0.05 will be considered significant. Univariate analysis and logistic regression can determine the most significant association with PDA.

2.9 Study Limitations

Due to the retrospective nature of this study, we will be relying on records available and may not get all the information desired.

2.10 Timing

TASK	START DATE	END DATE
Preparing Protocol	April 1st	May 31st
Protocol assessment	June 23rd	June 29th
Ethics application	June 30th	July 31st
Data collection	Aug 1st	Sept 30th
Data analysis	October 1st	December 31st
Thesis write up	January 1st 2017	March 1st 2017

2.11 Ethics

The protocol was cleared by the Human Research Ethics Committee (Medical) on the 1/08/2016. Clearance certificate number is M160732. A letter will be drafted to notify them of change of title.

2.12 Funding

A minimal cost of approximately R300.00 is anticipated due to the retrospective nature of the study. It will be borne by the researchers.

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DATASHEET

PATIENT
STUDY ID

DEMOGRAPHIC VARIABLES							
Age (>72)	On admission		On discharge				
Gender	Male		Female				
Birth Weight (grams)			Gestational Age (weeks)				
Multiple gestation	Yes		No		Not Known		
MATERNAL VARIABLES							
Antenatal care	Yes		No		Not Known		
Antenatal steroids	Yes		No		Not Known		
NEONATAL VARIABLES							
Resuscitation at birth	Yes		No		Not Known		
Bacterial sepsis ≤ 3 days	Yes		No		Not Known		
Apgar 5 minute (<6 or >6)							
Oxygen on day 28	Yes		No		Not Known		
Cranial sonar/CT/MRI before 28 days	Yes		No		Not Known		
Grade 3/4 PIVH	Grade 3		Grade 4		Not Known		
Cystic PVL	Yes		No		Not Known		
Respiratory diagnosis	Hyaline membrane disease		Yes		No		
	Pulmonary haemorrhage		Yes		No		
	Respiratory support after initial resuscitation		Yes		No		
Type of respiratory support	Oxygen		Yes		No		Not Known

Nasal CPAP			Yes		No		Not Known
Conventional Ventilation		Yes		No		Not Known	
Surfactant therapy at any time		Yes		No		Not Known	
Oxygen at 36 weeks		Yes		No		Not Known	
ROP Findings Grade 3/4		Grade 3		Grade 4		Not Known	
Patent ductus arteriosus		Yes		No		Not Known	
Indomethacin for any reason		Yes		No		Not Known	
Ibuprofen for PDA		Yes		No		Not Known	
PDA ligation		Yes		No		Not Known	
Pneumothorax		Yes		No		Not Known	
Necrotising enterocolitis (stage ≥2)		Yes		No		Not Known	
Blood transfusion		Yes		No		Not Known	
Sepsis ≥ day 3		Yes		No		Not Known	
Bacterial pathogen		Yes		No		Not Known	
Fungal sepsis		Yes		No		Not Known	
OUTCOME							
Survived		Yes		No			
Died		Yes		No			
Home oxygen		Yes		No		Not Known	

APPENDIX 2 – ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Nokukhanya Ngubane-Mwandla et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160732

NAME: (Principal Investigator)	Dr Nokukhanya Ngubane-Mwandla et al
DEPARTMENT:	Paediatrics and Child Health Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Cross-Sectional, Descriptive Study of Symptomatic Patent Ductus Arteriosus in Very Low Birthweight Neonates at Charlotte Maxeke Johannesburg Academic Hospital, 2013 - 2016
DATE CONSIDERED:	29/07/2016
DECISION:	Approved unconditionally
CONDITIONS:	Changed Title 08/08/2016
SUPERVISOR:	Dr F Motara
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/08/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Philip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 3 – AUTHOR GUIDELINES

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Conflicts of interest

We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest.

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- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
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- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
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Preparation notes by article type

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

- May include up to 6 illustrations or tables.
- A max of 20 - 25references

Structured abstract

- This should be no more than 250words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
    - Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
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- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. DOI:10.1000/hgjr.182
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A CROSS-SECTIONAL DESCRIPTIVE STUDY OF SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN VERY LOW BIRTHWEIGHT NEONATES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, 2013-2016

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A cross-sectional descriptive study of symptomatic Patent Ductus Arteriosus in very low birthweight neonates at Charlotte Maxeke Johannesburg Academic Hospital, 2013-2016

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ABSTRACT

Background: Very low birth weight neonates (VLBW) with symptomatic patent ductus arteriosus (PDA) are at increased risk of complications of prematurity.

Objective: To describe the incidence and clinical conditions associated with a symptomatic PDA in VLBW neonates.

Methods: This was a cross-sectional, retrospective, descriptive study of VLBW neonates admitted to CMJAH between 1 January 2013 to 30 June 2016. Survival outcome and characteristics between VLBW neonates with PDA and VLBW neonates without PDA were compared and anyalysed using univariate analysis. Binary logistic regression was used to obtain characteristics most significantly associated with a symptomatic PDA.

Results: There were 1844 eligible VLBW neonates. Three hundred and eight were excluded, leaving a final sample of 1536 VLBW neonates. There was echocardiographic confirmation of symptomatic PDA in 184 VLBW neonates (11.9%). The following five characteristics were most significantly associated with a symptomatic PDA in VLBW neonates at CMJAH: Blood transfusion (odd ratio 3.180, 95% confidence interval 1.578-6.405), surfactant therapy (3.190, 1.215-8.381), intermittent positive pressure ventilation (IPPV) (2.746, 1.703-4.429), age on discharge (1.028, 1.017-1.039), and antenatal steroids (0.459, 0.285-0.738). The majority of VLBW neonates with a symptomatic PDA received oral ibuprofen (n = 110) compared to conservative treatment (n = 60) and oral indomethacin (n = 5). A minority of VLBW neonates received surgical ligation (n = 9). Symptomatic PDA was not significantly associated with an increased risk of mortality

Conclusion Symptomatic PDA occurred in a minority of VLBW neonates and was not associated with an increased risk of mortality.

Keywords: very low birth weight, patent ductus arteriosus, echocardiography, blood transfusion, surfactant therapy, antenatal steroids, ibuprofen, indomethacin, ligation

Word count: 246

BACKGROUND

A patent ductus arteriosus (PDA) is amongst the most frequently occurring complications of the premature neonate, especially those with accompanying lung disease.[1,2] Multiple studies have been done aiming to improve survival of very low birth weight (VLBW) neonates at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)[3], no study has explored factors associated with a symptomatic PDA in VLBW neonates at CMJAH and whether not these factors have a significant influence on the survival outcome of these neonates.

The National Collaborative study reported an incidence of symptomatic PDAs ranging from 11% to 36% in 13 different neonatal units, with a higher incidence in neonates with hyaline membrane disease (HMD), <30 weeks gestation.[4] James E Dice et al. in a review article reports an incidence of 48% in neonates <1000g.[5] Clinical diagnosis of a symptomatic PDA (such as bounding pulses, active precordium, wide pulse pressure, systolic murmur on left sternal border, increase in ventilator requirements despite surfactant therapy, congestive cardiac failure and apnea) lacks accuracy, particularly in the early post-natal days.[5,6] Both false negative and false positive clinical findings are common in the first post-natal week. As a result, echocardiography has become an important non-invasive method for confirming ductal patency and determining its haemodynamic significance.[5]

In addition to prematurity and HMD, there are other risk factors associated with persistent ductal patency in VLBW neonates, these include female gender and sepsis.[7] Complications of prematurity which have been associated with a symptomatic PDA include: Necrotizing enterocolitis (NEC), Intraventricular haemorrhage (IVH), Cystic periventricular leukomalacia (PVL), chronic lung disease (CLD), and retinopathy of prematurity (ROP).[8]

Not all VLBW neonates with PDAs need treatment, and trying to define a target population becomes difficult.[8] Some studies use clinical, echocardiographic, pharmacokinetic and biochemical parameters to identify the target population needing treatment.[8] Time of treatment becomes debatable, whether prophylactically, pre-symptomatically, or when the neonate has symptoms.[8] In addition, individual variability exists as to the drug and dose choice.[8] At CMJAH, VLBW neonates are treated once symptomatic, after confirmation by echocardiography.

Over the past few years the approach to PDA has changed from early diagnosis and medical treatment (using indomethacin or ibuprofen), to conservative treatment.[8] The PDA in neonates is increasingly not being viewed as a pathological condition but as a physiological bystander.[8] There is further evidence that a PDA has no significant effects on major morbidities and mortalities in VLBW neonates.[8] However, a previous study done at CMJAH reported a significant rise in mortality in VLBW neonates with a PDA compared to those without PDA.[3]

Our current study, aims to highlight clinical conditions significantly associated with a symptomatic PDA, and analyse current practices in the management of a symptomatic PDA at CMJAH compared to other studies. The overall aim is to improve survival outcome of VLBW neonates with symptomatic PDAs at CMJAH.

METHODS

Study design

This study was a cross-sectional, retrospective, descriptive study of symptomatic PDAs in VLBW neonates weighing between 500 – 1500 grams (g), admitted at CMJAH between 1 January 2013 to 30 June 2016. Entry criteria included all VLBW neonates admitted for longer than 72 hours (hrs.) after birth. Exclusion criteria included unobtainable records, major birth defects as per Vermont Oxford Network (VON) (www.vtoxford.org) and neonates with cardiac conditions co-existing with a PDA.

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary hospital in the public sector at the Gauteng province in South Africa. The neonatal unit has 98 beds,including 14 intensive care be[6]. All neonates are seen by a paediatrician every day. Very low birth weight neonates with a clinically symptomatic PDA confirmed on echocardiogram, were [5]mpared to those without PDA. Echocardiography was obtained within 24 to 48 hrs. after clinical suspicion of a symp[24]atic PDA. Echocardiographic criteria of a symptomatic PDA included: a left atrial/aortic ratio >1.4 and a PDA diameter >1.4 millimeters (mm).

Database

Data was collected from an existing CMJAH neonatal database on the REDCap (Research Electronic Data Capture). REDCap is a web based program where all the neonatal records are verified, collected and then securely stored for quality improvement and clinical audit.[9] Diagnosis of a PDA was substantiated by records captured electronically at the department of Cardiology. Any missing information in both systems was verified through retrieval of patient files at the hospital records department. Data collected from REDCap included (i) Maternal data – antenatal steroids, antenatal care, multiple gestation; (ii) Neonatal data – gender, age on admis[12] age on discharge, birth weight; (iii) Neonatal ventilator support – resuscitation at birth, nasal continuous positive airway pressure (NCPAP), intermittent positive pressure ventilation (IPPV), surfactant at any point; (iv) Complications of prematurity – HMD, NEC stage 2 and 3 as per modified Bells staging criteria[10], blood transfusion, CLD, steroids for CLD, late onset sepsis (LOS), IVH grade 3 and 4 as per sonographic grading system by Papile et al.[11], pneumothorax, pulmonary haemorrhage, ROP stage 3 and 4 as per Quinn[12] and Cystic PVL. Management of PDA including conservative treatment), indomethacin, ibuprofen and surgical ligation was recorded. Conservative treatment included fluid restriction to 150 ml/kg/day beyond day 5 of life, treatment of cardiac failure with furosemide and optimising haemoglobin l[1]vels to 14 grams per decilitre (g/dl). Very low birth weight neonates who were discharged and those who were transferred out were grouped together as survivors for the purpose of analysis.

Statistical Analys[1]

Data was captured into an MS Excel (Microsoft, USA) spreadsheet and exported into a statistical software progr[8] SPSS 23 (IBM, USA) for analysis. Continuous variables were normally distributed and were described using mean and standard deviation. Categorical variables were described using frequencies and percentages. Comparison was made between VLBW neonat[16]ith symptomatic PDA vs those without PDA for clinical characteristics and outcome. Continuous variables were normally [10]tributed and compared using unpaired t test. Categorical variable[4] were compares using X^2 tests or Fisher's exact test, as appropriate. A p value <0.05 was considered significant. Variable with a p value <0.1 on univariate analysis were entered into a logistic regression model to determine the most

significant association with a symptomatic PDA. Only valid data was reported (i.e. missing variables were excluded).

Ethic

This study was approved by the Human Research Ethic Committee at the University of the Witwatersrand Johannesburg (clearance certificate number M160732).

RESULTS

There were 1844 eligible VLBW neonates. Three hundred and eight were excluded, leaving 1536 neonates in the final sample. One hundred and eighty-four (11.9%) had echocardiographically confirmed PDA and the remaining 1352 (88.0%) had no PDA (See Figure 1). The mean birth weight of all eligible neonates was 1157.0g (SD 222.1), the mean age on admission was 1.2 days (SD 7.0) and the mean age at discharge was 34.8 days (SD 21.9). The birth weight, age on admission and age on discharge are compared in Table 1.

Figure 1: Flow diagram of patient selection

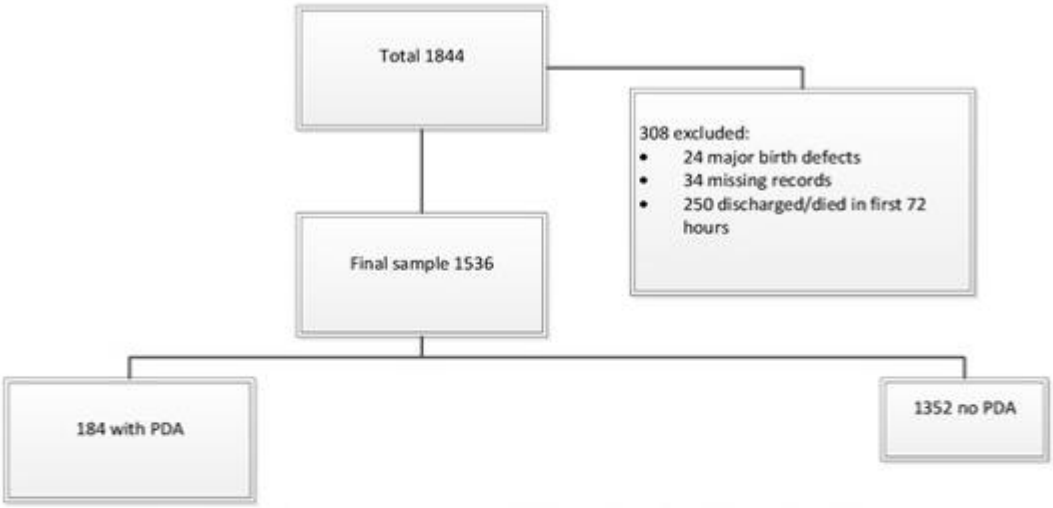


Table 1: Comparison between neonates with PDA and without PDA for continuous variables

Variable	PDA (mean SD)	No PDA (mean SD)	P value
Birth weight (grams)	1062.3 (118.0)	1169.9 (224.1)	<0.001
Age on admission (days)	1.4 (7.2)	1.2 (7.0)	0.76
Age on discharge (days)	54.2 (28.9)	32.2 (19.3)	<0.001

Clinical and demographic characteristics in VLBW neonates with a symptomatic PDA as compared to those without a PDA are shown in Table 2. Neonates with a symptomatic PDA were significantly less likely to have received antenatal steroids or to have a mother who attended antenatal care compared to those without a PDA Resuscitation at birth, HMD, NCPAP, IPPV, surfactant therapy, NEC and blood transfusion were significantly more common in VLBW neonates with a symptomatic PDA than those without PDA (155/183

(84.7%) vs 479/1321 (36.3%), p<0.001). Other complications of prematurity such as CLD, LOS, IVH grade 3 and 4, pneumothorax and pulmonary haemorrhage were all significantly more common in VLBW neonates with a symptomatic PDA (see Table 2). There was no significant difference in multiple gestation, ROP, cystic PVL and gender between VLBW neonates with a symptomatic PDA and those without a PDA (see Table 2). The overall mortality rate between VLBW neonates with PDA and those without PDA was 41/184 (22.3%) vs 229/1352 (16.9%) respectively, p = 0.074.

Table 2: Comparison between neonates with PDA and without PDA for clinical and demographic characteristics

Variable	Total sample (1536) n (% of total)	PDA (184) n (%)	No PDA (1352) n (%)	P value
Antenatal steroids	671/1363 (49.2)	54/151 (35.8)	617/1212 (50.9)	<0.001
Antenatal care	1154/1441(80.1)	117/165 (70.9)	1037/276 (81.3)	0.002
Resuscitation at birth	556/1411 (39.4)	82/159 (51.6)	474/1252 (37.9)	0.001
NCPAP	1015/1419 (71.5)	154/171(90.1)	861/1248 (69.0)	<0.001
IPPV	317/1386 (22.9)	101/177 (57.1)	216/1209 (17.9)	<0.001
Surfactant therapy	1054/1491 (70.7)	164/172 (95.3)	890/1319 (67.5)	<0.001
HMD	1352/1518 (89.1)	178/183 (97.3)	1174/1335(87.9)	<0.001
NEC 2 and 3	161/1533 (10.5)	33/183 (18.0)	128/1350 (9.5)	<0.001
Blood transfusion	634/1504 (42.2)	155/182 (84.7)	479/1321 (36.3)	<0.001
CLD	418/1508 (27.7)	119/183 (65.0)	299/1325 (22.6)	<0.001
Steroids for CLD	230/1485 (15.5)	70/174 (40.2)	160/1311 (12.2)	<0.001
LOS	505/1522 (33.2)	106/182 (58.2)	399/1340 (29.8)	<0.001
IVH 3 and 4	67/929 (7.2)	18/158 (11.4)	49/771 (6.4)	<0.001
Pneumothorax	10/1531 (0.7)	4/183 (2.2)	6/1348 (0.4)	0.006
Pulmonary haemorrhage	22/1536 (1.4)	6/184 (3.3)	16/1352 (1.2)	<0.026
Multiple gestation	271/1503 (18.0)	20/180 (11.1)	251/1323 (19.0)	0.010
ROP 3 and 4	16/467 (3.4)	4/82 (4.9)	12/385 (3.1)	0.120
Cystic PVL	14/1188 (1.2)	3/167 (1.8)	11/1021 (1.1)	0.425
Gender (Male)	719/1533 (46.9)	85/183 (46.4)	634/1350 (47.0)	0.896
Death	270/1536 (17.6)	41/184 (22.3)	229/1352 (16.9)	0.074

*Percentages are expressed in columns.

Variables with p<0.1 were entered into binary logistic regression to determine which are most significantly associated with a symptomatic PDA. Blood transfusion (p = 0.001), surfactant therapy (p = 0.019), IPPV (p<0.001), age on discharge (p<0.001) and antenatal steroids (p = 0.001) (see Table 3) were most significantly associated with a symptomatic PDA.

Table 3: Logistic regression for factors associated with PDA in VLBW neonates at CMJAH

Variable	OR	95%CI	P value
Blood Transfusion	3.180	1.578-6.405	0.001
Surfactant	3.190	1.215-8.381	0.019
IPPV	2.746	1.703-4.429	<0.001
Age on discharge	1.028	1.017-1.039	<0.001
Antenatal steroids	0.459	0.285-0.738	0.001

Ibuprofen was given to 110/184 (59.8%) of the VLBW neonates with symptomatic PDA, while indomethacin was given to 5/184 (2.7%). The patent ductus arteriosus was ligated in 9/184 (4.9%) of the VLBW neonates with symptomatic PDA. The remaining VLBW neonates were treated conservatively i.e. 60/184 (32.6%).

DISCUSSION

The PDA is a vascular structure allowing a left to right shunt from the proximal descending aorta to the main pulmonary artery.[6,13] It becomes persistent once there is failure of the ductus arteriosus (DA) to close within 72hrs. after birth.[6,13] In our study, the incidence of symptomatic PDAs at CMJAH was 11,9%, which was higher compared to previous studies done at CMJAH where it was reported to be 5,4% in 2006/2007 and 9,6% in 2013.[3] The increase in incidence may be due to increasing survival of extremely low birth weight (ELBW) neonates at CMJAH.[3] The incidence in our study is comparable to the National Collaborative study.[4]

There was a significant association between surfactant therapy and a symptomatic PDA in our study. This finding is in agreement with a study done by Abhay Kumar.[14] Exogenous surfactant therapy may increase shunting across PDAs following rapid decrease in pulmonary vascular resistance.[15] It is vital that VLBW neonates who received surfactant therapy for HMD, be monitored clinically and by echocardiogram for an appearance of a haemodynamically significant PDA.[14] A study hypothesized that therapies which result in less mechanical ventilation and improvement of lung function (such as surfactant therapy, fluid restriction, NCPAP) could be associated with lower incidence of symptomatic PDAs.[15] Our study supports this finding because a significantly lower number of VLBW neonates with symptomatic PDAs required mechanical ventilation, this may be due to the rise in use of surfactant therapy and NCPAP in ELBW neonates at CMJAH.[3] Our study is in agreement with other studies which found closure of symptomatic PDA to be less likely to occur in neonates who do not receive antenatal steroids.[6,16] Despite desperate measures to optimize respiratory function, there is still a strong association between symptomatic PDA and development of CLD.[17] This is further emphasized by a recent study done by Mphaphuli on CLD at CMJAH.[18] The presence of a PDA with sepsis substantially increases the risk of CLD.[17] Previous studies done around VLBW neonates at CMJAH revealed an increasing number of LOS in 2013 (19%) compared to 2006/2007 (12.5%).[3] The rate of sepsis in the current study was even higher – at 33.2%. Therefore, prevention of sepsis should be prioritized so that the adverse effects of ductal patency can be altered.[17]

Blood transfusion was significantly associated with PDA in our current study. This is unsurprising as a lower haematocrit after birth places VLBW neonates at greater risk of PDA.[19] All preterm neonates develop physiological anemia of prematurity and this is aggravated by iatrogenic blood loss.[20] However, PDA and blood transfusion in VLBW neonates may place the neonate at even greater risk of NEC than each of these factors alone.[19] This is further emphasized in our study which found a significantly greater number of VLBW neonates with symptomatic PDA developing NEC compared to those without PDA.

Over the years, the haemodynamic and pulmonary consequences of a persistent PDA justified closing the duct.[21] Neonates <28 weeks gestation or with birth weights ≤1000g are the target group for controversy since only 60% will develop significant debilitating PDA related symptoms but only 30% will spontaneously close their PDA.[16] Observational studies demonstrate that the majority of VLBW neonates with persistent PDA after the third day of life, especially those ≥1000g birth weight, can do well without any treatment.[21] Current recommendations prefer conservative treatment.[22] It is interesting to note that very few VLBW neonates in our current study received conservative treatment compared to medical treatment. It is unsurprising that in our current study ibuprofen was more popular than indomethacin. Only oral preparations of both drugs are available at CMJAH. Intravenous indomethacin is not registered in South Africa (SA). Oral ibuprofen is available as a syrup and is favoured at CMJAH because of its fewer side effects compared to indomethacin.[22] Intravenous ibuprofen is very expensive. A randomized pilot study by Cherif, et al. states that oral ibuprofen is as good as IV ibuprofen in terms of ductal closure and is associated with fewer side effects.[22]

Only 4.9% of VLBW neonates with symptomatic PDA underwent ligation. Studies show that delaying ligation (by more than 30 days) causes a reduction in several morbidities associated with ligation.[16,23]

The overall mortality rate of VLBW neonates in our study was 17.6%. There was no significant difference in the mortality rates between neonates with symptomatic PDA and those without PDA. This is encouraging because it is in agreement with other studies across the world which show failure of long term benefits of ductal closure from several adverse outcomes that are strongly associated with persistent PDA such as death, HMD, BPD, NEC, IVH etc.[21,23] Tools need to be developed to identify VLBW neonates at risk of detrimental outcomes related to a symptomatic PDA such as those with large left to right shunts.[17,21] This must be followed by intervention trials to conclude whether closing the PDA can avoid such outcomes.[17] Until then, choosing to aim to close a PDA of a VLBW neonate who is ill actually remains subjective.[17]

CONCLUSION

Our study described the incidence and clinical characteristics significantly associated with a symptomatic PDA. It highlighted the most common method of treatment used for symptomatic PDAs in VLBW neonates at CMJAH. Although management of a symptomatic PDA remains highly controversial, there is a move towards a more conservative approach at the CMJAH neonatal unit.

STUDY LIMITATIONS

Our study was limited as this was a secondary analysis of a database. . Timing of treatment or whether multiple courses of medication were given could not be established. The dose of medication and timing of complications could not be evaluated.

RECOMMENDATION

move towards conservative treatment because there is insufficient evidience sup ting that medical or surgical closure of the ductus is beneficial in preterm neonates and a more permissive approach does not result in worse outcomes. [21, 23]

Word count: 2656

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