Retinopathy of Prematurity in a cohort of neonates at Groote Schuur Hospital

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Thesis presented for the Degree of

MASTER OF PHILOSOPHY

in the Division of Neonatal Medicine,

Department of Paediatrics,

Faculty of Health Sciences,

UNIVERSITY OF CAPE TOWN

February 2016

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Declaration

I, Qaunitah Keraan, hereby declare that the work on which this dissertation is based, is my original work (except where acknowledgements indicate otherwise) and that neither the work nor any part of it is being submitted for a degree at any other university. This work has not been reported or published prior to registration for the MPhil (Neonatal Medicine) at the University of Cape Town.

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Preface

This thesis is presented in option I of the dissertation guidelines, the publication-ready format. The manuscript will be submitted to the South African Medical Journal for publication. A letter to the Editor will accompany the manuscript explaining the need for more than 15 references (as it exceeds the publication guidelines). The references cited are important as the study findings may potentially impact clinical services in the public health sector in South Africa.

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Abstract

Background:

Screening for Retinopathy of Prematurity (ROP) is recommended to prevent possible blindness. Prior to 2016, resource limitations precluded routine ROP screening at Groote Schuur Hospital (GSH). Previous pilot studies at GSH did not detect ROP requiring treatment. However, improved survival of very low birth weight infants may affect the prevalence of ROP.

Objectives

The study objectives were to: i) Determine the prevalence and severity of ROP in a prospective cohort of premature infants; ii) Describe the association with pre-specified potential risk factors; iii) Assess the feasibility of screening for ROP in our resource-limited setting.

Methods

Infants with a birth weight of < 1251 g or gestational age < 31 weeks admitted to the GSH neonatal unit from November 2012 to May 2013 were screened. A paediatric ophthalmologist examined the infants at 4 weeks chronological age or 32 weeks corrected gestational age, with follow-up examinations as indicated.

Results

Screening was performed in 135 of 191 eligible infants. A total of 313 ROP examinations were performed; 38.5% of infants required a single examination and 16.3% required more than four. The mean gestational age and weight at birth were 30.1 ± 1.9 weeks and 1056 ± 172 g respectively. Seventy-four infants were female (54.8%). Only black (57.0%) and coloured (42.9%) infants were represented. ROP was diagnosed in 40 (29.6%) infants: Eight (5.9%) infants had clinically significant ROP. No infants had stage 4 or 5 ROP. No infants weighing more than 1250 g required treatment. Two infants received laser treatment. Infants with ROP had a lower mean gestational age and lower mean birth weight than those without ROP: 29.2 ± 1.6 vs. 30.5 ± 1.9 weeks ($P < 0.002$) and 988 ± 181 g vs. 1085 ± 160 g ($P = 0.001$) respectively. Infants with ROP were more likely to have received a blood transfusion ($P < 0.002$); to have late onset sepsis ($P = 0.024$); and to have received exclusive

breast milk feeds (P = 0.005). There were no significant differences in the level of respiratory support, the need for oxygen therapy, the occurrence of apnoea, early sepsis or severe intraventricular haemorrhage in infants with ROP compared to no ROP.

On multivariate analysis, only gestational age was independently associated with ROP was gestational age (RR 0.85; 95% CI 95% 0.740-0.988; p=0.03). When gestational age was excluded in post-hoc analysis, birth weight (RR 0.99; 95% CI 0.997-0.999; P=0.03) and blood transfusions (RR 1.71; 95% CI 1.027-2.859; P=0.03) were independently associated with ROP. Infants <1000 g had a 2.5 times higher risk of having ROP than their larger counterparts (95% CI 1.05-5.90, P=0.03). ROP screening was completed in 91.1% (123/135) of infants.

Conclusion

Clinically significant ROP was found in this study. In contrast to previous studies conducted in this setting, two patients received laser treatment. Extensive resources were required for successful screening. The strong association with birth weight and gestational age suggests that infants with lower birth weights and gestational ages should be prioritized for screening in our resource limited setting.

Acknowledgements

The work presented in this thesis was possible due to a research award from the School of Child And Adolescent Health and funding from the Department of Ophthalmology, Groote Schuur Hospital.

I would like to acknowledge Dr Christopher Tinley, who tirelessly performed ophthalmic examinations, provided valuable input in the study planning and execution, comments on the manuscript and gentle encouragement; Mrs. Gadija Manuels, who meticulously dilated infants' eyes, assisted during examinations, completed administration and ensured good follow up of outpatients; Professor Michael Harrison, for his moral support, encouragement, access to important literature and advice on presentations; Dr Travis Pollock who assisted with ophthalmic examinations, ensuring that the study continued uninterrupted; Mr. Henri Carrara for statistical input during the study design; Dr Jonel Steffen and Dr James Rice for setting up and administering laser treatment; Alcon, for providing a laser machine for to use for treatment for the duration of the study; Dr Gerhardus Rossouw, Dr Shukri Raban and Dr Lloyd Tooke for their morale support and comments as the study progressed; the nurses and doctors at Groote Schuur Hospital who assisted with the recruitment and for helping to provide an outpatient service that is not usually available; parents and babies for participating in this research.

I would particularly like to thank Dr Yaseen Joolay and Professor Alan Horn who provided supervision, encouragement, advice and support in the form of access to important literature, access to funding, analysis and interpretation of data, critique of manuscripts and presentations.

Finally, I would like to thank my family and friends for their encouragement. A special thank you to my husband, Abdul Aziz Parker, who spent many late nights helping me overcome technical difficulties, creating my database, saving my data when my laptop was stolen and for convincing me to bring this work to completion; to my parents, for their amazing support and always encouraging me to pursue my

interests; my children, Farah, Iman and Mikaeel, for their eternal optimism and unwavering belief in me, providing me with the motivation to complete this work.

Abbreviations

BW	birth weight
C/S	caesarean section
CSROP	clinically significant ROP
CPAP	continuous positive airway pressure
ETROP	Early Treatment for Retinopathy of Prematurity Randomized Trial
ELBW	extremely low birth weight
GA	gestational age
GSH	Groote Schuur Hospital
HIV	Human Immunodeficiency Virus
IPPV	intermittent positive pressure ventilation
ICROP	International Classification of Retinopathy of Prematurity
IVH	intraventricular haemorrhage
ILCOR	International Liaison Committee on Resuscitation
PVH	periventricular haemorrhage
PET	pre-eclamptic toxaemia
ROP	retinopathy of prematurity
SA	South African
USANA	United South African Neonatal Association
VDRL	Venereal Disease Research Laboratory
VLBW	very low birth weight

Chapter 1: Introduction

1.1. Context

Retinopathy of prematurity (ROP) is a well-described preventable cause of visual impairment and blindness in premature infants.[1] It is a multifactorial vasoproliferative condition that affects the immature retina of premature infants.

ROP was first described in 1942 when surviving premature infants were noted to have a high incidence of blindness.[2] The role of oxygen therapy in the development of ROP was described in the 1950's.[3] This resulted in the more judicious use of oxygen, with a decrease in ROP. Low gestational age, low birth weight and prolonged oxygen exposure are risk factors for developing ROP.[1,4,5] Fluctuations in administered oxygen concentration also contribute to the development of ROP. Markers of the severity of neonatal illness such as the need for mechanical ventilation, blood transfusions, the presence of a patent ductus arteriosus, sepsis, significant intraventricular haemorrhage or poor post-natal weight gain have been described with an increased risk of developing ROP.[6] Furthermore, a genetic predisposition to the development of ROP may play a role.[7] As neonatal care advanced, infants with lower gestational ages and birth weights survived. Subsequently, the incidence of ROP increased, hence the 'second epidemic' noted in the 1960's. More recently, a 'third epidemic' of ROP has been described in middle-income countries with a combination of small premature infants, as well as larger more mature infants developing ROP. This has been attributed to a greater number of premature infants surviving due to improved neonatal care, but lack adequate monitoring when receiving oxygen therapy.[8,9]

Globally, 50 000 children have blindness secondary to ROP.[10] In resource rich countries the incidence is between 6-18% mainly affecting infants born at less than 32 weeks gestational age and less than 1250 g. In middle-income countries, the incidence ranges from 8-38%, with infants with a gestational age at birth of greater

than 32 weeks also affected. Figures for sub-Saharan Africa, with the exception of South Africa, are quoted at 0%.[10] The absence of ROP is ascribed to limited resources for healthcare with high neonatal and infant mortality rates. In South Africa, studies at several public institutions from 1991 to 2013 have found incidences of ROP ranging from 18.6-24%.[11-15]

Screening and early treatment is important to prevent morbidity related to this condition. The ROP Working Group of South Africa has recommended guidelines for the prevention, screening and treatment of ROP for South Africa, based on international guidelines.[16] The United South African Neonatal Association (USANA), the Ophthalmological Society of South Africa and the South African Vitreoretinal Society have endorsed these recommendations, but resource limitations are acknowledged as a limiting factor in implementation of these guidelines.[16]

The Groote Schuur Hospital (GSH) neonatal unit provides tertiary level care for over 500 very low birth weight (VLBW) and extremely low birth weight (ELBW) premature infants per year. A study at GSH in 1991 by Straker and van der Elst,[11] as well as an unpublished study in 2001 (MMed thesis) reported low rates of ROP and did not detect any ROP requiring treatment.[11,17] Based on these findings and resource constraints, an ROP screening service was not instituted. However, more recent data from other tertiary institutions in South Africa suggests cause for concern. A 2006 study at Chris Hani Baragwanath Hospital found that 16.3% of VLBW had ROP, with 1.6% of infants requiring treatment.[14] Mayet et al. stated that the findings were likely to be an underestimate as a high number of the study cohort was lost to follow up before complete vascularization of the retina was achieved. The authors speculated that 2.9% of the cohort would have severe ROP. No infants with a birth weight of more than 1250 g required treatment for ROP in this study. In 2002, a study at Kalafong Hospital in Pretoria by Delport et al. reported an incidence of 24.5% ROP, with 4.3% of infants less than 1500 g reaching threshold ROP.[13] The incidence of threshold ROP in infants weighing less than 1251 g was 3.2%. A 1995 study at Tygerberg Children's Hospital showed a prevalence of ROP of 31.1% with

7.1% of infants developing severe ROP.[12] In 2013, van der Merwe et al. from Tygerberg Children's Hospital reported an ROP prevalence of 21.8%, with clinically significant ROP in 4.4% of the cohort.[15] Six infants (1.5%) in this study received laser treatment. These studies all reported higher incidences of ROP than previously found at GSH. Based on this data, we secured funding to conduct a six month pilot study with the following aims: 1) determine the prevalence and severity of ROP in a prospective cohort of preterm infants; 2) describe the association of pre-specified potential risk factors; and 3) to assess the feasibility of screening for ROP in a relatively resource-limited setting.

Methodological Aspects

Consent

Written informed parental consent was obtained for both the screening examination, as well as inclusion into the study. The consent form, information on ROP and the screening examination was made available to parents in English, Afrikaans and Xhosa. Consent for ROP screening was obtained from the medical superintendent for abandoned infants and infants who were being placed for adoption. Parents who refused consent for the study were offered ROP screening for their infants without inclusion into the study.

Medical management

Infants delivered at less than 30 weeks gestation or with an estimated foetal weight of less than 1200 g were placed in a plastic bag after birth to prevent hypothermia. The International Liaison Committee on Resuscitation (ILCOR) guideline (2010) was followed. Infants with respiratory distress received CPAP or intermittent positive pressure ventilation via T-piece resuscitator and/or endotracheal intubation if required in the delivery room. Blended oxygen was utilised in the neonatal unit. Infants were monitored with pulse oximetry, targeting saturations of 88-92%. Standardised protocols were followed for the administration of surfactant and blood transfusions. Exclusive breast milk feeds were encouraged for all infants – donor

breast milk was variably available to infants weighing less than 1200 g, as per unit policy at the time. Cranial ultrasounds were performed in the first week of life and repeated at discharge, or earlier if indicated.

Screening ophthalmic examination

A paediatric ophthalmologist performed ROP examinations once a week. A clinician reviewed the neonatal unit's admissions book daily to identify eligible infants. A register and diary was kept to facilitate the timing of examinations.

The first ophthalmology examination occurred at 4 weeks chronological age or at 32 weeks corrected gestational age, whichever occurred later. After the initial screening, follow up was scheduled according to standard guidelines described below. If infants were clinically unstable at the time scheduled for screening or follow up, the examination was deferred until the clinical condition improved. A research assistant was employed for the duration of the study.

Two milligrams of Cyclopentolate hydrochloride and 10mg phenylephrine hydrochloride (Cyclomydril®) drops were instilled into each eye in preparation for screening; one drop per eye every 15-20 minutes commencing approximately 45-60 minutes prior to eye examination until pupils were dilated (up to a maximum of 3 drops per eye). Benoxinate hydrochloride 0.4% was used for local anaesthetic. The nasolacrimal duct was compressed for 3 minutes after insertion of the eye drops to limit systemic absorption. The lights in the area were dimmed at the time of insertion of eye drops to limit discomfort to infants. Inpatients were monitored as per standard practice in the neonatal unit. Outpatients received limited clinical observation and were discharged once they successfully fed post examination. Infants were swaddled and nested during the ophthalmology examination. A 24% oral sucrose solution was placed in the mouth of infants at the start of the examination to provide analgesia. The infants' retinas were examined by binocular indirect ophthalmoscopy using a 28 dioptre condensing lens, with a lid retractor and scleral indentation in order to visualize the ora serrata.

Follow up of ROP

Follow up was according to standard guidelines listed below[18]:

≤ 1-week follow-up

- Stage 1 or 2 ROP in zone I
- Stage 3 ROP in zone II

1 to 2 week follow up

- Immature vascularization in zone I (no ROP)
- Stage 2 ROP in zone II
- Regressing ROP in zone II

2 week follow up

- Stage 1 ROP in zone II
- Regressing ROP in zone II

2 to 3 week follow up

- Immature vascularization in zone II (no ROP)
- Stage 1 or 2 ROP in zone III
- Regressing ROP in zone III

All infants who required follow up were booked in a ROP diary. If infants were transferred, the receiving hospitals were informed that the screening process needed to be completed. Infants who were discharged home had appropriate follow up appointments made and communicated to parents. The appointment dates were documented on a hospital appointment card and in the Road to Health booklet. The research assistant reminded parents telephonically 3 days prior to the appointment. If infants did not arrive for appointments, parents were telephoned with a new appointment date for the next session. If the three consecutive appointments were missed, no further attempts to contact the parents were made. If a healthcare

worker or parent contacted the research assistant after missing appointments, the infant was scheduled for the next screening session.

Infants were discharged from screening if one of the following findings were observed[16]:

- Zone III retinal vascularisation attained without previous zone I or II ROP (if the gestational age was < 35 weeks further examinations were considered)
- Full retinal vascularisation present
- Gestational age of 45 weeks and no pre-threshold disease (stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present
- Regression of ROP (no abnormal vascular tissue present)

Initial and subsequent follow up was done at the GSH neonatal unit. Infants requiring prolonged follow up were reviewed at the outpatient clinic of the Ophthalmology Department at the Red Cross War Memorial Children's Hospital. A maximum of 20 patients were booked per session.

Treatment of ROP

Treatment was performed according to the Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP) guidelines, and was initiated for the following findings[19]:

- Zone I ROP: any stage with plus disease
- Zone I ROP: stage 3, no plus
- Zone II ROP: stage 2 or 3 with plus disease

Plus disease was defined as the degree of dilation and tortuosity of the posterior retinal blood vessels as defined by standard criteria.

A retinal specialist was available to deliver laser treatment within 72 hours of diagnosis to minimize the risk of retinal detachment. Treatment took place in the GSH neonatal unit, where a dedicated laser machine was housed for the duration of the study.

1.2. Ethical considerations

This study was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee and conforms to the principles of the 2013 Declaration of Helsinki.

Screening for ROP is a standard of care in adequately resourced neonatal units caring for premature infants and is a routine examination the in private health sector in South Africa. In this pilot study, all infants fulfilling the inclusion criteria were eligible for screening and informed written parental consent was obtained prior to examination. Parents were offered screening for their infants if they chose not to consent to inclusion into study. Despite being informed of the potential benefits, one parent refused consent for ROP screening. The medical superintendent gave consent for screening of infants who had been abandoned or were being placed for adoption.

HREC number 509/2012

1.3. Author guidelines

The publication ready manuscript will be submitted to the South African Medical Journal. This journal was chosen for publication, as the research is applicable to the public service health care setting in South Africa. This work motivates for the use of stricter criteria for retinopathy of prematurity screening in a tertiary hospital setting where resource limitations may otherwise prevent an effective ROP screening program. It differs from a recently published guideline for the prevention, screening and treatment of ROP, which may not be feasible to implement and sustain in South Africa's tertiary referral setting.[16]

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

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Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

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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. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

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8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

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Chapter 2: Publication-ready manuscript

Abstract

Background

Severe Retinopathy of Prematurity (ROP) can cause blindness. Prior to 2016, resource limitations precluded routine screening for ROP at Groote Schuur Hospital (GSH). Previous pilot studies at GSH found no patients ROP requiring treatment, however, improved preterm infant survival may affect the prevalence.

Objectives

To determine the prevalence and severity of ROP, describe potential risk factors and assess the feasibility of ROP screening.

Method

Infants with a birth weight (BW) of < 1251 g or gestational age (GA) < 31 weeks were screened from November 2012 to May 2013.

Results

Three hundred and thirteen ROP examinations were performed in 135 of 191 eligible infants. The mean GA and BW were 30.1 ± 1.9 weeks and 1056 ± 172 g respectively. ROP was diagnosed in 40 (29.6%) infants; eight (5.9%) had severe ROP and 2 received laser treatment. Infants with ROP had a lower mean GA, 29.2 ± 1.6 vs. 30.5 ± 1.9 weeks (P<0.002) and lower mean BW, 988 ± 181 g vs. 1085 ± 160 g (P=0.001) than those without ROP. Infants < 1000 g had a 2.5 times higher risk of having ROP (95% CI 1.05-5.90, P=0.03). Blood transfusions (P<0.002) and late onset sepsis (P=0.024) were strongly associated with ROP. ROP screening was completed in 91.1% (123/135) of infants.

Conclusion

The prevalence and severity of ROP has increased in GSH. The strong association with BW and GA suggests that infants with lower weights and gestational ages should be prioritized for screening in our resource limited setting.

Introduction

Retinopathy of prematurity (ROP) is a preventable cause of visual impairment in premature neonates.[1] Screening and early treatment is important to prevent related morbidity. An increase in ROP has been reported in middle-income countries, as greater numbers of premature infants survive due to improved neonatal care but lack adequate monitoring when receiving oxygen therapy.[2] The ROP Working Group of South Africa has recommended guidelines for the prevention, screening and treatment of ROP for South Africa, based on international guidelines.[3] The United South African Neonatal Association, the Ophthalmological Society of South Africa and the South African Vitreoretinal Society have endorsed these recommendations, but resource limitations are acknowledged as a limiting factor in implementation of these guidelines.

The Groote Schuur Hospital (GSH) neonatal unit provides tertiary care for over 500 very low birth weight (VLBW) and extremely low birth weight (ELBW) premature infants from the West Metro region of the Western Cape per year. A study at GSH in 1991 by Straker et al, as well as an unpublished study in 2001, did not detect any ROP requiring treatment.[4, 5] Based on these findings and resource constraints, an ROP screening service was not instituted.

More recent data from other tertiary South African hospitals suggested that a review is required. Studies between 1995 and 2013 reported an incidence of ROP ranging from 16.3% to 31.1%.[6-9] The incidence of severe ROP varied from 4.3% to 7.1%, with no infants weighing more than 1250 g requiring treatment. These studies all reported infants requiring treatment for ROP. Based on these data, we secured funding to conduct a six-month pilot study. The aims of the study were to: 1) determine the prevalence and severity of ROP in a prospective cohort of preterm infants; 2) describe the association of pre-specified potential risk factors; and 3) to assess the feasibility of screening for ROP in a relatively resource-limited setting.

Methods

A prospective cohort study of a pilot ROP screening program was conducted at GSH from November 2012 to May 2013. The duration of the study was limited by the available funding for the support staff. This study was approved by the University of Cape Town Health Sciences Faculty Human Research Ethics Committee and conforms to the principles of the 2013 Declaration of Helsinki.

Inclusion criteria

- Birth weight (BW) < 1251 g OR
- Birth gestational age (GA) confirmed by Ballard score $\leq$ 31 weeks at birth

Exclusion criteria

- Lethal congenital conditions
- Infants of parents who refused consent

Consent

Written informed parental consent was obtained for ROP examination and inclusion into the study. Consent was obtained from the medical superintendent for infants being fostered or adopted.

Medical management

The International Liaison Committee on Resuscitation (ILCOR 2010) guideline was followed. Infants were monitored with pulse oximetry, targeting saturations of 88-92%. Exclusive breast milk feeds were encouraged for all infants – donor breast milk was variably available to infants weighing less than 1200 g. Cranial ultrasounds were performed in the first week of life and repeated at discharge, or earlier if indicated.

Screening ophthalmic examination

A paediatric ophthalmologist examined infants once a week. The neonatal unit's admissions book was reviewed daily to identify eligible infants. A register and diary was kept to facilitate the timing of examinations. The first examination occurred at 4 weeks chronological age or at 32 weeks corrected GA, whichever occurred later. Examination was deferred in clinically unstable infants. A research assistant was employed for the duration of the study to complete administration and assist during examinations. Cyclopentolate hydrochloride and phenylephrine hydrochloride drops, one drop every fifteen minutes up to a maximum of three, was instilled into each eye in preparation for screening. Benoxinate hydrochloride 0.4% was used for local anaesthetic. Inpatients were monitored as per standard practice in the neonatal unit. Outpatients were discharged once they were successfully fed post examination. The infants' retinas were examined by binocular indirect ophthalmoscopy. The ophthalmologist determined follow up as per standard guidelines.[10]

If infants were transferred, receiving hospitals were informed that screening needed to be completed. On discharge, appointments were communicated to parents and documented. Reminders were sent three days prior to appointments. If three consecutive appointments were missed, no further contact was attempted. However, if the research assistant was contacted, a booking was made for the next session.

Infants were discharged from screening as per recommended SA guidelines.[3] Initial and subsequent follow up was done at the GSH neonatal unit. Infants requiring prolonged follow up were reviewed at the ophthalmology outpatient clinic at Red Cross War Memorial Children's Hospital. A maximum of 20 patients were examined per session.

Treatment of ROP

Treatment was administered as per Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP) guidelines.[11] A retinal specialist performed laser

treatment in the neonatal unit within 72 hours of diagnosis.

Data collection and statistics

The following information was collected:

1. Demographic details

2. Clinical information: early (< 72hours post-delivery) or late (> 72 hours post-delivery) onset of sepsis; intraventricular/ periventricular haemorrhage (grade 3 or 4); type of enteral nutrition (in the first six weeks of life)

3. Findings of screening examination:

- Presence or absence of ROP
- Grade of ROP if present (ICROP revisited)[12]
- Findings at follow up examination
- Need for ROP treatment

Stata Version 12 was used for statistical analysis. Demographic and clinical data were presented with descriptive statistical methods. Comparative statistics were done on infants grouped according the presence of ROP as a primary outcome, infants with mild ROP and those with clinically significant ROP (CSROP). The presence of stage 3 ROP or any stage of ROP with plus disease was classified as CSROP.

Factors associated with different severity grades were described. The Chi square or Fisher's exact tests were used for categorical comparisons, depending on the expected values. The Student's t and the Wilcoxon rank sum tests were used for comparison of parametric and non-parametric continuous variables respectively. All statistical tests are 2-sided at alpha= 0.05. Multivariate analysis was performed on statistically significant risk factors (P value < 0.2). Multivariate analysis was done using a Poisson regression model with a robust error variance for relative risk.

Results

Screening was performed in 135 of the 191 eligible infants. Figure 1 shows the derivation of the final dataset. The pre-specified perinatal characteristics of the cohort are shown in Table 1. The mean GA and weight at birth were 30.1 ± 1.9 weeks and 1056 ± 172 g respectively. Seventy-four infants were female (54.8%). Only black (57.0%) and coloured (42.9%) infants were represented in the sample. One infant had a family history of ROP.

Table 2 shows the numbers of examinations per infant. In total, 313 examinations were performed; 38.5% of infants required one, 31.9% required two and 16.3% had four or more examinations. Three (2.2%) infants had 8 ROP examinations.

The stages of ROP in the cohort, including infants in whom screening was not completed, are indicated in Table 3. ROP was diagnosed in 40 (29.6%) infants; eight (5.9%) had clinically significant ROP. No infants had stage 4 or 5 ROP. Stage 3 ROP occurred in one infant with a BW more than 1250 g, but regressed and did not require treatment. Two infants received laser treatment. Screening was completed in 91.1% (123/135). Twelve infants were lost to follow up. Of these, seven (58.3%) had ROP and two (16.7%) infants had CSROP.

Table 4 shows comparisons of pre-specified potential risk factors. Infants with ROP had a lower mean GA and BW than those without ROP: 29.2 ± 1.6 vs. 30.5 ± 1.9 weeks ($P<0.002$) and 988 ± 181 g vs. 1085 ± 160 g (P=0.001) respectively. Infants with ROP were more likely to have received a blood transfusion ($P < 0.002$), shown in Figure 2; to have late onset sepsis (P=0.024), shown in Figure 3; and to receive exclusive breast milk feeds (P=0.005).

The comparison of potential risk factors in infants with mild ROP and CSROP is shown in Table 5 – there were no significant differences. The comparison of potential risk factors in infants with no ROP/mild ROP and infants with CSROP are shown in Table 6 – Infants delivered via caesarean section were less likely to develop CSROP (P=0.007).

On multivariate analysis, the GA at birth was the only variable independently associated with ROP (RR 0.85; 95% CI 0.740-0.988; P=0.03). If GA was excluded, BW

(RR 0.99; 95% CI 0.997-0.999; P=0.03) and blood transfusions (RR 1.71; 95% CI 1.027-2.859; P=0.03) were independently associated with ROP. ELBW infants had a 2.5 times higher risk of having ROP than their larger counterparts (95% CI 1.05-5.90, P=0.03). The prevalence of ROP according to BW is described further in Figure 4.

Discussion

ROP occurred in 29.6% of the study cohort; 5.9% developed CSROP and two (1.5%) received laser treatment. Infants that required treatment weighed below 1250 g at birth. The prevalence in this study is significantly higher than in previous studies at GSH.[4, 5] Infrastructure and resources in the health care facilities referring to GSH have improved in the past two decades. Additionally, surfactant therapy and non-invasive ventilation are more accessible, contributing to improved preterm survival.[13] Straker et al. reported an incidence of ROP of 19.2%, including all infants with a BW of less than 1500 g; 1.5% of infants developed severe ROP and no infants required treatment.[4] However, infants in their study were small for gestational age. This study's lower weight inclusion criteria with a potentially greater proportion of less mature infants being included, may explain the higher prevalence of ROP. Growth restriction was not specifically assessed. Richards reported an overall ROP incidence of 3.6% in infants weighing less than 1500 g increasing to 14.5% in infants less than 28 weeks gestation at birth, with no infants requiring treatment.[5] However, infants were assessed at 6 weeks chronological age and then again at term if no ROP was initially detected, potentially missing infants who developed ROP and then regressed before review - repeat examinations in our study occurred more frequently, every 2 to 3 weeks. In Richards' study, 73% of infants attended follow-up, but only 44% of infants less than 28 weeks were seen more than once.[5] The higher rate of ROP in our study may be due to the higher proportion attending follow-up.

Other South African studies show a significant prevalence of ROP. In 1997, Gilbert et al. found that ROP accounted for 10.6% of blindness.[13] In 1995, Kirsten et al. showed a ROP prevalence of 31.1% in mechanically ventilated VLBW infants, with 7.1% stage 3 or worse ROP, likely due to the exclusive inclusion of mechanically ventilated infants.[8] In 2002, Delport et al. found an incidence of ROP of 24.5% at

Kalafong Hospital in VLBW infants - only two infants with a BW above 1250 g developed ROP, similar to our findings.[7] The incidence of severe ROP was 3.2% in infants weighing below 1250 g at birth, with 4.3% requiring treatment, slightly higher than in our study. In a study in Johannesburg in 2006, Mayet et al. showed a 16.3% prevalence of ROP in VLBW infants – 1.6% of infants received treatment.[6] As in other South African studies, the majority of infants with ROP weighed less than 1250 g and no infants weighing more than 1250 g required treatment.[6] The higher follow up rate in our study may account for the apparent higher ROP prevalence. A study at Tygerberg hospital in 2013, reported an ROP prevalence of 21.8% in ELBW infants, with 4.4% of infants developing CSROP.[9] The percentage of infants needing treatment was the same as in our study. Although the BW and GA criteria were lower than the inclusion criteria we used, the prevalence of ROP and CSROP were significantly lower, possibly explained by the exclusion of infants mechanically ventilated in the first week of life.

Infants in our study with ROP had a lower mean GA and mean BW, similar to other South African and certain middle-income country studies.[2, 6, 7, 9, 14, 15] On multivariate analysis, only GA was independently associated with ROP, however GA assessment may be inaccurate as it was based on antenatal ultrasound, which often occurred only after 20 weeks gestation, and/or Ballard score which is only accurate to ± 2 weeks. When GA is removed from the analysis, lower BW remains an independent risk factor for ROP.

Infants with ROP were more likely to have received a blood transfusion and, as in other studies, more likely to have late onset sepsis.[15] Small numbers of these patients due to restrictive transfusion policies and low incidence of sepsis prevented meaningful interpretation of their risk to develop CSROP.

Contrary to other studies citing a protective role or no effect of breast milk,[16-18] infants in our study who received exclusive breast milk feeds were more likely to have ROP. Unit policy at the time restricted the use of donor breast milk feeds to infants < 1200 g. The use of exclusive breast milk feeding was therefore associated with lower birth weight.

Previous studies have found a low occurrence of severe ROP in black patients or

darkly pigmented fundi.[6, 19] Interpretation of this risk factor was not possible, as only black and coloured infants were represented in our cohort. Genetics may play a role in developing ROP.[20] Only one infant had a family history of ROP, which probably reflects the lack of ROP screening services in the public health sector. There were no significant differences in maternal risk factors, place of birth, mode of delivery and need for resuscitation between the groups with and without ROP.

The level of respiratory support, the need for oxygen therapy, the occurrence of apnoea, early sepsis or severe intraventricular haemorrhage was also similar between infants with and without ROP.

The role of oxygen has been well described in the development of ROP.[1] No statistical significance was found when comparing oxygen concentration and duration of oxygen received in the two groups. This finding may be due to strict saturation targeting in infants receiving oxygen therapy. One infant who had never received oxygen therapy developed ROP – prematurity may be a more significant factor than exposure to oxygen therapy.[21]

When analyzing risk factors in infants with mild/no ROP and CSROP, infants delivered via caesarean section were less likely to have CSROP. The association could be related the potential for greater exposure to both hypoxia and hyperoxia in vaginal deliveries. Moreover, patients with pre-eclamptic toxaemia (PET) may be more likely to deliver via caesarean section. A negative correlation between ROP and PET has been described.[22] The association of delivery via caesarean section and decreased incidence of ROP may be due to chance. The small numbers in our study precluded further analysis.

Successful ROP screening required extensive resources. A research assistant was employed to assist with administrative tasks, preparation for screening and also assisted during examination. ROP examination was only available at GSH, which posed the potential problem of overcrowding with the associated risks. If transfer needed to be effected, logistical challenges faced included ambulance services' availability and accommodation in a tertiary service with limited bed capacity when transfer back for ROP examination was required. Outpatient facilities, staffing and equipment had to be provided when infants were discharged prior to completion of

screening.

Laser treatment was performed in the neonatal unit within 72 hours of diagnosis for infants requiring treatment. Challenges included the provision of theatre facilities in the neonatal unit, equipment and staffing, including the availability of a retinal surgeon. Centralized care must be considered when infants require treatment of ROP. Theatre facilities need to accommodate the specific needs of preterm infants. Facilities for treatment, in addition to skilled clinicians for ophthalmic examination and treatment of ROP, should be available before embarking on a screening program.

The follow up rate in this study was 91.1%. Study funding ensured that resources were allocated to facilitate this. Parents were well informed, aware of follow up appointments and were contacted when appointments were missed. Transport costs were reimbursed if required. Despite this, 12 infants were lost to follow up, including two with CSROP. The lost to follow-up rate is similar to that of van der Merwe et al. (13.8%), significantly lower than in other South African studies.[9] The major strength of this study was the high enrolment and follow up rates, which support the validity of the sample. All screening was performed by two ophthalmologists- this ensured consistency in reporting and management of ROP findings. The major limitation of the study was the potential inaccuracy of gestational age assessment, limiting the use of this parameter in clinical guidelines for screening. Additionally, all race groups were not represented in the study population. Although the ROP prevalence is similar to other South African studies, it may be different if all race groups were represented in the sample. The use of WINROP®, an online surveillance system that identifies infants at risk of developing severe ROP, would have been useful given resource constraints.[23] Due to limited staffing and funding, we were not able to explore this tool. Further studies comparing the incidence of ROP in various provincial hospitals, possibly using WINROP®, would be of value.

Conclusion

The prevalence of ROP in this study is similar to that in other reported South African studies, which do not reflect the 'third epidemic' of ROP. No infants over 1250 g required laser treatment. The independent association of ROP with birth weight and the absence of treatment requiring ROP in the larger infants suggest that infants with lower birth weights should be prioritized for screening in our resource-limited setting. It was feasible to screen for ROP using the criteria in our study, but additional funded nursing and administrative assistance, skilled personnel, laser treatment, theatre facilities within or outside the neonatal unit, as well as neonatal intensive care, had to be readily accessible to infants requiring treatment. ROP screening has been implemented at GSH based on the study findings. If broader screening criteria were applied, further resources such as medical staffing and facilities would need to be made available. However, if appropriate oxygen targets are in place, the yield of ROP requiring treatment in larger and/or more mature infants is likely to be very low.

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Figure 1: Derivation of the final data set

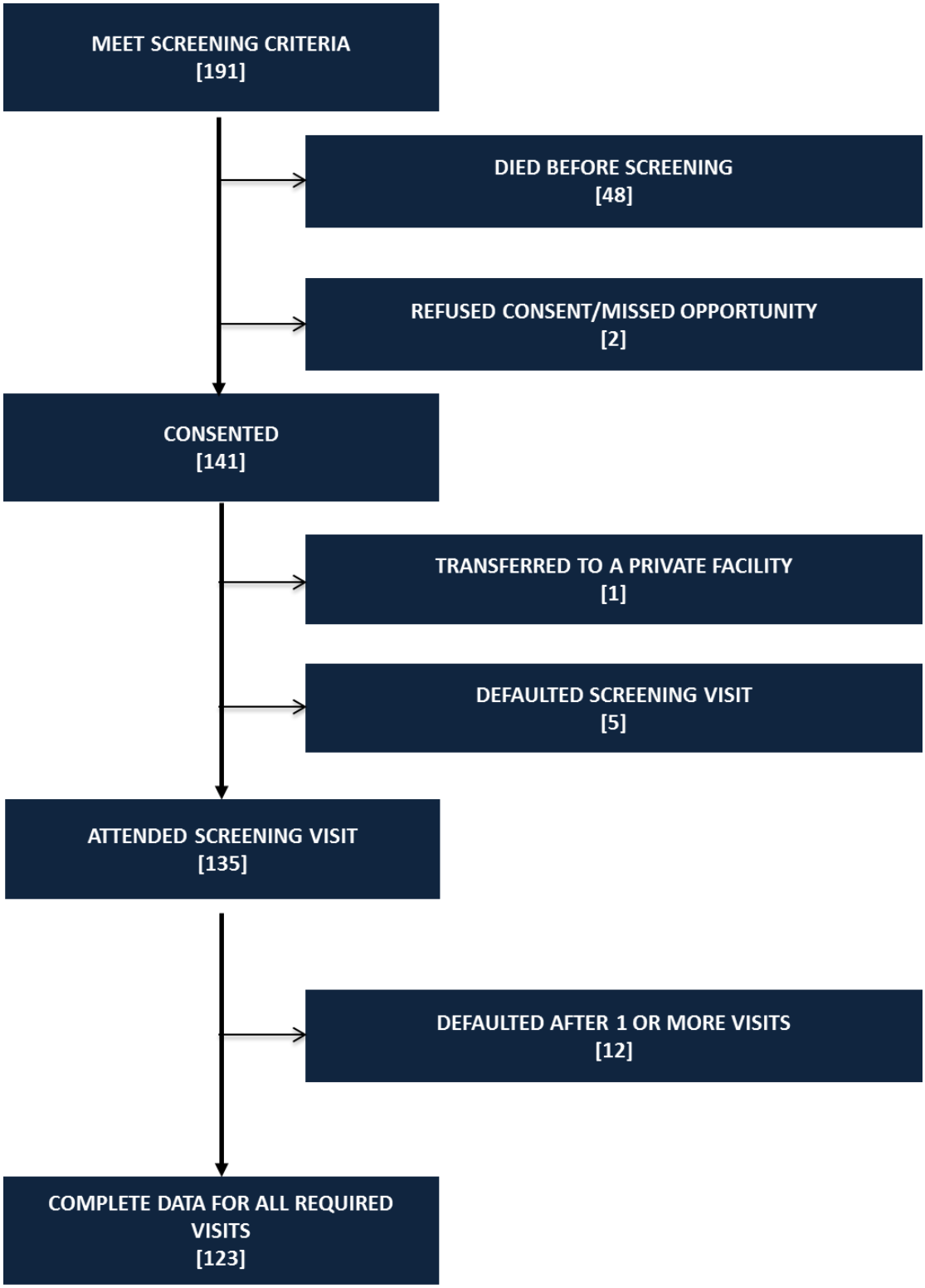

Figure 2: Incidence of ROP in infants receiving blood transfusions (n=135)

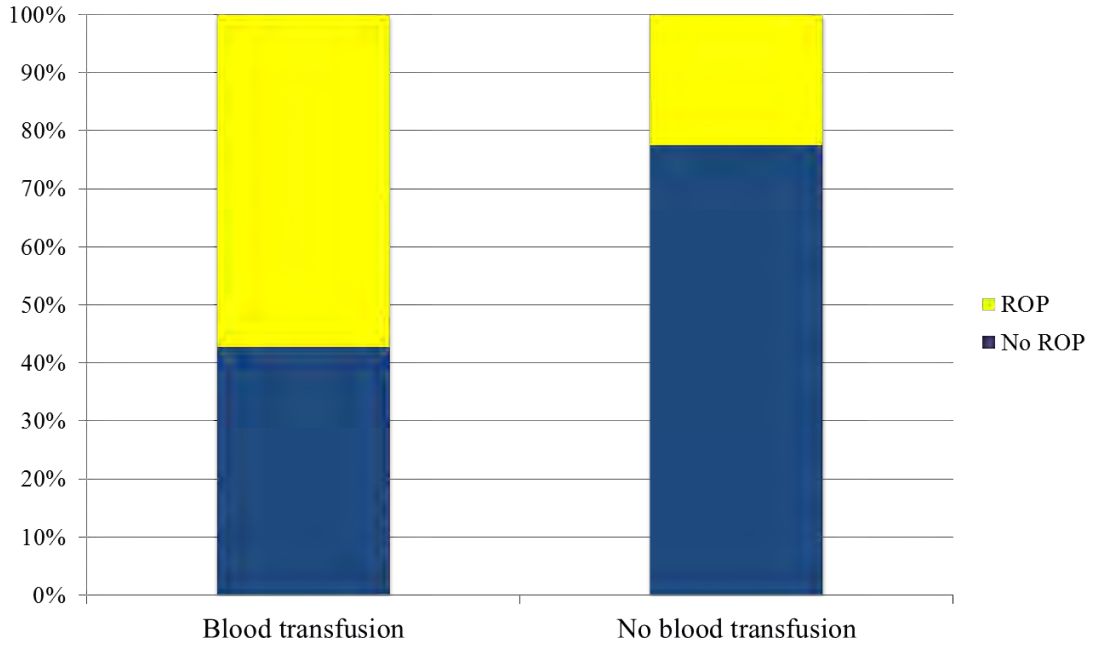

Figure 3: Incidence of ROP in infants with late onset sepsis (n=135)

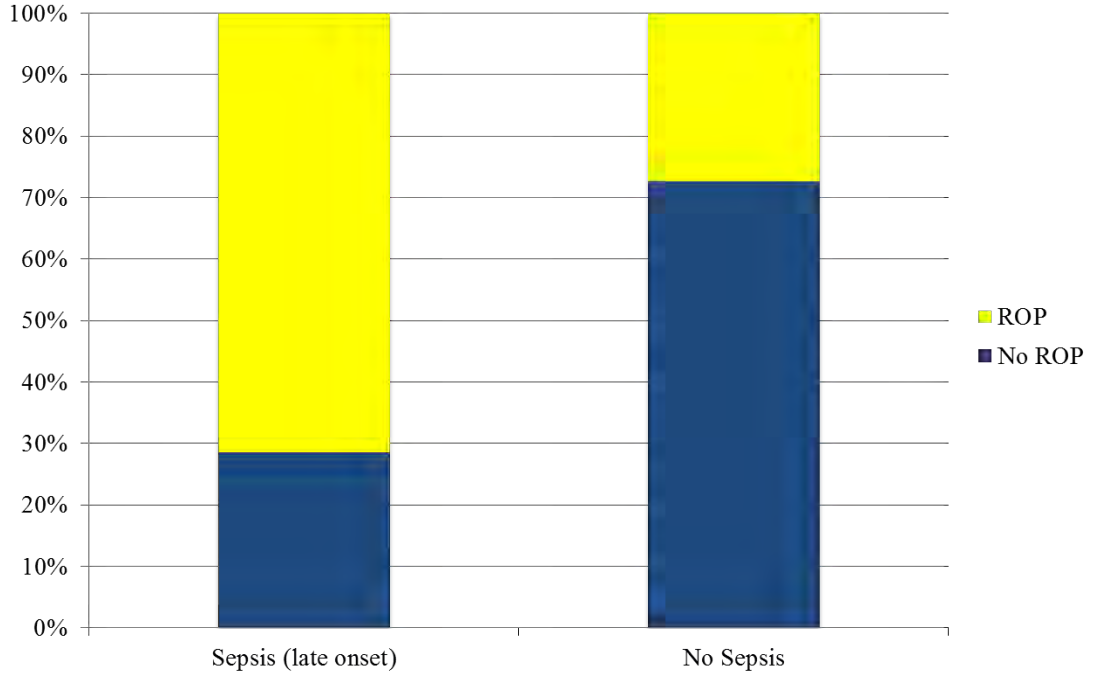

Figure 4: Incidence of ROP in birth weight categories (n=135)

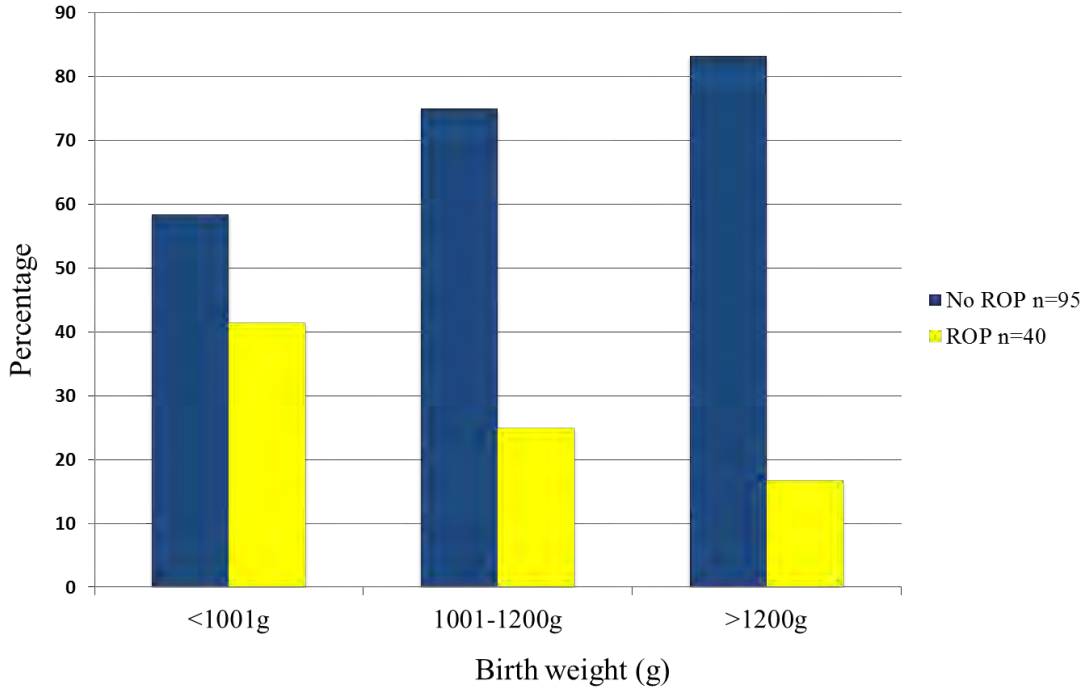

Table 1: Perinatal characteristics of the cohort n = 135

Characteristics	**n (%) /mean (+/-SD) / median (IQR)**
I**nfant characteristics**	
Birth weight (g)	1056 (172)
Gestational Age (weeks)	30.1 (1.9)
Race – Black	77 (57.0)
– Coloured	58 (43.0)
Female gender	74 (54.8)
Family history of ROP	1 (0.7)
Maternal history	
Maternal VDRL positive	2 (1.5)
Maternal HIV positive	22 (16.3)
Maternal medication use	58 (43.0)
Cigarettes/ tik /alcohol use	16 (11.9)
Illness	73 (54.9)
Birth and resuscitation history	
Out born	10 (7.4)
Mode of delivery- C/S	95 (71.1)
Apgar score (1 minute) †	7 (4-8)
Apgar score (5minutes) †	9 (7-9)
Resuscitation required ††	85 (64.9)
Oxygen administered	103 (76.3)
Facemask/ T-piece ventilation ††	85 (64.9)
Endotracheal intubation ††	13 (9.9)
Chest compressions ††	26 (19.9)
Neonatal period	
Respiratory support	
O2 therapy	122 (90.4)
CPAP/ HHFNC/ nasal cannula O2	95 (70.4)
Mechanical ventilation	27 (20.0)
Duration of O2 therapy (days)	5 (2-10)
Highest concentration of O2 received	0.3 (0.25-0.37)
Surfactant	40 (29.6)
Apnoea	37 (27.4)
Blood transfusion	28 (20.7)
Sepsis-early	1 (0.7)
Sepsis-late	7 (5.2)
IVH (grade 3 or 4) †††	4 (3.0)
Exclusive breast milk feeds	50 (37.0)

† n = 133 †† n = 131 ††† n = 132

CPAP = Continuous Positive Airway Pressure
C/S = Caesarean Section
g = grams
HHFNC = Humidified High Flow Nasal Cannula
HIV = Human Immunodeficiency Virus
IVH = Intraventricular haemorrhage
n = number
02 = Oxygen
ROP = Retinopathy of Prematurity
VDRL = Venereal Disease Research Laboratory

Table 2: Number of ROP examinations per infant, n= 135

Number of examinations	Number of infants, n (%)
1	52 (38.5)
2	43 (31.9)
3	18 (13.3)
4	7 (5.2)
5	5 (3.7)
6	5 (3.7)
7	2 (1.5)
8	3 (2.2)

n = number
ROP = Retinopathy of prematurity

Table 3: Prevalence of different stages of ROP (including infants lost to follow up)

Stage of ROP, n (%)	n=135 (100)	Lost to follow up, n=12 (100)
No ROP	95 (70.4)	5 (41.7)
ROP	40 (29.6)	7 (58.3)
Stage 3 or plus disease	8 (5.9)	2 (16.7)
Stage 4 or 5	0 (0.0)	0 (0.0)
Laser treatment	2 (1.5)	-

n = number
ROP= Retinopathy of Prematurity

Table 4: Potential risk factors in No ROP (n=95) compared to ROP (n=40)

Potential risk factors	**No ROP n (%)/ mean (SD)/ median (IQR)**	**ROP n (%)/ mean (SD)/ median (IQR)**	**P value**
Infant characteristics			
Birth weight (g)	1084 (±160)	988 (±931)	0.002
Gestational Age (weeks)	30.5 (±1.9)	29.2 (±1.6)	<0.001
Race – Black	58 (61.0)	19 (47.5)	0.146
– Coloured	37 (39.0)	21 (52.5)	
Female gender	50 (52.6)	24 (60.0)	0.432
Family history of ROP	0 (0.0)	1 (2.5)	0.296*
Maternal history			
Maternal VDRL positive	1 (1.1)	1 (2.5)	0.506*
Maternal HIV positive	15 (15.8)	7 (17.5)	0.806
Maternal medication use	39 (41.1)	19 (47.5)	0.490
Cigarettes/ tik /alcohol use	10 (10.5)	6 (15.0)	0.377*
Illness	51 (54.3)	22 (56.4)	0.820
Birth and resuscitation history			
Out born	7 (7.4)	3 (7.5)	1.000*
Mode of delivery- C/S	73 (76.8)	23 (57.5)	0.024
Apgar score (1 minute) †	7 (4-8)	7 (3-8)	0.796**
Apgar score (5minutes) †	9 (7-9)	9 (7-9)	0.775**
Resuscitation required††	61 (66.3)	24 (61.5)	0.601
Oxygen administered	74 (77.9)	29 (72.5)	0.501
Facemask/ T-piece ventilation††	61 (66.3)	24 (61.5)	0.601
Endotracheal intubation††	6 (6.3)	7 (17.5)	0.132
Chest compressions††	15 (15.8)	11 (27.5)	0.288

Neonatal period			
Respiratory support			
O2 therapy	85 (89.5)	37 (92.)	0.755*
CPAP/ HHFNC/ nasal cannula O2	66 (69.5)	29 (72.50)	0.725
Mechanical ventilation	19 (20)	8 (20)	1.000*
Duration of O2 therapy (days)	4 (2-8)	5.5 (2-14)	0.360**
Highest concentration of O2 received (FiO_2)	0.3 (0.25-0.4)	0.3 (0.25-0.35)	0.859**
Surfactant	27 (28.4)	13 (32.5)	0.636
Apnoea	24 (25.3)	13 (32.5)	0.389
Blood transfusion	12 (12.6)	16 (40.0)	<0.001
Sepsis-early	0 (0.0)	1 (2.5)	0.122
Sepsis-late	2 (2.1)	5 (12.5)	0.024*
IVH (grade 3 or 4) †††	4 (4.2)	0 (0.0)	0.553*
Breast milk feeds	28 (29.5)	22 (55.0)	0.014*

† n=133 †† n=131 ††† n = 132
* Fisher's exact ** Wilcoxon rank-sum

CPAP=Continuous Positive Airway Pressure
C/S = Caesarean Section
g = grams
HHFNC = Humidified High Flow Nasal Cannula
HIV = Human Immunodeficiency Virus
IQR = interquartile range
IVH = Intraventricular haemorrhage
n = number
02 = Oxygen
ROP= Retinopathy of Prematurity
SD = standard deviation
VDRL = Venereal Disease Research Laboratory

Table 5: Potential risk factors Mild ROP (n=32) compared to CSROP (n=8)

Potential risk factors	**Mild ROP n (%)/ mean (SD)/ median (IQR)**	**CSROP n (%)/ mean (SD)/ median (IQR)**	**P value**
Infant characteristics			
Birth weight (g)	984 (± 185)	1006 (± 171)	0.769
Gestational Age (weeks)	29.2 (± 1.6)	29.4 (± 1.3)	0.755
Race – Black	17 (53.1)	2 (25.0)	0.154
– Coloured	15 (46.9)	6 (75.0)	
Female gender	20 (62.5)	4 (50.0)	0.690*
Family history of ROP	1 (3.1)	0 (0.0)	1.000*
Maternal history			
Maternal VDRL positive	1 (3.1)	0 (0.0)	1.000*
Maternal HIV positive	6 (18.8)	1 (12.5)	1.000*
Maternal medication use	17 (53.1)	2 (25.0)	0.241*
Cigarettes/ tik /alcohol use	4 (12.5)	2 (25.0)	0.414*
Illness	20 (35.5)	2 (25.0)	0.059*
Birth and resuscitation history			
Out born	2 (6.3)	1 (12.5)	0.498*
Mode of delivery- C/S	21 (65.6)	2 (25.0)	0.053*
Apgar score (1 minute)	7 (3-8)	7 (3-9)	0.891**
Apgar score (5minutes)	9 (7-9)	9 (6-10)	0.729**
Resuscitation required†	20 (62.5)	4 (50.0)	0.749*
Oxygen administered	24 (75.0)	5 (62.5)	0.660*
Facemask/ T-piece ventilation†	20 (62.5)	4 (50.0)	0.749*
Endotracheal intubation†	6 (18.8)	1 (12.5)	1.000*
Chest compressions†	8 (25.0)	3 (37.5)	0.731*

Neonatal period			
Respiratory support			
O2 therapy	30 (93.8)	7 (87.5)	0.498*
CPAP/ HHFNC/ nasal cannula O2	22 (68.8)	7 (87.5)	0.405*
Mechanical ventilation	8 (25.0)	0 (0.0)	0.173**
Duration of O2 therapy (days)	5 (2-19.5)	8.5 (3.5-10.5)	0.786**
Highest concentration of O2 received (FiO_2) ††	0.3 (0.25-0.35)	0.3 (0.3-0.35)	0.388**
Surfactant	11 (34.4)	2 (25.0)	1.000*
Apnoea	9 (28.1)	4 (50.0)	0.400*
Blood transfusion	14 (43.8)	2 (25.0)	0.439
Sepsis-early	1 (3.1)	0 (0.0)	1.000*
Sepsis-late	4 (12.5)	1 (12.5)	1.000*
IVH (grade 3 or 4)	1 (3.1)	0 (0.0)	1.000*
Exclusive breast milk feeds	18 (56.3)	4 (50.0)	1.000*

† n = 39
†† n = 37
* Fisher's exact
** Wilcoxon rank-sum

CPAP=Continuous Positive Airway Pressure
C/S = Caesarean Section
g = grams
HHFNC = Humidified High Flow Nasal Cannula
HIV = Human Immunodeficiency Virus
IQR = interquartile range
IVH = Intraventricular haemorrhage
n = number
02 = Oxygen
ROP= Retinopathy of Prematurity
SD = standard deviation
VDRL = Venereal Disease Research Laboratory

Table 6: Potential risk factors No/Mild ROP (n=127) compared to CSROP (n=8)

Potential risk factors	**No/Mild ROP n (%)/ mean (SD)/ median (IQR)**	**CSROP n (%)/ mean (SD)/ median (IQR)**	**P value**
Infant characteristics			
Birth weight (g)	1059 (±172)	1006 (±171)	0.391
Gestational Age (weeks)	30.2 (±1.9)	29.4 (± 1.3)	0.260
Race – Black	75 (59.1)	2 (25.0)	0.074*
– Coloured	52 (40.9)	6 (75.0)	
Female gender	70 (55.1)	4 (50.0)	1.000*
Family history of ROP	1 (0.8)	0 (0.0)	1.000*
Maternal history			
Maternal VDRL positive	2 (1.6)	0 (0.0)	1.000*
Maternal HIV positive	21 (16.5)	1 (12.5)	1.000*
Maternal medication use	56 (44.1)	2 (25.0)	0.466*
Cigarettes/ tik /alcohol use	14 (11.1)	2 (25.0)	0.292*
Illness	71 (56.8)	2 (25.0)	0.140*
Birth and resuscitation history			
Out born	9 (7.1)	1 (12.5)	0.469*
Mode of delivery- C/S	94 (74.1)	2 (25.0)	0.007*
Apgar score (1 minute) †	7 (4-8)	7 (3-9)	0.833**
Apgar score (5minutes) †	9 (7-9)	9 (6-10)	0.661**
Resuscitation required††	81 (63.8)	4 (50.0)	0.571*
Oxygen administered	98 (77.2)	5 (62.5)	0.394*
Facemask/ T-piece ventilation††	81 (63.8)	4 (50.0)	0.571*
Endotracheal intubation††	12 (9.5)	1 (12.5)	0.670*
Chest compressions††	23 (18.1)	3 (37.5)	0.371*

Neonatal period			
Respiratory support			
O2 therapy	115 (90.5)	7 (87.5)	0.565*
CPAP/ HHFNC/ nasal cannula O2	88 (69.3)	7 (87.5)	0.435*
Mechanical ventilation	27 (21.3)	0 (0.0)	0.357*
Duration of O2 therapy (days)	5 (2-10)	9 (4-10)	0.418**
Highest concentration of O2 received (FiO_2) ‡	0.3 (0.25-0.38)	0.3 (0.3-0.35)	0.582**
Surfactant	38 (29.9)	2 (25.0)	1.000*
Apnoea	33 (26.0)	4 (50.0)	0.214*
Blood transfusion	26 (20.5)	2 (25.0)	0.670*
Sepsis-early	1 (0.8)	0 (0.0)	1.000*
Sepsis-late	6 (4.7)	1 (12.5)	0.355*
IVH (grade 3 or 4) ‡‡	4 (3.2)	0 (0.0)	1.000*
Exclusive breast milk feeds	46 (36.2)	4 (50.0)	0.534*

† n = 133 †† n = 131 ‡ n = 122 ‡‡ n = 132
*Fisher's exact ** Wilcoxon rank-sum

CPAP=Continuous Positive Airway Pressure
C/S = Caesarean Section
g = grams
HHFNC = Humidified High Flow Nasal Cannula
HIV = Human Immunodeficiency Virus
IQR = interquartile range
IVH = Intraventricular haemorrhage
n = number
02 = Oxygen
ROP= Retinopathy of Prematurity
SD = standard deviation
VDRL = Venereal Disease Research Laboratory

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Appendix 1: Ethical approval letter

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

08 November 2012

HREC REF:509/2012

Dr Q Keraan
c/o Dr Y Joolay
Neonatology
H-floor
OMB

Dear Dr Keraan

PROJECT TITLE: RETINOPATHY OF PREMATURITY IN A COHORT OF NEONATES AT GROOTE SCHUUR HOSPITAL

Thank you for addressing the issues raised by the Human Research Ethics Committee.

It is a pleasure to inform you that the Ethics Committee has **formally approved** your collaboration in the above mentioned study.

Approval is granted for one year till the 15 November 2013.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

Signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

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

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

sAriefdien

Appendix 2: Parental information sheet

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

1. Parental Information: Retinopathy of Prematurity

We are doing a study on Retinopathy of Prematurity (ROP), an eye condition that affects the blood vessels of the retina. The retina is the delicate tissue lining the back of the inside of the eye, which detects light and allows us to see.

Premature babies are at risk of developing ROP because the retina has not yet fully formed when they are born. After birth, the blood vessels of the retina may develop abnormally. The condition is usually very mild and settles on its own without any treatment. In a very few babies (usually the smallest and most premature) the ROP does not get better and treatment is needed. If this development is severely abnormal, the baby is at high risk of being blind.

What is screening for ROP?

ROP screening is the eye examination by an ophthalmologist (or eye specialist) to look for any signs of ROP. Babies weighing less than 1251 grams at birth or born more than 9 weeks early would need at least one eye screening examination.

What is this study all about?

We are trying to find out how commonly ROP occurs in our patients. By participating in this study you will help us find that out. You will also benefit by the screening, by allowing us to identify whether your baby is at a high risk of blindness. If the screening examination shows that your baby has a higher risk of blindness due to severe ROP then we have an opportunity to treat your baby and reduce the chance of blindness.

Participation in this study is completely voluntary. Medical information will be recorded from your baby's hospital folder, but no names or other identifying information will be recorded. The results from this study may be published in a medical journal. If you decide to take part, you can at any time decide to withdraw your baby from the study; this will not affect how we care for your baby at all.

Why does ROP occur?

No one knows exactly why. When a baby is born early, the blood vessels of the retina are not fully developed. After birth something triggers the blood vessels to start to grow abnormally and this forms scar tissue which, if severe, can damage the retina. The main cause of ROP is prematurity itself.

When will the screening be done?

The first screening examination will be done when your baby is between 4 and 6 weeks old. Some babies will need only one examination although most babies need at least two.

What happens during screening?

About an hour before the examination, eye drops are put in the eye to make the pupil open widely so the retina can be seen. The ophthalmologist examines the retina using an ophthalmoscope placed gently on the surface of your baby's eye. They may also use a speculum (to hold the eyelid open).

Is the examination painful?

Eye examinations can be uncomfortable even for adults and babies sometimes cry or show signs of distress when their eyes are examined. The baby will receive a local anesthetic to minimize the discomfort. The ophthalmologist will make the examination as quick as possible although they do need enough time to see the retina properly.

What happens if ROP is found?

This depends on how serious it is. If ROP is mild; there will need to be a follow-up examination 1 to 2 weeks later. If the follow-up examination shows it has not become worse, the ROP will settle on its own. In a very few cases the ROP may be severe enough to require treatment. If your baby requires treatment at any stage the ophthalmologist will talk to you to explain exactly what will happen.

Will screening finish before my baby goes home?

Your baby will be discharged as soon as they are well enough to go home. This might be before the last eye screening. If this is the case, staff should arrange an outpatient appointment before you take your baby home. **It is very important that you bring your baby back for his/her eyes to be checked if you are asked to.** When you are ready to take your baby home ask the staff if you need to bring him/her back and when. They will also write to remind you about the appointment.

What about confidentiality?

The information collected will be stored in a password-protected database to ensure that the information remains confidential.

Principal investigator: Dr Qaunitah Keraan

Contact details: Department of Neonatology, H46 Old Main Building, Groote Schuur Hospital, Anzio Road, Observatory, 7925

Telephone number: (021) 404 6029/ 082 7868121

FHS HREC: Room E52-24 Old Main Building, Groote Schuur Hospital, Observatory, 7925

FHS HREC telephone number: (021) 406 6338

HREC/REF: 509/2012

Appendix 3: Consent form

1. Consent Form

I ..... the parent of .....

have read and discussed this form with the researchers and understand what the research project entitled **'Retinopathy of prematurity in a cohort of neonates at Groote Schuur Hospital'** is about.

My questions have been answered

I freely agree: (tick appropriate block/s)

☐ To take part in the above study

☐ I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary and I am free to withdraw at any time, without giving a reason

☐ I agree that my data gathered in this study may be stored in a specialist data centre and may be used for future research

☐ I consent to my baby undergoing screening examination for Retinopathy of prematurity

Name of parent	Signature	Date
Name of researcher	Signature	Date
Name of witness	Signature	Date

Name of Patient:

Folder Number:

Sex: Date of Birth

Appendix 4: Case report form

1. Case Report Form

Sticker / Patient Name _____

Folder Number _____

Date of birth _____

Birth weight	_____g		
Gestational Age at birth	_____weeks (*confirmed with Ballard*)		
Sex	□Male	□Female	
Ethnicity	□1.Black	□2.Coloured	□3.White
	□4.Indian	□5.Other (*please detail*)	_____
Family hx of ROP	□Yes	□No	
VDRL	□ Positive	□Negative	
HIV	□Positive	□Negative	
Medication	□Yes	□No	If yes, specify_____
Recreational drug use	□Yes	□No	If yes, specify_____
Maternal illness	_____		
Place of delivery	□Inborn	□Out born	
Mode of delivery	□Vaginal	□Caesarean Section	
Apgars	1min _____	5min _____	10min _____
Initial Resuscitation	O2 administered	□Yes	□No
	Face mask / Neopuff Vent	□Yes	□No
	Endotracheal Tube Vent	□Yes	□No
	Cardiac Compressions	□Yes	□No
Oxygen Therapy	□Yes □No	**Duration of O2 therapy** _____days	
Mode of O_2 delivery	□1.Nasal Cannula	**Highest concentration O2 received** _____%	
	□2.CPAP / Vapotherm		
	□3.IPPV		
	□4.Mechanical Ventilation		
	□5.HFOV		
Surfactant	□Yes	□No	
Apnoea	□Yes	□No	**Duration**_____
Blood transfusion	□Yes	□No	
if yes, number of transfusions	_____		
Sepsis – *early*	□Yes	□No	
Sepsis – *late*	□Yes	□No	
IVH Grade 3/4	□Yes	□No	
Type of feed (first 6/52)	□Breast milk	□Formula	

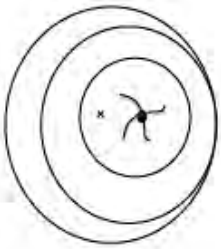
0

INITIAL OPHTHALMOLOGICAL EXAMINATION

Date _____ **Weight** _____ **Chronological Age**_____

Findings

Plus□



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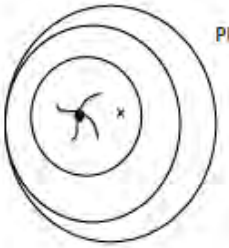


Plus□

Left

Assessment _____

_____

Plan _____

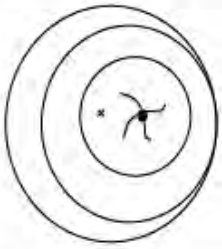
STAGE: □1 □2 □3 □4 □5

FOLLOW-UP OPHTHALMOLOGICAL EXAMINATION

Date _____ **Weight** _____ **Chronological Age**_____

Findings

Plus□



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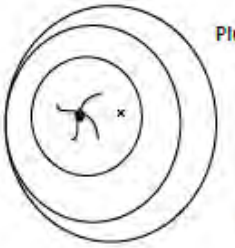


Plus□

Left

Assessment _____

_____

Plan _____

STAGE: □1 □2 □3 □4 □5

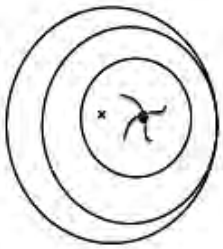
1

FOLLOW-UP OPHTHALMOLOGICAL EXAMINATION

Date _____ **Weight** _____ **Chronological Age**_____

Findings

Plus□



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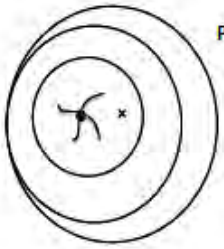


Plus□

Left

Assessment _____

_____

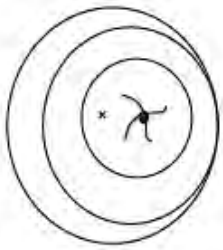
Plan _____

FOLLOW-UP OPHTHALMOLOGICAL EXAMINATION

Date _____ **Weight** _____ **Chronological Age**_____

Findings

Plus□



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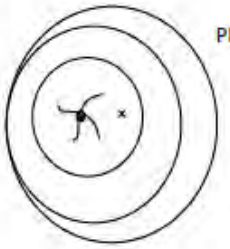

Plus□

Left

Assessment _____

_____

Plan _____

2