Frequency and Outcome of Retinopathy of Prematurity at Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: To describe the frequency and outcome of Retinopathy of prematurity (ROP).

Study Design: Observational study.

Place and Duration of Study: Ophthalmology Department, Shifa International Hospital (SIH) Islamabad from May 2014 to December 2019.

Methodology: All preterm infants with gestational age ≤35 weeks and/or birth weight ≤2000g were included while those born at greater than 35 weeks of gestation and having a gestational weight more than 2000g were excluded from this study. Studied variables included gender, gestational age, birth weight, form and duration of supplemental oxygen, systemic diseases, presence or absence of ROP, ROP stage, treatment, and outcome.

Results: Six hundred and twenty-two met the inclusion criteria out of whom 316 were screened. The majority (n=202, 64%) of the screened infants were males. Supplemental oxygen was given to 244 (77.2%) infants. The mean gestational age was 31.94 ± 2.2 weeks. The mean birth weight was 1632 ± 446 g. ROP was diagnosed in 10 (3.2%) infants with stage 1 in 3 (0.9%) infants, stage 2 in 1 (0.3%), stage 3 in 5 (1.5%), and stage 4B in 1 (0.3%) infant. In the infants diagnosed with ROP, mean gestational age was 30.4 ± 2.9 weeks, and mean birth weight was 1393 ± 416 g. ROP regressed spontaneously in 3 infants with stage 1 and 1 infant with stage 2 disease. Infants with stage 3 disease also had disease regression after treatment with intravitreal Ranibizumab (n=3) or intravitreal Bevacizumab (n=2) injection along with concurrent laser photocoagulation (n=1). The infant with 4B ROP underwent bilateral vitrectomy with the complete attachment of retina on follow-up.

Conclusion: There was a low frequency of 3.2 % of ROP reported in this study. The infants diagnosed with ROP had favorable outcomes following timely treatment of this dreadful disease.

Key Words: *Retinopathy of prematurity, Eye, Retina, Supplemental oxygen, Screening.*

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INTRODUCTION

Retinopathy of prematurity (ROP) is the development of abnormal retinal blood vessels which affects neonates that are born prematurely or have low birth weight. This abnormal vasculature leads to tractional retinal detachment and consequently blindness.[1] With emerging healthcare facilities leading to the improved survival of premature and low birth weight infants, the frequency of ROP is also on the rise.[2] Poor understanding of the disease process along with the deficiency of resources and screening protocols has set the developing countries at substantial risk of ROP related blindness.[3,4]

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A study was done in 2018 established that more than 40% of at-risk premature infants develop some stage of ROP while 12.5% of these infants suffer from its severe form.[5] ROP is the second leading cause of childhood blindness in the United States as well.[6] In Pakistan, a study was done in 2016 at Lahore showed the frequency of ROP to be 16%.[7] Another local study has attributed the high frequency of ROP-related blindness in the country to lack of appropriate referral and screening.[8] However, the data available in the Pakistan is limited in its sample size and follow-up period with studies focused on certain specific regions.

Guidelines for ROP screening were created to ensure that the eyes with a high likelihood of requiring treatment were detected as soon as possible while reducing the number of tests for newborns who were not at risk.[9] The purpose of this study was to report the frequency and outcome of ROP following the guidelines of timely screening.

METHODOLOGY

This is an observational study conducted at the Ophthalmology Department of Shifa International Hospital (SIH) Islamabad from

May 2014 to December 2019. Data of the pre-term infants who were treated during the study period was retrospectively analysed. This study was approved by Institutional Review Board (IRB) (Reference number: IRB # 212-1032-2020). Patients were identified using their assigned medical record number. Inclusion criteria encompass all the preterm infants born at a gestational age of ≤35 weeks OR birth weight ≤2000g who were examined by a single consultant ophthalmologist (MAA) were included in the study to remove the bias resulting from the difference in the observation by different doctors. While the infants born at greater than 35 weeks of gestation and having a gestational weight more than 2000g, those leaving against medical advice, expired, lost to follow-ups and those examined by any other consultant were excluded from this study.

Ocular examination was carried out using a 28 diopter lens with a binocular indirect ophthalmoscope at 4 weeks of age with prior dilatation using 0.5% Cyclopentolate eye drops three times ten minutes apart. Eyelid speculum and scleral indentation were utilised for sufficient examination under topical anesthesia. Further examination was done according to the stage of ROP till vascularisation was found to be complete. Screened infants were defined as the preterm infants born in SIH at a gestational age of ≤35 weeks OR birth weight ≤2000 g examined by a single consultant ophthalmologist (MAA) following the proposed guidelines of ROP screening.[9]

Collected data included gender, gestational age, birth weight, form and duration of supplemental oxygen, systemic diseases, presence or absence of ROP, ROP stage, treatment, and outcome. Data analysis was done using a statistical package for social sciences (SPSS 21 software). For qualitative variables, frequency and percentage were used while mean and standard deviation were calculated for quantitative variables. Treatment was given to type 1 Stage 3 ROP and stage 4 ROP following the recommendations of the Early Treatment for ROP trial (ET-ROP).[10]

RESULTS

Total 622 infants meeting the inclusion criteria were enrolled in the study. About half of them (306) did not undergo screening. Among them; 102 expired, 21 were transferred to another facility, 10 left against medical advice (LAMA) and 173 were lost to follow-ups were excluded from this study. Among the remaining 316 infants that underwent screening (by MAA), 202 (63.9%) were males. Supplemental oxygen was administered to 244 (77.2%) infants keeping pulse oximeter readings between 89 -92% while oxygen was not administered in the remaining 72 infants (22.7%). A comparison between the two groups is given in Table I. Mean gestational age was 31.94 ± 2.2 weeks (ranging: from 24-36 weeks). Mean birth weight was 1632 ± 446 g., ranging from 500-2800 g.

ROP was diagnosed in 10 (3.2%) infants with stage 1 (zone 2=2, zone 3=1) in 3(0.9%), stage 2 (zone 2) in 1(0.3%), stage 3 (zone 1=1, zone 2=4) in 5 (1.5%) and stage 4B in 1 (0.3%) infant. The mean gestational age in these infants was 30.4 ± 2.9 weeks (Range: 27-36 weeks) and the mean birth weight was 1393 ± 416 g (Range: 860-2000g). ROP was identified in one infant with gestational age of 36 weeks and one infant with the weight of 2000g. All had bilateral disease. Among these infants, 9 (90%) had supplemental oxygen in some form which is a known risk factor for ROP. Nine (90%) infants had sepsis while 1 (10%) had hydrocephalus with meningitis and 6 (60%) also received multiple blood transfusions. A systematic review of these infants highlighted the presence of other systemic risk factors as well. The various stages along with their corresponding mean gestational ages, birth weights, Systemic risk factors, and their management along with the duration and form of supplemental oxygen are given in Table II.

ROP regressed spontaneously in three babies with stage 1 and one baby with stage 2 disease. They were examined regularly every 2 weeks till vascularisation was complete. Two babies with stage 3 disease (Zone 1=1, Zone 2=1) were treated with intravitreal Ranibizumab injection (0.25mg) under topical anesthesia. A baby with stage 3 ROP with zone 2 involvement also had combined retinal laser photocoagulation and intravitreal Ranibizumab injection (0.25mg). Two babies with stage 3, zone 2 disease had intravitreal injection Bevacizumab at a dose of 0.652mg under topical anesthesia. A baby with stage 4B ROP underwent vitrectomy in both eyes under general anesthesia. All the babies with stage 3 disease showed regression after treatment and they were examined repeatedly in the OPD first day after the procedure, then after 1 week, after 1 month for 3 months followed by 4 monthly examinations for a period of 2 years. This showed no recurrence of the disease. The baby with stage 4B ROP also had a complete attachment of the retina in both eyes.

Table I: Comparison of mean gestational age and weight in infants who received supplemental oxygen and in those who did not.

Supplemental oxygen	Mean gestational age (Mean ± SD)	Mean weight in grams (Mean ± SD)
Yes (n = 244)	32 ± 2.1 weeks	1624 ± 378 g
No (n =72)	31.7 ± 2.6 weeks	1659 ± 627g

DISCUSSION

With the advancements in neonatal health care facilities, the survival of neonates is increasing. ROP is one of the premature complications frequently encountered among survivors. Various studies have been conducted worldwide assessing the frequency of ROP and its risk factors. Internationally it has been reported to be 12% in a large multicenter study conducted in 2018 in the US and Canada.[5] while its frequency was found to be as high as 46.4% in Oman.[11] In a study conducted in 2016 in Lahore, its frequency was around 16%.[7] However, this study reports it to be 3.2% which is significantly lower compared to data from other hospitals. It is primarily due to the well-controlled oxygen therapy which is being given to the preterm neonates in our setup keeping the target oxygen between 89-92%. Our trained NICU staff has a major contributing role in this regard. They undergo periodic workshops and education sessions regarding this.

Table II: Stage of ROP along with gestational age, birth weight (g=grams), systemic risk factors along with their management, and form of supplemental oxygen administered.

Stage of ROP	Mean birth weight in grams (Range)	Mean gestational age (Range)	Systemic profile	Treatment	Form of supplemental Oxygen
Stage 1 (n=3)	1083g (860-1390g)	29 weeks (28-30 weeks)	Sepsis (n=3), Small PDA (n=1), RDS (n=2), Pulmonary htn (n=1)	IV Antibiotics (n=3), Blood transfusion (n=1)	24-36 hrs on bCPAP (n=1), 120-150 hrs on vent followed by >100 hrs on supplemental O_2 (n=1), <100 hrs on vent followed by <100 hrs on supplemental O_2 (n=1)
Stage 2 (n=1)	1900g	32 weeks	Sepsis, Anemia, Thrombocytopenia (n=1)	Multiple blood transfusions, IV Antibiotics (n=1)	Nil (Room Air)
Stage 3 (n=5)	1476 g (1000-2000g)	30.4 weeks (27-36 weeks)	Sepsis (n=4), Hydrocephalo-us with meningitis (n=1), RDS (n=3), Anemia (n=3), Small PDA (n=1), Large PDA (n=2),Hypoth-yroidism (n=1)	Multiple blood transfusions (n=3) IVAntibiotics (n=5), IVAntifungals (n=2), VP shunting (n=1), PDA ligation (n=2), Thyroxine (n=1)	120-150 hrs on vent followed by >100 hrs on supplemental O_2(n=3), >150 hours on vent (n=2) followed by bCPAP (n=1)
Stage 4 (n=1)	1400g	33 weeks	Sepsis, Hydrocephalo-us, Pulmonary htn (n=1)	Multiple blood transfusions, VP Shunting, IV and Intra-thecal Antibiotics (n=1)	100-120hrs on vent followed by <100hrs on supplemental O_2 (n=1)

PDA: Patent ductus arteriosus, VP: Ventriculo-peritoneal, RDS: Respiratory distress syndrome, Htn: Hypertension, IV: Intravenous, O2: Oxygen, bCPAP: Bubble continuous positive airway pressure, vent: Ventilator, hrs: Hours.

A study in South India has also suggested that the increasing awareness of oxygen therapy hazards to NICU staff has greatly led to the reduction in severe cases of ROP.[12]

Our reported frequency is also lower because of using a broader criterion for screening than that being followed internationally. We have followed the criteria recommended for the middle income countries *i.e*. screening of infants with a birth weight of less than 2000 grams, gestational age of less than 35 weeks, multiple births, and eventful postnatal periods like oxygenation, sepsis, respiratory distress syndrome, and blood transfusions.[2] Although a local study[3] suggests using the international criteria recommended for high-income countries for screening of ROP in our country as well. However, the authors do not recommend this as the data shows the presence of ROP in birth weight of more than 1500 g and gestational age of more than 30 weeks as well.

In literature, various risk factors linked with the development of ROP include; low gestational age, low birth weight, sepsis, supplemental oxygen, respiratory distress syndrome (RDS), and use of packed red cell blood transfusions.[13] Results of our study also establish that multiple factors contribute simultaneously to the development of abnormal vasculature of the retina. Prematurity and low birth weight are not solely responsible for the disease process.

Three studies have been conducted on ROP in various regions of Pakistan so far.[3,7,14] All have not only analysed the frequency of ROP but also urged the healthcare workers, especially neonatologists and ophthalmologists to work as a team considering the increasing rate of ROP- related blindness. However, this data shows that there is still lacking of parental guidance and counseling considering the increased loss of follow-ups (27.8%) without initial screening in our study. Moin *et al*. evaluated the awareness of ROP in pediatricians in Pakistan in 2016 and concluded that even though the majority (93%) are well aware of the disease risk, most of them (77.4%) do not have an ophthalmologist available for screening.[15] This suggests that education along with frequent workshops for ophthalmologists on ROP screening need to be conducted on regular basis. Every health care institution providing childbirth facility must have a trained ophthalmologist available for the screening and earlier detection of ROP.

The study may not represent the whole population as it is conducted in a tertiary care hospital and a large part of the population has no access to required ROP screening. However, it has reported the frequency of ROP with the earliest possible screening and controlled oxygen supplementation over a period of five years.

CONCLUSION

There was a low frequency of 3.2 % of ROP reported in this study. The infants diagnosed with ROP had favourable outcomes following timely treatment of this dreadful disease.

ETHICAL APPROVAL:

This study was done after obtaining ethical approval from the Institutional Review Board (IRB) of Shifa International Hospital, Islamabad (Reference No. IRB # 212-1032-2020).

PATIENT'S CONSENT:
Informed verbal consent were taken from the patient's guardians to publish the data.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MAA: Conception and design, data collection, and review.
AH: Data collection and manuscript writing.
FS: Data Collection, data interpretation, and manuscript writing.
SN, SC: Review.
All authors approved the final version of the manuscript to be published.

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