AN EVALUATION OF RETINOPATHY OF PREMATURITY IN VERY LOW BIRTH WEIGHT BABIES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Paediatric neonatologist Charlotte Maxeke Johannesburg Academic Hospital

Degree report submitted for: MMed (Paed)

25 May 2016

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DECLARATION

I declare that the contents of the paper are all the work of the author.

Zahedah Dadoo

25 May 2016

LETTER BY COAUTHOR

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

15 February 2016

TO WHOM IT MAY CONCERN

Re: An evaluation of screening for retinopathy of Prematurity in Very Low birth Weight Babies at a Tertiary Hospital in Johannesburg, South Africa.

This is to confirm that Dr Z Dadoo conducted the research in fulfilment for her MMed. She was the primary author. I supervised the research process, including protocol development, data collection and analysis and write up of the final paper and research report. I am a co-author on the paper accepted for publication in the South African Journal of Child Health.

I agree that Dr Dadoo may submit this paper for her MMed degree.

Yours truly

Daynia Ballot (Prof)

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ABSTRACT

Background. Retinopathy of prematurity (ROP) is a leading cause of blindness for very low birth weight (VLBW, <1500g) babies. ROP screening identifies babies that require treatment to prevent major visual impairment.

Objectives. To evaluate the screening for ROP at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) by reviewing the number of babies screened according to the CMJAH guidelines, the grades of ROP found and the treatment modality received.

Methods. This was a retrospective record review of VLBW babies born between 1 January 2013 and 31 December 2013 at CMJAH, whether inborn or transferred in. The babies were divided into 2 groups based on age at final outcome. Final outcome was defined as death, discharge or transfer out of the unit. The 'early' outcome group had their final outcome before day 28 of life. The 'late' outcome group had their final outcome at day 28 or more of life. The early outcome group qualified for outpatient ROP screening and the late outcome group qualified for inpatient ROP screening.

Results. There were a total of 572 VLBW babies at CMJAH during this time period. The babies had a mean birth weight of 1127g (SD 244.75) and gestational age of 29 weeks (SD 2.743). The mean duration of stay was 29 days (SD 21.66) and there were 309 female babies. Of these 572 babies, 304 comprised the early outcome group and 268 comprised the late outcome group.

In the early outcome group babies that were transferred out of the unit or died were excluded, therefore the remaining 147 babies discharged home qualified for outpatient ROP screening. Inpatient ROP Screening was carried out in 36/147 (24.4%) of these babies (not in accordance with ROP screening guidelines). ROP was documented in 4/36 (11.1%). Outpatient ROP screening records were unavailable.
Exclusions from the late outcome group included 5 babies. In the late outcome group 111/263 (42.2%) were screened for ROP. ROP was found in 17%. One baby required treatment with intravitreal anti-VEGF and 3 babies required surgery.

Conclusions. More than half of the babies in the late outcome group were not screened during their stay (57.8%). More than one third of babies were discharged prior to reaching the current recommended age for screening. Efforts need to be intensified to identify and screen all eligible babies prior to discharge. Outpatient ROP screening is not well documented, therefore prevalence cannot be established.

INTRODUCTION

Retinopathy of prematurity (ROP) is known to be an important cause of visual impairment and blindness in the surviving premature population. Over the last ten to fifteen years an estimated 50 000 children are blind from ROP, and it is likely that many more are unilaterally blind or visually impaired. [(1)] As the disease can be present without any symptoms or clinical signs, it is necessary to screen premature babies for ROP. Most ROP will resolve by itself and only requires continued monitoring until resolution or maturation of retinal vessels occurs. However, severe forms of ROP require treatment to preserve or salvage vision and to improve quality of life.

In developed countries two epidemics of blindness due to ROP have been described. The first occurred predominantly in the United States of America in the 1940s – 1950s and affected premature babies. The principal risk factor was the supply of unmonitored supplemental oxygen to the premature baby. The subsequent restriction in oxygen use led to a decrease in blindness due to ROP. The second epidemic started in the 1970s as a result of the higher survival rates of extremely premature babies secondary to advances in neonatal intensive care units (NICUs).[(1)]

A third epidemic of ROP is currently said to be occurring in middle-income countries[(2)] like South Africa. Reasons for this include improved survival of premature babies in these countries together with a lack of adequate monitoring of oxygen therapy. Countries with infant mortality rates (IMRs) greater than 60 per 1000 live births usually do not have neonatal intensive care units (NICUs) therefore premature babies usually do not survive and these countries have a low incidence of ROP.[(2)] Countries with IMRs of 9 to 60 per 1000 live births represent the highest burden of blindness caused by ROP as more premature babies survive in NICUs

where oxygen administration may be poorly monitored.[1] South Africa's IMR for 2011 was 35 per 1000 live births.[3] As we succeed in improving our IMR, strategies need to be in place to target prevention of known risk factors for ROP and screening for ROP that may require treatment.

If screening programs are not put into place, the incidence of blindness from untreated ROP is likely to increase. It was first reported in 1988 that treatment could improve the outcome for severe ROP.[4] This makes ROP screening a priority. The World Health Organization's vision 2020 program has recognized ROP as an important cause of childhood blindness in industrialized and middle-income countries.[5] Their strategies advocate examining premature babies at risk of ROP, treating those premature babies with severe ROP and promoting oxygen monitoring to all premature babies receiving oxygen therapy.

The two important aspects of screening for ROP are who to screen and when to screen them. Knowledge of risk factors for ROP helps us to identify who needs to be screened. Risk factors for ROP are divided into two groups – prenatal and postnatal.[6] Prenatal factors include gestational age and birth weight. Postnatal factors include prolonged exposure to oxygen and other identified markers of neonatal illness severity. Examples of neonatal illness severity include the need for mechanical ventilation, the presence of sepsis or intraventricular haemorrhage, the administration of blood transfusions and poor postnatal weight gain.[7] Low levels of serum IGF-1 are found in babies with poor postnatal weight gain. [8] General criteria used in screening programs are birth weight and gestational age combined with sickness criteria.[9] The recommended age for screening is based on the timing of the occurrence of ROP and is related to the maturity of the retinal vessels.

There are concerns that in middle and low-income countries more older and larger babies are presenting with ROP compared to high-income countries. In a large prospective study of ROP done at Chris Hani Baragwanath Academic Hospital to establish the frequency of ROP it was concluded that this was not the case, and the screening weight could safely be lowered to 1250g.[10]

According to the latest ROP guidelines published in the South African Medical Journal (SAMJ), all very low birth weight (VLBW) babies <1500g or 32 weeks GA should be screened for ROP.[11] Screening is repeated until retinal vascularization has reached a stage where the risk of a serious adverse outcome is considered minimal. ROP screening is carried out by an ophthalmologist and by means of indirect ophthalmoscopy. Newer screening techniques involve the use of digital cameras to capture images of the retina. The 2013 SAMJ guidelines recommend screening all VLBW babies at 4 to 6 weeks chronological age or 31 to 33 weeks corrected GA – whichever comes last. The guidelines detail where and how to screen, as well as how to follow up and manage patients and when to stop screening. [11] These guidelines are in line with the WHO Vision 2020 strategy. Vision 2020 ensures the availability of ophthalmologists experienced in indirect ophthalmoscopy who can identify premature babies who require treatment for ROP, that babies at risk for ROP have their fundi examined starting 4–6 weeks after birth, and that those with severe disease are treated immediately. [5]

ROP is classified according to the International Classification of ROP (ICROP) and was standardised in 1984 and updated in 1987 and again in 2005. [12] ROP is characterized by using four components (see table 1): location (zone 1-3), severity (stage 1-5), extent (circumferential location of the disease reported as clock hours) and plus disease (tortuosity of posterior retinal vessels). [7] Two important definitions

are that of threshold ROP and prethreshold ROP (refer to table 2). Threshold ROP carries a risk of blindness of 50%, which can be reduced to 25% with treatment. Prethreshold ROP can require either treatment or close observation – depending on the type. The various treatment options available for ROP include cryotherapy, laser ablative therapy, intravitreal anti - vascular endothelial growth factor (VEGF) and retinal reattachment. [7] Not all of these options are available in our setting.

In South Africa, approximately 1 in 5 of all VLBW babies are affected by ROP. A study at Chris Hani Baragwanath Academic Hospital found the incidence to be approximately 17%. [10] In another study undertaken at Tygerberg Children's Hospital in Cape Town, the incidence was found to be 21.8%. [13] A study by Delport et al at Kalafong Hospital found the incidence of ROP to be 24.5%. [14] The incidence at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is unknown.

The present study aimed to review the screening program for ROP in VLBW babies at CMJAH.

Table 1. The four components included in the classification of ROP [7]

COMPONENT	DESCRIPTION
LOCATION	• How far the developing retinal blood vessels have progressed • The retina is divided into 3 concentric circles or zones **Zone 1** Imaginary circle with optic nerve at the center **Zone 2** Extends from the edge of zone 1 to the ora serrata on the nasal side of the eye and half the distance to the ora serrata on the temporal side **Zone 3** The outer crescent-shaped area extending from zone 2 out to the ora serrata temporally
SEVERITY	• The stage of the disease **Stage 1** a demarcation line between normal and avascular retina **Stage 2** a ridge of fibrovascular tissue replaces the demarcation line **Stage 3** abnormal blood vessels and fibrous tissue develop on the edge of the ridge and extend into the vitreous **Stage 4** partial retinal detachment **Stage 5** complete retinal detachment
EXTENT	• Circumferential location of the disease and reported as clock hours in the appropriate zone
PLUS DISEASE	• Refers to the presence of vascular dilatation and tortuosity of the posterior retinal vessels in at least 2 quadrants

Table 2. Important definitions used in ROP screening [7]

Threshold ROP	Zone 1 or 2: • 8 cumulative clock hours of stage 3 with plus disease
Prethreshold ROP	Zone 1: • any ROP less than threshold Zone 2: • stage 2 ROP with plus disease • stage 3 without plus disease • stage 3 with plus disease but less than 8 cumulative clock hours

METHODS

This study was undertaken at CMJAH, a tertiary care institution that serves as a referral center for the primary care clinics and other hospitals in the area. It was a retrospective record review of all the VLBW babies admitted to CMJAH from 1 January 2013 to 31 December 2013, whether inborn or transferred in. Babies that died or were transferred out before day 28 of life were excluded from the present study.

Patient information was obtained from an existing neonatal VLBW database at CMJAH, which is kept for the purpose of clinical audit purposes. The database consists of standard information that is collected upon the discharge of each baby. Data is managed using REDCAP (Research Electronic Data Capture) tools hosted by the University of the Witwatersrand.[15] All definitions in the database are according to the Vermont Oxford Network (VON) (www.vtoxford.org)

The ROP screening guidelines for CMJAH were derived from the SAMJ 2013 ROP screening guidelines and state that all VLBW babies or those born at a GA below 32 weeks should be screened at 4-6 weeks chronological age. In babies who were screened more than once, the worst grade of ROP recorded was used for the purpose of the study. Intravitreal anti VEGF and surgery for ROP were available at CMJAH at the time of the study.

Prior to discharge, all VLBW babies at CMJAH were transferred to Kangaroo Mother Care (KMC) once their current weight was above 1000 grams, they were tolerating full enteral feeds and they were off supplemental oxygen. Whenever possible, these babies were transferred to regional hospitals for continuing care. The VLBW babies

were discharged from hospital once they had reached a weight above 1600 grams, were taking full oral feeds (either by cup or breast) and were maintaining their blood glucose levels. Babies were referred for ROP screening to the ophthalmologist at the discretion of the attending paediatric registrar, in accordance with the above guidelines. Babies in KMC were included in the screening program. Results of the ROP screening were recorded on the daily charts for each patient.

Groups

The VLBW babies in the study population were divided into two groups based on the calculated chronological age at final outcome, in accordance with the ROP screening guidelines above. Final outcome was defined as death, discharge or transfer out of the unit. The 'early' outcome group had their final outcome before day 28 of life. The 'late' outcome group had their final outcome on day 28 or more of life. The early outcome group qualified for outpatient ROP screening and the late outcome group qualified for inpatient ROP screening.

Statistical Analysis

The relevant data for the present study was extracted from the neonatal database and exported to a Microsoft Excel spreadsheet. Demographic information, outcome, whether ROP screening had been performed and the grade and treatment of ROP (intravitreal anti-VEGF or surgery) were collected for each patient. Duration of stay and chronological age at final outcome (discharge, death or transfer out to a regional hospital) were calculated.

The data from the Excel spreadsheet was imported to the statistical software IBM SPSS Statistics version 22 for analysis. Data was described using standard statistical methods. Categorical variables were described using frequencies and percentages, and continuous variables by using measures of central tendency - mean and standard deviation - as the data was normally distributed.

The study was approved by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg. (Clearance certificate no. M130947)

RESULTS

A total of 572 VLBW babies were admitted to the neonatal unit during the study period. A total of 162 babies were excluded. There were 128 deaths and 29 transfers to regional hospitals prior to 28 days. Five babies were transferred in to the unit after 28 days of life for surgical procedures; 2 died immediately and 3 were transferred back to their original hospitals within 2 days. The final sample therefore included 410 babies. The mean birth weight was 1127g with a standard deviation (SD) of 244.75 and the mean GA was 29 weeks (SD 2.743). The mean age at admission was 1 day (SD 5.806) and the babies had a mean duration of stay of 28 days (SD 21.66). The majority of babies (309; 54%) were female. There were 147 babies in the early outcome group and 263 babies in the late outcome group (see Figure 1).

ROP screening was documented in 147 / 410 (35.9%) VLBW babies. The ROP findings are summarized in table 3. Plus disease was not found in any of the babies. Intravitreal anti VEGF treatment was used in 1 baby and surgical treatment was documented in 3 babies.

Although the 147 babies in the early outcome group were not required to be screened as inpatients, ROP screening was carried out in 36 (24.4%) and 4 (11%) had evidence of ROP. Screening for ROP was undertaken in 111/263 (42.2%) of babies in the late outcome group and 19 (17.1%) had evidence of ROP.

Figure 1. Diagram showing number of babies in each group and their final outcome

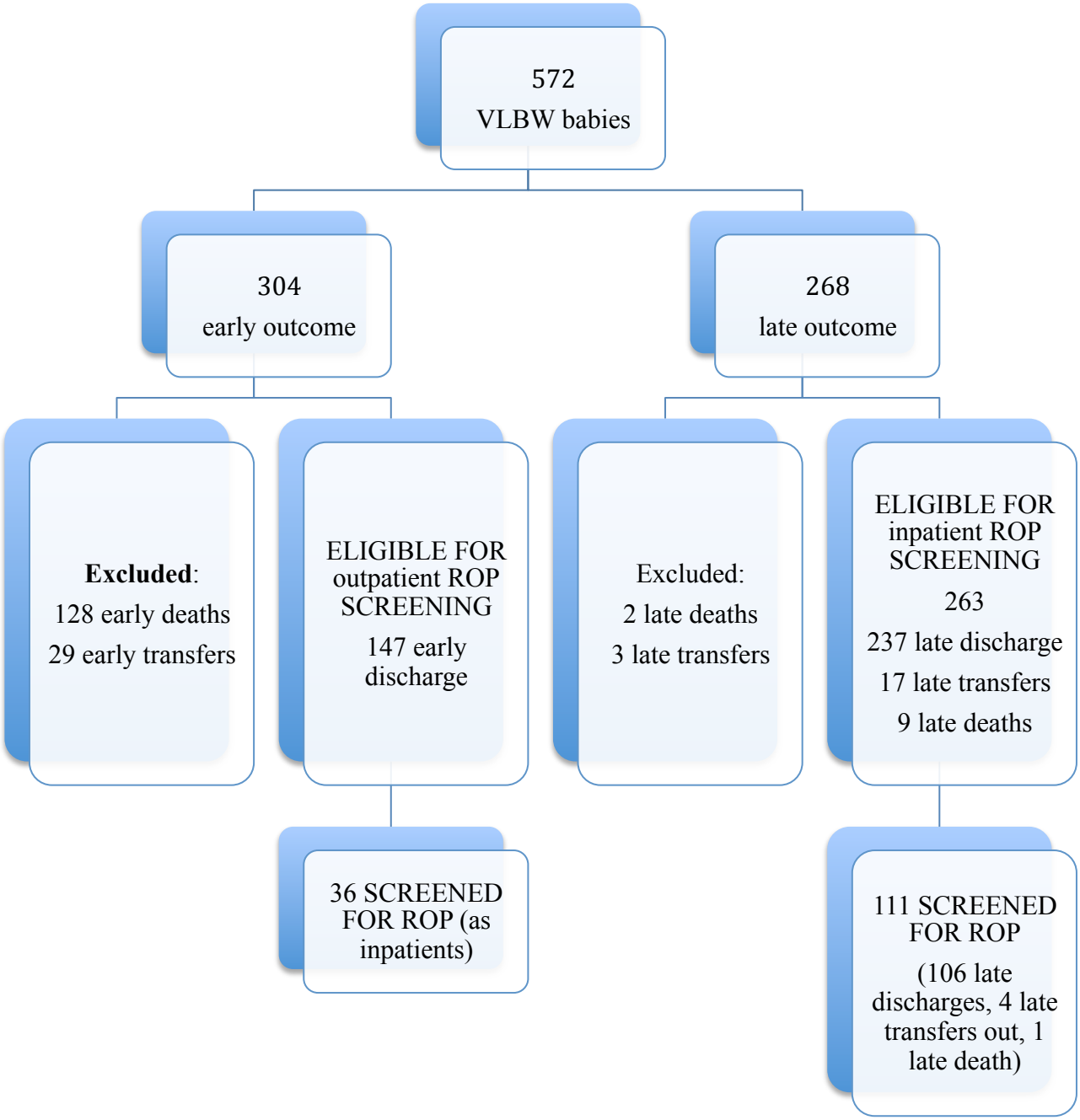

Table 3. ROP grading results in babies screened as inpatients

	No Rop N (%)	Grade 1 ROP N (%)	Grade 2 ROP N (%)	Grade 3 ROP N (%)	Grade 4 ROP N (%)	Grade not recorded N (%)	Total N
Early outcome group	28 (77.8)	2 (5.6)	2 (5.6)	0 (0)	0 (0)	4 (11)	36
Late outcome group	81 (73)	11 (9.9)	5 (4.5)	2 (1.8)	1 (0.9)	11 (9.9)	111

DISCUSSION

This study shows that less than half of the VLBW babies at CMJAH eligible for inpatient ROP screening according to the hospital's guidelines were actually screened for ROP.

More than one third of babies were discharged before they had reached the required age for screening. Despite this, 24% of these babies were screened before 4 weeks of life. Of concern is that 11% of these babies had ROP. This group of early discharges is important as they require outpatient ROP follow up. It is not known whether these babies attended screening for ROP as outpatients, so it is possible that a number of babies with ROP were missed. Education of caregivers in this group is essential, as defaulters to follow up are at risk of presenting with more severe grades of ROP and increased morbidity.

Although a true prevalence for ROP at CMJAH for 2013 cannot be calculated, due to the low level of screening, ROP was found in 15.6% of VLBW babies which is similar to the 17% rate reported at Chris Hani Baragwanath Hospital. [10] Other South African studies reported slightly higher rates – 21.8% at Tygerberg Children's Hospital and 24.5% at Kalafong Hospital. [13] [14]

This review shows that the inpatient ROP screening at CMJAH is not optimal and needs to be improved. Inpatient ROP screening was not carried out in 57.8%. Babies at risk need to be promptly identified. The attending medical staff (interns, medical officers, registrars and consultants) should to be familiar with the guidelines. Junior staff will need to be educated on the harms of oxygen therapy and the subsequent complication of ROP and its consequences. Although it may seem attractive to delay

the discharge of VLBW babies until they have achieved the recommended age for ROP screening, this is not feasible due to high patient numbers and extreme pressure for beds. Adjusting the screening protocol to allow ROP screening at a younger age in those babies who will be discharged before 28 days of age would be a simpler solution and would prevent missed opportunities to identify babies with ROP.

No babies were recorded to have plus disease. This data may have not been captured on discharge, was truly not present or may have been under reported by the ophthalmologist performing the screening. Bigger babies are also at risk of ROP. The ROP guideline published in February 2013 in the SAMJ suggests that premature babies with weights between 1500-2000g may also be at risk if they have risk factors and if oxygen monitoring in this group of babies has been suboptimal then screening should be considered. [11] This group of babies were not included in the present study, but should not be overlooked in screening programs for ROP.

Ideally an electronic prospective data capture system needs to be implemented to capture all the results of ROP screening – both inpatient and outpatient. This would only be possible in conjunction with the Department of Ophthalmology, especially regarding the outpatient screening. This will assist greatly with future research and in gauging the incidence of ROP at CMJAH.

One limitation is the design of the study - the retrospective nature of the study means a pre-collected dataset was used. ROP information is not available for babies on the low birth weight (LBW) database who may have a GA of <32 weeks but a weight of

>1500g. Another potential limitation is that of inter-observer error in classifying the grade of ROP present, as different ophthalmology registrars did the screening, with different levels of skill and experience.

More than half of VLBW babies that met criteria for ROP screening according to CMJAH ROP screening guidelines were not screened during their inpatient stay. Efforts need to be intensified to identify these babies and screen them prior to discharge.

Records for outpatient ROP screening are not well organized and not easily accessible at both the neonatal follow up clinic and the ophthalmology unit. There is a need for a coordinated database between the two specialties. In this regard, a true prevalence for ROP at CMJAH cannot be established.

Screening for ROP should include all babies with a GA of <32 weeks (even if their weight is >1500g). In addition, babies weighing between 1500g and 2000g with risk factors for ROP should not be omitted from screening programs.

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APPENDICES

Appendix 1 Email for editor of SAJCH

Appendix 2 Reprint of article

Appendix 3 Ethics clearance

Appendix 4 Protocol

APPENDIX 1 EMAIL FROM EDITOR OF SAJCH

John M Pettifor <sajch.editor@hmpg.co.za>
To: Zahedah Dadoo <drzdadoo@gmail.com>
Dear Dr Dadoo:

We are please to inform you that your submission to South African Journal of Child Health, "An Evaluation of the Screening for Retinopathy of Prematurity in Very Low Birth Weight Babies at a Tertiary Hospital in Johannesburg, South Africa", has been accepted for publication.

Nearer the date of publication you will receive proofs of the manuscript. Please go through these carefully to correct any errors.

regards
John Pettifor

John M Pettifor
sajch.editor@hmpg.co.za
Emeritus Professor and Editor: South African Journal of Child Health

South African Journal of Child Health
Editor: Emeritus Professor John Pettifor
www.sajch.org.za

APPENDIX 2 ARTICLE ACCEPTED FOR PUBLICATION IN SAJCH

SAJCH 2016; 10(1):79-82

An Evaluation of the Screening for Retinopathy of Prematurity in Very Low Birth Weight Babies at a Tertiary Hospital in Johannesburg, South Africa

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Department of Paediatrics and Child Health, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

***Corresponding author**: Z Dadoo (drzdadoo@gmail.com)*

ABSTRACT

Background. Retinopathy of prematurity (ROP) is a leading cause of blindness for very low birth weight (VLBW, <1500g) babies. ROP screening identifies babies that require treatment to prevent major visual impairment.

Objectives. To evaluate the screening for ROP at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) by reviewing the number of babies screened according to the CMJAH guidelines, the grades of ROP found and the treatment modality received.

Methods. This was a retrospective record review of VLBW babies born between 1 January 2013 and 31 December 2013 at CMJAH, whether inborn or transferred in. The babies were divided into 2 groups based on age at final outcome. Final outcome was defined as death, discharge or transfer out of the unit. The 'early' outcome group had their final outcome before day 28 of life. The 'late' outcome group had their final

outcome at day 28 or more of life. The early outcome group qualified for outpatient ROP screening and the late outcome group qualified for inpatient ROP screening.

Results. There were a total of 572 VLBW babies at CMJAH during this time period. The babies had a mean birth weight of 1127g (SD 244.75) and gestational age of 29 weeks (SD 2.743). The mean duration of stay was 29 days (SD 21.66) and there were 309 female babies. Of these 572 babies, 304 comprised the early outcome group and 268 comprised the late outcome group.

In the early outcome group babies that were transferred out of the unit or died were excluded, therefore the remaining 147 babies discharged home qualified for outpatient ROP screening. Inpatient ROP Screening was carried out in 36/147 (24.4%) of these babies (not in accordance with ROP screening guidelines). ROP was documented in 4/36 (11.1%). Outpatient ROP screening records were unavailable.

Exclusions from the late outcome group included 5 babies. In the late outcome group 111/263 (42.2%) were screened for ROP. ROP was found in 17%. One baby required treatment with intravitreal anti-VEGF and 3 babies required surgery.

Conclusions. More than half of the babies in the late outcome group were not screened during their stay (57.8%). More than one third of babies were discharged prior to reaching the current recommended age for screening. Efforts need to be intensified to identify and screen all eligible babies prior to discharge. Outpatient ROP screening is not well documented, therefore prevalence cannot be established.

BACKGROUND

Retinopathy of prematurity (ROP) is known to be an important cause of visual impairment and blindness in the surviving premature population. Over the last ten to fifteen years an estimated 50 000 children are blind from ROP, and it is likely that many more are unilaterally blind or visually impaired. [(1)] As the disease can be present without any symptoms or clinical signs, it is necessary to screen premature babies for ROP. Most ROP will resolve by itself and only requires continued monitoring until resolution or maturation of retinal vessels occurs. However, severe forms of ROP require treatment to preserve or salvage vision and to improve quality of life.

In developed countries two epidemics of blindness due to ROP have been described. The first occurred predominantly in the United States of America in the 1940s – 1950s and affected premature babies. The principal risk factor was the supply of unmonitored supplemental oxygen to the premature baby. The subsequent restriction in oxygen use led to a decrease in blindness due to ROP. The second epidemic started in the 1970s as a result of the higher survival rates of extremely premature babies secondary to advances in neonatal intensive care units (NICUs).[(1)]

A third epidemic of ROP is currently said to be occurring in middle-income countries[(2)] like South Africa. Reasons for this include improved survival of premature babies in these countries together with a lack of adequate monitoring of oxygen therapy. Countries with infant mortality rates (IMRs) greater than 60 per 1000 live births usually do not have neonatal intensive care units (NICUs) therefore premature babies usually do not survive and these countries have a low incidence of

ROP.[2] Countries with IMRs of 9 to 60 per 1000 live births represent the highest burden of blindness caused by ROP as more premature babies survive in NICUs where oxygen administration may be poorly monitored.[1] South Africa's IMR for 2011 was 35 per 1000 live births.[3] As we succeed in improving our IMR, strategies need to be in place to target prevention of known risk factors for ROP and screening for ROP that may require treatment.

If screening programs are not put into place, the incidence of blindness from untreated ROP is likely to increase. It was first reported in 1988 that treatment could improve the outcome for severe ROP.[4] This makes ROP screening a priority. The World Health Organization's vision 2020 program has recognized ROP as an important cause of childhood blindness in industrialized and middle-income countries.[5] Their strategies advocate examining premature babies at risk of ROP, treating those premature babies with severe ROP and promoting oxygen monitoring to all premature babies receiving oxygen therapy.

The two important aspects of screening for ROP are who to screen and when to screen them. Knowledge of risk factors for ROP helps us to identify who needs to be screened. Risk factors for ROP are divided into two groups – prenatal and postnatal.[6] Prenatal factors include gestational age and birth weight. Postnatal factors include prolonged exposure to oxygen and other identified markers of neonatal illness severity. Examples of neonatal illness severity include the need for mechanical ventilation, the presence of sepsis or intraventricular haemorrhage, the administration of blood transfusions and poor postnatal weight gain.[7] Low levels of serum IGF-1 are found in babies with poor postnatal weight gain. [8] General criteria used in screening programs are birth weight and gestational age combined with sickness

criteria.[9] The recommended age for screening is based on the timing of the occurrence of ROP and is related to the maturity of the retinal vessels.

There are concerns that in middle and low-income countries more older and larger babies are presenting with ROP compared to high-income countries. In a large prospective study of ROP done at Chris Hani Baragwanath Academic Hospital to establish the frequency of ROP it was concluded that this was not the case, and the screening weight could safely be lowered to 1250g.[10]

According to the latest ROP guidelines published in the South African Medical Journal (SAMJ), all very low birth weight (VLBW) babies <1500g or 32 weeks GA should be screened for ROP.[11] Screening is repeated until retinal vascularization has reached a stage where the risk of a serious adverse outcome is considered minimal. ROP screening is carried out by an ophthalmologist and by means of indirect ophthalmoscopy. Newer screening techniques involve the use of digital cameras to capture images of the retina. The 2013 SAMJ guidelines recommend screening all VLBW babies at 4 to 6 weeks chronological age or 31 to 33 weeks corrected GA – whichever comes last. The guidelines detail where and how to screen, as well as how to follow up and manage patients and when to stop screening. [11] These guidelines are in line with the WHO Vision 2020 strategy. Vision 2020 ensures the availability of ophthalmologists experienced in indirect ophthalmoscopy who can identify premature babies who require treatment for ROP, that babies at risk for ROP have their fundi examined starting 4–6 weeks after birth, and that those with severe disease are treated immediately. [5]

ROP is classified according to the International Classification of ROP (ICROP) and was standardised in 1984 and updated in 1987 and again in 2005. [12] ROP is characterized by using four components (see table 1): location (zone 1-3), severity

(stage 1-5), extent (circumferential location of the disease reported as clock hours) and plus disease (tortuosity of posterior retinal vessels). [7] Two important definitions are that of threshold ROP and prethreshold ROP (refer to table 2). Threshold ROP carries a risk of blindness of 50%, which can be reduced to 25% with treatment. Prethreshold ROP can require either treatment or close observation – depending on the type. The various treatment options available for ROP include cryotherapy, laser ablative therapy, intravitreal anti - vascular endothelial growth factor (VEGF) and retinal reattachment. [7] Not all of these options are available in our setting.

In South Africa, approximately 1 in 5 of all VLBW babies are affected by ROP. A study at Chris Hani Baragwanath Academic Hospital found the incidence to be approximately 17%. [10] In another study undertaken at Tygerberg Children's Hospital in Cape Town, the incidence was found to be 21.8%. [13] A study by Delport et al at Kalafong Hospital found the incidence of ROP to be 24.5%. [14] The incidence at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is unknown.

The present study aimed to review the screening program for ROP in VLBW babies at CMJAH.

Table 1. The four components included in the classification of ROP [7]

COMPONENT	DESCRIPTION
LOCATION	• How far the developing retinal blood vessels have progressed • The retina is divided into 3 concentric circles or zones **Zone 1** Imaginary circle with optic nerve at the center **Zone 2** Extends from the edge of zone 1 to the ora serrata on the nasal side of the eye and half the distance to the ora serrata on the temporal side **Zone 3** The outer crescent-shaped area extending from zone 2 out to the ora serrata temporally
SEVERITY	• The stage of the disease **Stage 1** a demarcation line between normal and avascular retina **Stage 2** a ridge of fibrovascular tissue replaces the demarcation line **Stage 3** abnormal blood vessels and fibrous tissue develop on the edge of the ridge and extend into the vitreous **Stage 4** partial retinal detachment **Stage 5** complete retinal detachment
EXTENT	• Circumferential location of the disease and reported as clock hours in the appropriate zone
PLUS DISEASE	• Refers to the presence of vascular dilatation and tortuosity of the posterior retinal vessels in at least 2 quadrants

Table 2. Important definitions used in ROP screening [7]

Threshold ROP	Zone 1 or 2: • 8 cumulative clock hours of stage 3 with plus disease
Prethreshold ROP	Zone 1: • any ROP less than threshold

	Zone 2: • stage 2 ROP with plus disease • stage 3 without plus disease • stage 3 with plus disease but less than 8 cumulative clock hours

METHODS

This study was undertaken at CMJAH, a tertiary care institution that serves as a referral center for the primary care clinics and other hospitals in the area. It was a retrospective record review of all the VLBW babies admitted to CMJAH from 1 January 2013 to 31 December 2013, whether inborn or transferred in. Babies that died or were transferred out before day 28 of life were excluded from the present study.

Patient information was obtained from an existing neonatal VLBW database at CMJAH, which is kept for the purpose of clinical audit purposes. The database consists of standard information that is collected upon the discharge of each baby. Data is managed using REDCAP (Research Electronic Data Capture) tools hosted by the University of the Witwatersrand.[15] All definitions in the database are according to the Vermont Oxford Network (VON) (www.vtoxford.org)

The ROP screening guidelines for CMJAH were derived from the SAMJ 2013 ROP screening guidelines and state that all VLBW babies or those born at a GA below 32 weeks should be screened at 4-6 weeks chronological age. In babies who were screened more than once, the worst grade of ROP recorded was used for the purpose of the study. Intravitreal anti VEGF and surgery for ROP were available at CMJAH at the time of the study.

Prior to discharge, all VLBW babies at CMJAH were transferred to Kangaroo Mother Care (KMC) once their current weight was above 1000 grams, they were tolerating

full enteral feeds and they were off supplemental oxygen. Whenever possible, these babies were transferred to regional hospitals for continuing care. The VLBW babies were discharged from hospital once they had reached a weight above 1600 grams, were taking full oral feeds (either by cup or breast) and were maintaining their blood glucose levels. Babies were referred for ROP screening to the ophthalmologist at the discretion of the attending paediatric registrar, in accordance with the above guidelines. Babies in KMC were included in the screening program. Results of the ROP screening were recorded on the daily charts for each patient.

Groups

The VLBW babies in the study population were divided into two groups based on the calculated chronological age at final outcome, in accordance with the ROP screening guidelines above. Final outcome was defined as death, discharge or transfer out of the unit. The 'early' outcome group had their final outcome before day 28 of life. The 'late' outcome group had their final outcome on day 28 or more of life. The early outcome group qualified for outpatient ROP screening and the late outcome group qualified for inpatient ROP screening.

Statistical Analysis

The relevant data for the present study was extracted from the neonatal database and exported to a Microsoft Excel spreadsheet. Demographic information, outcome, whether ROP screening had been performed and the grade and treatment of ROP (intravitreal anti-VEGF or surgery) were collected for each patient. Duration of stay

and chronological age at final outcome (discharge, death or transfer out to a regional hospital) were calculated.

The data from the Excel spreadsheet was imported to the statistical software IBM SPSS Statistics version 22 for analysis. Data was described using standard statistical methods. Categorical variables were described using frequencies and percentages, and continuous variables by using measures of central tendency - mean and standard deviation - as the data was normally distributed.

ETHICS APPROVAL

The study was approved by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg. (Clearance certificate no. M130947)

RESULTS

A total of 572 VLBW babies were admitted to the neonatal unit during the study period. A total of 162 babies were excluded. There were 128 deaths and 29 transfers to regional hospitals prior to 28 days. Five babies were transferred in to the unit after 28 days of life for surgical procedures; 2 died immediately and 3 were transferred back to their original hospitals within 2 days. The final sample therefore included 410 babies. The mean birth weight was 1127g with a standard deviation (SD) of 244.75 and the mean GA was 29 weeks (SD 2.743). The mean age at admission was 1 day (SD 5.806) and the babies had a mean duration of stay of 28 days (SD 21.66). The majority of babies (309; 54%) were female. There were 147 babies in the early outcome group and 263 babies in the late outcome group (see Figure 1).

ROP screening was documented in 147 / 410 (35.9%) VLBW babies. The ROP findings are summarized in table 3. Plus disease was not found in any of the babies. Intravitreal anti VEGF treatment was used in 1 baby and surgical treatment was documented in 3 babies.

Although the 147 babies in the early outcome group were not required to be screened as inpatients, ROP screening was carried out in 36 (24.4%) and 4 (11%) had evidence of ROP. Screening for ROP was undertaken in 111/263 (42.2%) of babies in the late outcome group and 19 (17.1%) had evidence of ROP.

Figure 1. Diagram showing number of babies in each group and their final outcome

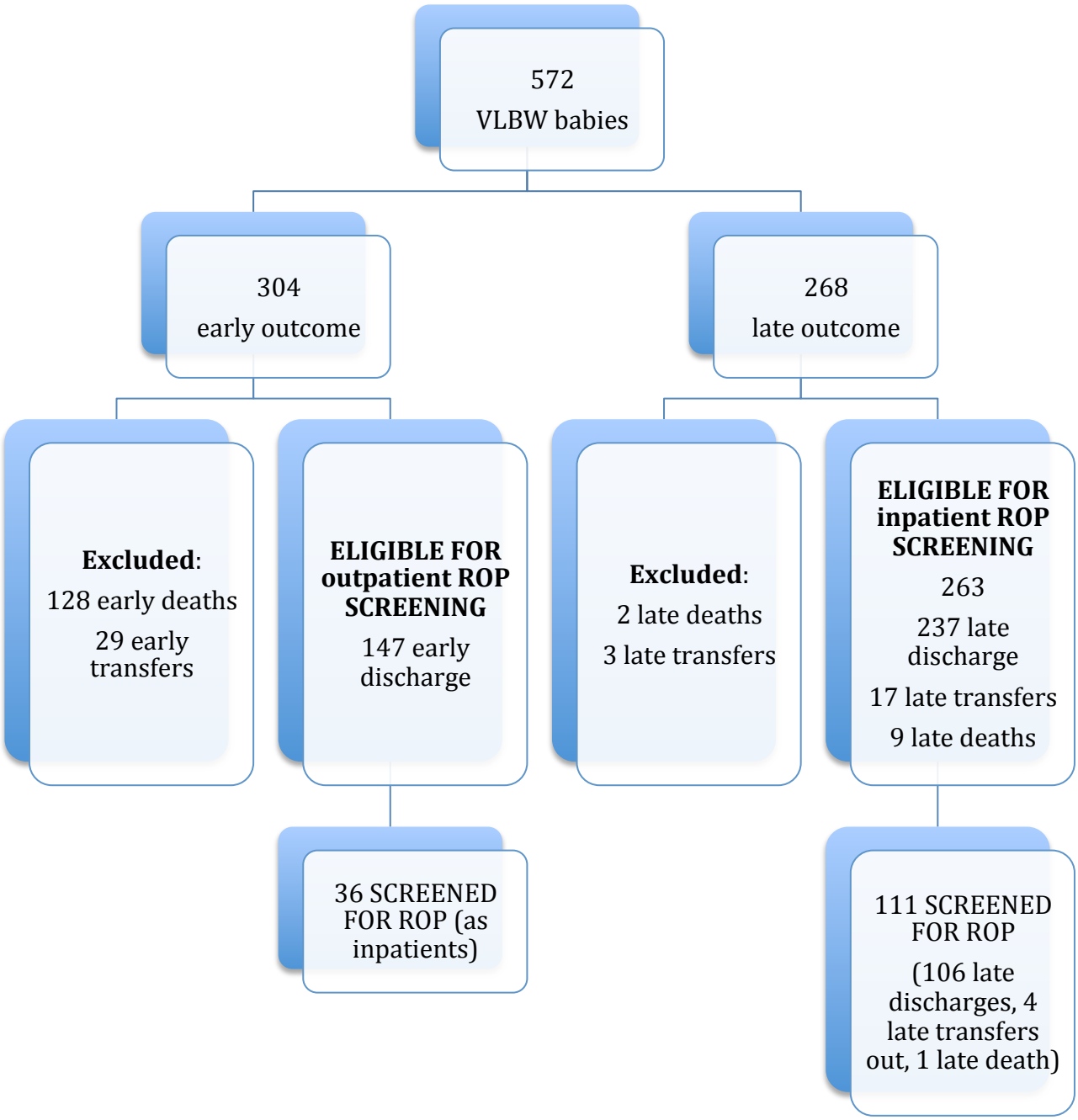

Table 3. ROP grading results in babies screened as inpatients

	No Rop N (%)	Grade 1 ROP N (%)	Grade 2 ROP N (%)	Grade 3 ROP N (%)	Grade 4 ROP N (%)	Grade not recorded N (%)	Total N
Early outcome group	28 (77.8)	2 (5.6)	2 (5.6)	0 (0)	0 (0)	4 (11)	36
Late outcome group	81 (73)	11 (9.9)	5 (4.5)	2 (1.8)	1 (0.9)	11 (9.9)	111

DISCUSSION

This study shows that less than half of the VLBW babies at CMJAH eligible for inpatient ROP screening according to the hospital's guidelines were actually screened for ROP.

More than one third of babies were discharged before they had reached the required age for screening. Despite this, 24% of these babies were screened before 4 weeks of life. Of concern is that 11% of these babies had ROP. This group of early discharges is important as they require outpatient ROP follow up. It is not known whether these babies attended screening for ROP as outpatients, so it is possible that a number of babies with ROP were missed. Education of caregivers in this group is essential, as defaulters to follow up are at risk of presenting with more severe grades of ROP and increased morbidity.

Although a true prevalence for ROP at CMJAH for 2013 cannot be calculated, due to the low level of screening, ROP was found in 15.6% of VLBW babies which is similar to the 17% rate reported at Chris Hani Baragwanath Hospital. [10] Other South African studies reported slightly higher rates – 21.8% at Tygerberg Children's Hospital and 24.5% at Kalafong Hospital. [13] [14]

This review shows that the inpatient ROP screening at CMJAH is not optimal and needs to be improved. Inpatient ROP screening was not carried out in 57.8%. Babies at risk need to be promptly identified. The attending medical staff (interns, medical officers, registrars and consultants) should to be familiar with the guidelines. Junior staff will need to be educated on the harms of oxygen therapy and the subsequent complication of ROP and its consequences. Although it may seem attractive to delay the discharge of VLBW babies until they have achieved the recommended age for ROP screening, this is not feasible due to high patient numbers and extreme pressure for beds. Adjusting the screening protocol to allow ROP screening at a younger age in those babies who will be discharged before 28 days of age would be a simpler solution and would prevent missed opportunities to identify babies with ROP.

No babies were recorded to have plus disease. This data may have not been captured on discharge, was truly not present or may have been under reported by the ophthalmologist performing the screening. Bigger babies are also at risk of ROP. The ROP guideline published in February 2013 in the SAMJ suggests that premature babies with weights between 1500-2000g may also be at risk if they have risk factors and if oxygen monitoring in this group of babies has been suboptimal then screening should be considered. [11] This group of babies were not included in the present study, but should not be overlooked in screening programs for ROP.

Ideally an electronic prospective data capture system needs to be implemented to capture all the results of ROP screening – both inpatient and outpatient. This would only be possible in conjunction with the Department of Ophthalmology, especially

regarding the outpatient screening. This will assist greatly with future research and in gauging the incidence of ROP at CMJAH.

LIMITATIONS

One limitation is the design of the study - the retrospective nature of the study means a pre-collected dataset was used. ROP information is not available for babies on the low birth weight (LBW) database who may have a GA of <32 weeks but a weight of >1500g. Another potential limitation is that of inter-observer error in classifying the grade of ROP present, as different ophthalmology registrars did the screening, with different levels of skill and experience.

CONCLUSION

More than half of VLBW babies that met criteria for ROP screening according to CMJAH ROP screening guidelines were not screened during their inpatient stay. Efforts need to be intensified to identify these babies and screen them prior to discharge.

Records for outpatient ROP screening are not well organized and not easily accessible at both the neonatal follow up clinic and the ophthalmology unit. There is a need for a coordinated database between the two specialties. In this regard, a true prevalence for ROP at CMJAH cannot be established.

Screening for ROP should include all babies with a GA of <32 weeks (even if their weight is >1500g). In addition, babies weighing between 1500g and 2000g with risk factors for ROP should not be omitted from screening programs.

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APPENDIX 3 ETHICS CLEARANCE

R14/49 Dr Zahedah Dadoo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130947

NAME: (Principal Investigator)	Dr Zahedah Dadoo
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	An Evaluation of Retinopathy of Prematurity in Very Low Birth Weight Babies at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	27/09/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof DE Ballot
APPROVED BY:	Professor Charles Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/12/2013

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4 PROTOCOL

AN EVALUATION OF RETINOPATHY OF PREMATURITY IN VERY LOW BIRTH WEIGHT BABIES AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Investigator: Dr Zahedah Dadoo

Student No: 0101288H

Qualification: MBBCH (Wits), FCPaed (SA)

Degree protocol is submitted for: MMed (Paed)

Supervisor: Prof Daynia Ballot

Qualification: MBBCh (Wits), FCPaed (SA), PhD

Paediatric neonatologist Charlotte Maxeke Johannesburg Academic Hospital

1. GLOSSARY

CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
ROP	Retinopathy of prematurity
VLBW	Very low birth weight babies
GA	Gestational age
NICU	Neonatal intensive care unit
IMRs	Infant mortality rates
ICROP	International Classification of ROP
VEGF	Vascular endothelial growth factor

2. INTRODUCTION AND BACKGROUND

Globally there are 50 000 children who are blind from retinopathy of prematurity (ROP).[1] The Prevalence of ROP in high-income countries is around 60% for VLBW babies. [2] ROP occurs worldwide, except in countries with such high infant mortality rates (IMRs) where premature babies do not survive. Countries with IMRs greater than 60 per 1000 live births usually do not have neonatal intensive care units (NICUs) therefore preterm babies usually do not survive. [2] Countries with IMRs of 9 to 60 per 1000 live births represent the highest burden of blindness caused by ROP as more premature infants survive in NICUs where oxygen administration may be poorly monitored.[1] In these countries, ROP screening and treatment programs are not often in place. South Africa's IMR for 2011 was 35 per 1000 live births.[3]

In developed countries two epidemics of blindness due to ROP have been described. The first occurred predominantly in the United States of America in the 1940s – 1950s and affected premature infants. The principal risk factor was that of the supply of unmonitored supplemental oxygen to the premature infant, and the subsequent restriction of oxygen use led to a decrease in blindness due to ROP. The second epidemic started in the 1970s as a result of the higher survival rates in extremely premature babies due to advances in neonatal intensive care units (NICUs) [1] A third epidemic of ROP is occurring in middle-income countries[2] like South Africa. As the standard of living increases and medical care improves, an increase in survival of premature babies ensues, with a resultant increase in treatable ROP in the surviving premature infants.[2]

If screening programs are not put into place, the incidence of blindness from untreated ROP is likely to increase. It was first reported in 1988 that treatment could improve the outcome for severe ROP.[4] This makes ROP screening a priority. The World Health Organization's (WHO) vision 2020 program has recognized ROP as an important cause of childhood blindness in industrialized and middle-income countries.[5] Their strategies advocate examining premature infants at risk of ROP, treating those premature infants with severe ROP and promoting oxygen monitoring to all premature infants receiving oxygen therapy. Also included in their strategy is ensuring the availability of ophthalmologists experienced in indirect ophthalmoscopy who can identify premature infants who require treatment for ROP and ensure that infants at risk for ROP have their fundui examined starting 4–6 weeks after birth, and that those with severe disease are treated immediately.

The two important aspects of screening for ROP are who to screen and when to screen. Different countries have differences in their standard of neonatal care and screening guidelines. The purpose of screening is to identify ROP that may require treatment. General criteria used in screening programs are birth weight (BW) and gestational age (GA) combined with sickness criteria.[6] There are concerns that in middle and low-income countries more older and larger infants are presenting with ROP compared to high-income countries. In a large prospective study of ROP done at Chris Hani Baragwanath Academic Hospital to establish the frequency of ROP it was concluded that the screening weight could safely be lowered to 1250g.[7] However according to recent guidelines published in the South African Medical Journal, all infants <1500g or 32 weeks GA should be screened for ROP[8]. Screening is repeated until retinal vascularization has reached zone III – at this stage the risk of a serious adverse outcome is minimal. Infants are screened by opthalmologists using indirect

ophthalmoscopy. Newer screening techniques include use of digital cameras to image the retina.

ROP is a multifactorial vasoproliferative retinal disorder.[9] The completely vascularised retina of the term infant is not susceptible to ROP.[10] During normal development, the retinal elements migrate from the optic disc and move outwards. At 28 weeks gestation, the photoreceptors have progressed 80% of the distance to their final resting place – the ora serrata. The retinal vessels begin to migrate outward at 16 weeks gestation. Migration is complete by 36 weeks on the nasal side and 40 weeks on the temporal side.[9] Growth factors such as vascular endothelial growth factor (VEGF) are essential for normal development of retinal vessels. The pathogenesis of ROP consists of two phases. In the first phase VEGF is suppressed by hyperoxia and this suppresses normal vessel development. This vessel loss can be inhibited by the intravitreal injection of VEGF. During the second phase, VEGF is over expressed and neovascularization occurs. During this stage, intravitreal injections of anti-VEGF can be used as treatment.[11] ROP is classified according to the International Classification of ROP (ICROP) which was standardised in 1984 and updated in 1987 and again in 2005.[12] ROP is characterized by using four parameters: stage (severity), zone (location), plus disease (tortuosity of vessels) and extent (circumferential location of the disease reported as clock hours).[9] There are 5 stages of ROP. Stage I is characterised by a demarcation line, which separates the normal vascularised retina from the avascular retina. Stage II is characterised by an elevated ridge. In Stage III abnormal vessels grow onto the ridge and then into the vitreous. Stage IV refers to partial retinal detachment, and stage V is total retinal detachment. The three zones are the innermost area of the retina surrounding the macula (zone I), the middle third of

the retina nasally extending to the edge of the retina (zone II) and the most peripheral area of the retina on the temporal side (zone III). Threshold ROP carries a risk of blindness of 50%, which can be reduced to 25% with treatment. Treatment is considered for type 1 prethreshold ROP and type 2 prethreshold ROP requires close observation. Treatment options include cryotherapy, laser ablative therapy, intravitreal VEGF or anti VEGF depending on the phase, and retinal reattachment.[9] Not all of these options are available in our setting.

Risk factors for ROP are divided into two groups – prenatal and postnatal.[13] Prenatal factors include GA and BW. Postnatal factors include prolonged exposure to oxygen and other identified markers of neonatal illness severity – also referred to as sickness criteria. Examples of these include the need for mechanical ventilation, the presence of sepsis and intraventricular haemorrhage, the administration of blood transfusions and poor postnatal weight gain.[9] The parameter of poor postnatal weight gain is linked to the presence of low levels of serum IGF-1.[11]

2.1 JUSTIFICATION FOR THE STUDY

ROP is a leading cause of blindness for VLBW infants.(10) Severe ROP is a treatable condition while less severe stages of ROP resolve spontaneously and without visual impairment in most patients.(10) The purpose of ROP screening is to identify severe ROP that requires treatment to prevent major visual impairment. This is part of the WHO Vision 2020 strategy to reduce avoidable blindness in children. The purpose of the study is to evaluate ROP at CMJAH, including the incidence, screening program and risk factors.

3. AIM AND OBJECTIVES

3.1 Aim:

The broad aim of the study is to audit the effectiveness of the screening program for ROP at CMJAH between 1 January 2013 and 31 December 2013. Furthermore, the proportion of infants with ROP at CMJAH will be determined.

3.2 Objectives:

1. To determine the proportion of infants in the neonatal unit who are screened for ROP and how many infants who fit the screening criteria are not screened.

2. To determine the prevalence of ROP in the neonatal unit of CMJAH for the period 1 January 2013 to 31 December 2013.

3. To determine the proportion of infants with severe ROP who require surgical therapy

4. To determine the proportion of infants with ROP who do not meet screening criteria

4. METHODOLOGY

4.1 Study design

A retrospective record review of data from the CMJAH neonatal unit's electronic neonatal database

4.2 Site of study

The neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital, which consists of 72 authorised neonatal beds, excluding ICU beds(14).

4.3 Study population

All newborns admitted to neonatal unit of CMJAH between 1 January 2013 and 31 December 2013, whether inborn or transferred in.

4.4 Inclusion criteria

1. All newborns admitted to the neonatal unit at CMJAH between I January 2013 and 31 December 2013

2. All infants with VLBW or a GA less than 32 weeks

3. Any infant with a weight less than or equal to 2000g who had an unstable clinical course

4.5 Exclusion Criteria

Nil

5.1 Data collection

Study data will be collected and managed using REDCap electronic data capture tools hosted at CMJAH. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Definitions of terms used in the database are according to the Vermont Oxford Network (VON) coding. There are measures in place to ensure that the data collected is complete – it is verified at various stages before its final entry onto the electronic neonatal database. A data sheet has been drawn up that incorporates only the variables that the researcher thinks are applicable to this study (appendix A). A single researcher will capture this data using the data sheet. Identifying information will be removed from the dataset and a separate key linking study number to patient identifiers will be kept by the investigator. Data will be coded and entered onto Excel and the database exported to SSPS for analysis.

At CMJAH the ROP screening guidelines include all infants with VLBW or a GA less than 32 weeks to be screened at 4-6 weeks chronological age, or babies more than 1500g who were ventilated for more than 2 weeks or required supplemental oxygen for more than 2 weeks(14). Infants that fit the screening criteria are identified weekly by attending medical staff and this list is passed on to the ophthalmology registrar who does the ROP screening. The results of the screening are only recorded in the infants file. If any babies are identified with type II prethreshold ROP, they are screened again at a date given at the discretion of the attending ophthalmology registrar. Any babies with type I prethreshold ROP or threshold ROP are treated according to the department of ophthalmology guidelines.

5.2 Sample size

There is no previous existing information for incidence of ROP at CMJAH. Based on a study undertaken at another tertiary institute in Johannesburg, Chris Hani Baragwanath Academic Hospital, the incidence can be predicted to be approximately 17%(7). In another study undertaken at Tygerberg Children's Hospital in Cape Town, incidence was found to be 21.8%(15). Thus far there are approximately 350 babies in the CMJAH neonatal database, so it is anticipated that 60 of those babies will be found to have ROP.

5.3 Source of bias

Nil

5.4 Data analysis and statistics

Data will be described using standard methods. Categorical data will be described using frequencies and percentages, and continuous data using measures of central tendency - mean and standard deviation, or median and interquartile range - depending on distribution of data. Depending on numbers of babies with ROP, risk factors for ROP will be determined by univariate analysis using Chi-square or Fisher's exact tests for comparison of categorical variables, and continuous variables will be compared using Student t-tests or non-parametric tests as appropriate. Regression analysis will then be done to determine significant risk factors.

6. ETHICS

This study proposal will be submitted to the ethics committee of the University of the Witwatersrand for research on human subjects for approval prior to commencement. The neonatal dataset of CMJAH, to be used for this study, is confidential and has limited accessibility. Furthermore, all identifying markers for the patient will be removed from the dataset to be analysed. As this is a record review, there will be no interaction with study participants and therefore they are not at risk of exploitation.

Consent for the proposed has been obtained from the Chief Executive Officer of CMJAH.

Approval from Human Research Committee has been granted – Clearance certificate no. M130947

Informed consent – Not applicable as this is a retrospective study

Confidentiality - All patient-identifying markers (for example file numbers) will be removed from the dataset and kept in a separate file by the investigator

7. TIMING

Most activities will be undertaken in conjunction with the investigators usual clinical and study workload. However, a dedicated two months block will be devoted to data collection and analysis.

Sep 2013: Literature review and preparation of protocol

Oct – Nov 2013: Submission of Ethics Committee and Protocol Assessor Group

Dec 2013 - Mar 2014: Corrections to protocol

April-May 2014: Data collection and analysis

June - September 2014: Write up of MMed

8. FUNDING

The costs for this study are minimal and the researcher will absorb any miscellaneous expenses incurred. A personal computer with will be used for the data analysis.

Item	Estimated cost	Source of funds
Travel to site	R1000	Self
Stationary	R200	Self
Printing	R500	Self

9. LIMITATIONS

One limitation is the design of the study. The retrospective nature of the study means a pre-collected dataset will be used and there is a chance that data will be found to be incomplete. Another limitation is that of inter-observer error in classifying the ROP, as different ophthalmology registrars are doing the screening, with different levels of experience.

10. ANTICIPATED OUTPUT

1. This will form the basis of the investigator's future MMed thesis
2. The study will be helpful in providing the prevalence of ROP at CMJAH, and help to improve the screening program for ROP at CMJAH
3. A future presentation at a medical conference
4. Possible publication in a medical journal

11. APPENDICES

Appendix A: Data Sheet

Appendix B: List of corrections following assessor group meeting

Appendix A

Data sheet

ROP Study Number:

REDCap Database Number:

Demographic information:

Date of birth (Y/M/D)		
Date of admission		
Date of initial outcome (death or discharge)		
Gender	M □	F □
GA (weeks)		
BW (grams)		
Discharge weight (grams)		

Prenatal and maternal factors:

Maternal age <18(years)	Y □	N □
Antenatal care	Y □	N □
Antenatal steroids	Y □	N □
Maternal hypertension	Y □	N □
Chorioamnionitis	Y □	N □
Maternal HIV	Y □	N □
Maternal syphilis	Y □	N □

Birth details:

Mode of deliverey	vaginal □	caesarian section □
Initial resuscitation in delivery room	N □	(none or oxygen)
	Y □	(face mask ventilation/endotracheal tube ventilation/nasal CPAP)

Outcomes:

Outcome	□ Died
	□ Transferred to another hospital
	□ Discharged

KMC:

KMC	Y □	N □
Type of KMC	□ Intermittent	

Respiratory:

Respiratory diagnosis	□ HMD
	□ Other
Respiratory support	
	□ Oxygen or NCPAP after initial resuscitation
	□ Conventional/high frequency ventilation after initial resuscitation
Duration NCPAP (days)	
Duration of ventilation (days)	
NCPAP without ET ventilation	Y □ N □
Surfactant therapy at any time	Y □ N □
Oxygen on day 28	Y □ N □
Respiratory support at 36 weeks	□ none
	□ Oxygen
	□ Conventional/high frequency vent
Steroids for CLD	Y □ N □
Pneumothorax	Y □ N □
Home oxygen	Y □ N □

ROP:

ROP Screening	Y □ N □
ROP Findings	□ normal
	□ Grade 1
	□ Grade 2
	□ Grade 3
	□ Grade 4
	□ Plus disease
ROP surgery	Y □ N □

Sickness criteria:

Bacterial sepsis on or before day 3	Y □ N □
Necrotising enterocolitis	Y □ N □
PDA	Y □ N □
Blood transfusion	Y □ N □
Exchange transfusion	Y □ N □
Sepsis after day 3	Y □ N □
Bacterial pathogen	Y □ N □
Fungal sepsis	Y □ N □
Worst grade of PIVH	□ normal
	□ Grade 1
	□ Grade 2
	□ Grade 3
	□ Grade 4
Cystic PVL	Y □ N □

Appendix B

List of corrections to protocol (as per assessor group and to satisfaction of supervisor)

1. Literature review – grammar corrections in paragraph one, two, three and five. Paragraphs five and seven were combined into one paragraph
2. Aim reworded to include the time frame of the study
3. Objectives reformatted: shortened from six original objectives to 4 objectives
4. Study design: reworded to specify that the database belongs to CMJAH
5. Inclusion criteria has changed to include infants less than 2000g with unstable clinical course
6. All exclusion criteria removed
7. Data collection: grammar correction in paragraph one
8. Under the heading 'Sample size': grammar has been corrected
9. The source of bias has been removed
10. The reasons for timing of the timeline has been justified
11. Breakdown of budget described in more detail
12. Data sheet (appendix A): 3 variables were removed. Two form the subheading 'outcomes' and one from the subheading 'KMC'
13. References have been reviewed and corrected to Vancouver style

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