An Assessment of Associated Risk Factors for Retinopathy of Prematurity (ROP) among Neonates of NICU of a Tertiary Care Hospital: A Cohort Study

Authors

Dr Saurabh Vijay Doifode¹, Dr Satish Dattu Ashtekar²*, Dr Shishir Prabhakar Mirgunde³, Dr Swati Khot⁴

¹Junior Resident, Department of Pediatrics, Government Medical College, Miraj
²Associate Professor, Department of Pediatrics, Government Medical College, Miraj
³Professor and Head of Department of Pediatrics, Government Medical College, Miraj
⁴Assistant Professor, Department of Pediatrics, Government Medical College, Miraj

*Correspondence Author

Dr Satish Dattu Ashtekar
Associate Professor, Department of Pediatrics, Government Medical College, Miraj, Maharashtra, India

Abstract

Background: Due to improved survival of Neonates, Incidence of Retinopathy of Prematurity (ROP) has also increased, which is a serious complication among premature neonates. It can lead to blindness unless recognized early.

Aims & Objectives: To Estimate the proportion and various associated risk factors of Retinopathy of Prematurity among high risk neonates in the NICU.

Materials and Methods: A Prospective Cohort Study was conducted enrolling all neonates admitted in NICU of a Tertiary Care Hospital from January 2018 to August 2018, with a gestational age <36 weeks and birth weight <1800 gms and Neonates with gestational age >36 weeks or birth weight >1800 gms who are exposed to oxygen were included. A total of 96 neonates underwent retinal evaluation by indirect ophthalmoscopy after Fourth postnatal week. Perinatal risk factors for Retinopathy of Prematurity were assessed using statistical analytical tests like Chi Square test and Mid P Exact test.

Results: Out of 96 neonates, 13 neonates (13.54%) developed ROP; Among them 09 (69.23%) cases of stage 1, 1 (7.69%) case of stage 2, and 3 (23.07%) cases of stage 3. None of the neonates presented ROP at stages 4 or 5. Significant relationship was found between the occurrence of ROP and gestational age, oxygen therapy, blood transfusions, mode of oxygen delivery and sepsis. No association was found between the occurrence of ROP and gender, mode of delivery, birth weight, respiratory distress syndrome, patent ductus arteriosus, birth asphyxia, IUGR babies, intraventricular hemorrhage, meconium aspiration syndrome, phototherapy and duration of oxygentherapy.

Conclusion: The incidence of ROP in this study was 13.54%; low gestational age, oxygen therapy, blood transfusion and mode of oxygen delivery and sepsis are significant risk factors for ROP occurrence.

Keywords: Prematurity, Retinopathy of Prematurity, Oxygen therapy.

Introduction

Retinopathy of prematurity (ROP) is an important and Emerging cause of preventable blindness in children.¹ 26 million children are born per year in India out of which 7.8 million are premature and LBW which are at risk of developing ROP.

Increasing neonatal survival rate with unavailability of standardized neonatal careis...
important cause for increasing incidence of ROP. In India, incidence is reported between 24% and 47% among high risk infants.\(^2\) The incidence of blindness in India is 6.5 per 10000 children based on population based studies from south India.\(^3\) Early identification and appropriate timely intervention prevent blindness due to ROP and offer child better development.\(^4\)

ROP is a disorder of the immature developing retinal vasculature characterized by cessation of normal vasculogenesis followed by abnormal neovascularization in the retina of premature infants.\(^5\) These abnormal blood vessels are fragile and can leak or bleed, scarring the retina and pulling it out of position. This causes a tractional retinal detachment, which is the main cause of visual impairment and blindness in ROP.\(^6\)

The stages of ROP according to the International Classification of Retinopathy of Prematurity\(^7\) (ICROP) describe the retinal findings at the junction between the vascularized and a vascular retina as follows:

**Stage 1:** Thin Demarcation line  
**Stage 2:** An elevated Ridge  
**Stage 3:** Extraretinal Fibrovascular tissue  
**Stage 4:** Subtotal retinal detachment  
**Stage 5:** Total Retinal Detachment.

In addition, Plus disease refers to presence of vascular dilation and tortuosity of posterior retinal vessels in at least 2 quadrants. Preplus disease describes vascular abnormalities of the posterior pole (mild dilatation or arterial tortuosity) that are present but are insufficient for the diagnosis of Plus disease.

Retrolental Fibroplasia now known as Retinopathy of Prematurity was first described with implication of oxygen therapy as the causative agent. However, reports have found ROP in cases without oxygen therapy and even after oxygen therapy, not all develop ROP.\(^8\) Three factors have shown consistent and significant association with ROP: Low Gestational Age, Low Birth Weight and Prolonged exposure to oxygen.\(^9\) Other probable risk factors\(^10\) include Mechanical Ventilation, Sepsis, Intraventricular Hemorrhage, Surfactant Therapy, Anemia, frequent Blood Transfusions, and Apnea.

The aim of this Prospective Cohort Study was to estimate the proportion of ROP in Preterm infants at the Neonatal Intensive Care Unit (NICU) of Tertiary Care Hospital and to identify the risk factors which predispose to ROP.

**Aims & Objective**
1. To Estimate the proportion of ROP in High Risk Neonates in the NICU.  
2. To Identify the Risk Factors which predispose to ROP.

**Materials and Methods**
- **Study Design:** Prospective Cohort Study  
- **Place:** Neonatal intensive Care Unit of Tertiary Care Hospital  
- **Duration:** January 2018 to August 2018  
- **Study Participants:** Considering expected proportion of ROP 35% ±10% based on previous study results, sample size calculated was 88. To avoid attrition we have included 96 Neonates who were admitted in NICU during the study period and fulfilling inclusion criteria.

**Inclusion Criteria**
- All Neonates with Gestational Age of 36 weeks or less at birth.  
- All Neonates with Birth Weight less than 1800 grams.  
- Neonates exposed to oxygen therapy with gestational age >36 weeks or birth weight >1800 grams.

**Exclusion Criteria**
- Neonates who died before the first Ophthalmologic examination were excluded.  
- Neonates with Congenital Anomalies, Chromosomal Abnormalities & Inborn Errors of Metabolism.

**Procedure**

Neonates fulfilling inclusion and exclusion criteria were selected after taking informed consent from their parents. Detailed perinatal history taken to detect risk factors such as Prematurity, Birth Asphyxia, Meconium Aspiration Syndrome,
Sepsis. Present history included; the most common symptoms of respiratory distress requiring oxygen therapy, first mode of oxygen therapy, sepsis. The gestational age assessment done by Expanded New Ballard Score.

All enrolled neonates were examined by the Paediatric Ophthalmologist after 4th postnatal week. The eyes were dilated with a combination of tropicamide 0.8% and phenylephrine 5% eyedrops applied one hour before the examination. Indirect Ophthalmoscopy with a 20 diopter lens was performed with speculum and Scleral Depression.

The ROP was classified by location on the retina (zone 1–3), and severity (stage 1–5) according to the criteria established by the International Committee for Classification of ROP (ICROP).7

After that we examined suspected pre and postnatal risk factors for ROP to identify independent risk factors associated with the development of mild and severe forms of this disease in Tertiary Care Hospital NICU conditions.

Statistical Analysis

The pre-natal variables were Gestational Age, Birth Weight, Sex, and Mode of delivery. The post-natal variables were Respiratory Distress Syndrome, Birth asphyxia, MAS, oxygen therapy, Phototherapy, Blood transfusion, IVH, PDA, Sepsis. Relative risk was calculated and Pearson chi-square test was applied where ever possible or else Mid P exact test applied to categorical variables to test whether the relationship exists if any. Data was analysed using open-Epi online statistical software. A p-value of less than 0.05 was considered as Statistically Significant.

Results

Out of 96 screened Neonates, 13 developed ROP after 4th postnatal week. That means proportion of ROP in our study was 13.54% among high risk Neonates. Out of 13 ROP cases, 09 (69.23%) cases were stage 1, 1 (7.69%) case stage 2, and 3 (23.07%) cases were stage 3. None of the studied Neonates presented with stage 4 and stage 5 ROP.

Table 1: Neonatal variables & ROP among Neonates

<table>
<thead>
<tr>
<th>Neonatal variable</th>
<th>ROP n (%)</th>
<th>Normal n (%)</th>
<th>Total</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>07 (13.2)</td>
<td>46 (86.8)</td>
<td>53</td>
<td>0.94 (0.34,2.60)</td>
<td>p = 0.91</td>
</tr>
<tr>
<td>Female</td>
<td>06 (13.9)</td>
<td>37 (86.1)</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVD</td>
<td>06 (12.5)</td>
<td>42 (87.5)</td>
<td>48</td>
<td>0.69 (0.25,1.90)</td>
<td>p = 0.48</td>
</tr>
<tr>
<td>LSCS</td>
<td>07 (14.6)</td>
<td>32 (66.7)</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1 kg</td>
<td>01 (3.3)</td>
<td>02 (66.7)</td>
<td>03</td>
<td>2.08 (0.76,5.64)</td>
<td>p=0.17</td>
</tr>
<tr>
<td>1.0–1.49 kg</td>
<td>05 (20)</td>
<td>20 (80)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5–1.8 kg</td>
<td>05 (15.6)</td>
<td>27 (84.4)</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1.8 kg</td>
<td>02 (5.6)</td>
<td>34 (94.4)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maturity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32 wk</td>
<td>04 (33.3)</td>
<td>08 (66.7)</td>
<td>12</td>
<td>6.6 (1.97,22.54)</td>
<td>p=0.001</td>
</tr>
<tr>
<td>32–34 wk</td>
<td>06 (30)</td>
<td>14 (70)</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;36weeks</td>
<td>02 (5.3)</td>
<td>36 (94.7)</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>13 (13.5)</td>
<td>83 (86.5)</td>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* After pooling data Mid-P exact test applied

As per Table 1. No association was found between the occurrence of ROP and gender, mode of delivery and birth weight. But Low Gestational age (upto 34 weeks) has 6.6 times more risk of getting ROP than others and it was statistically significant.

33.3% of Neonates with <32 weeks of gestational age developed ROP out of which 50% developed stage 1 ROP and 50% developed stage 3ROP. 30% of Neonates with 32-34 weeks of gestational age developed ROP out of which 66.7% developed stage 1 ROP, 16.7% developed stage 2 ROP and 16.7% developed stage 3 ROP.

3.84% of Neonates with >34 weeks of gestational age developed ROP all of them developed stage 1 ROP. Whereas 5.26% of Neonates with >36 weeks of gestational age developed ROP.

Table 2: Association of occurrence of ROP with treatment modalities given to neonates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ROP n (%)</th>
<th>Normal n (%)</th>
<th>Total No.</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not given</td>
<td>07 (16.3)</td>
<td>36 (83.7)</td>
<td>43</td>
<td>1.43 (0.52,3.96)</td>
<td></td>
</tr>
<tr>
<td>SSPT</td>
<td>04 (12.5)</td>
<td>28 (87.5)</td>
<td>32</td>
<td>1.3 (0.26,6.53)</td>
<td>p=0.48</td>
</tr>
<tr>
<td>DSPT</td>
<td>02 (9.5)</td>
<td>19 (90.5)</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received</td>
<td>05 (27.7)</td>
<td>13 (72.2)</td>
<td>18</td>
<td>2.70 (1.07,3)</td>
<td>**p=0.07</td>
</tr>
<tr>
<td>Not received</td>
<td>08 (10.3)</td>
<td>70 (89.7)</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>13</td>
<td>83</td>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*After pooling data Chi square test applied

**Mid-P exact test applied as expected values of few cells are <5
In table 2 when tried to find out association of occurrence of ROP with treatment modalities given to neonates, no association seen between occurrence of ROP with type of phototherapy. Occurrence of ROP observed 2.7 times more with blood transfusion although it wasn’t statistically significant. 27.7 % of those who received blood transfusion developed ROP out of which 60 % developed stage 1 ROP and 40 % developed stage 3 ROP.

Oxygen therapy was significantly associated with occurrence of ROP among neonates almost 5.7 times more than those who didn’t receive oxygen therapy though it was not consistent. 18.5% of babies who received oxygen therapy developed ROP out of which 50 % developed stage 1 ROP, 25 % developed stage 2 ROP and 25 % developed stage 3 ROP.

**Table 3:** Association of occurrence of ROP and duration and mode of oxygen therapy given to neonates

<table>
<thead>
<tr>
<th>Duration of Oxygen Therapy</th>
<th>Mode of Oxygen Therapy</th>
<th>Total No.</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 3 days</td>
<td>Hood</td>
<td>05 (15.6)</td>
<td>83 (24.4)</td>
<td>04 (36.4)</td>
</tr>
<tr>
<td>4-5 days</td>
<td>CPAP</td>
<td>03 (15.6)</td>
<td>75 (85)</td>
<td>03 (16.6)</td>
</tr>
<tr>
<td>&gt;5 days</td>
<td>Mechanical Ventilator</td>
<td>04 (36.4)</td>
<td>04 (63.6)</td>
<td>04 (50)</td>
</tr>
</tbody>
</table>

According to table 4, Sepsis was significantly associated with occurrence of ROP. Almost 3.5 times more risk of ROP observed in neonates with sepsis than other morbidities. 33.3% of neonates diagnosed with sepsis developed ROP out of which 75% developed stage 1 ROP and 25 % developed stage 3 ROP.

No association was seen between occurrence of ROP with Respiratory Distress Syndrome, Birth Asphyxia, Meconium Aspiration Syndrome, IUGR Babies, Patent Ductus Arteriosus, Intraventricular Haemorrhage, Congenital Heart Diseases.

**Table 4:** Type of morbidity and ROP

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ROP</th>
<th>Normal</th>
<th>No of patients</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEPSIS</td>
<td>04  (33.3)</td>
<td>05 (22.7)</td>
<td>17 22</td>
<td>3.59 (1.30,9.89)</td>
<td>*p = 0.04</td>
</tr>
<tr>
<td>RDS</td>
<td>01 (4.5)</td>
<td>05 (0)</td>
<td>05 25</td>
<td>2.7 (1.9,9.4)</td>
<td></td>
</tr>
<tr>
<td>BIRTH ASPHYXIA</td>
<td>03 (0.3)</td>
<td>07 10</td>
<td>27.7 (1.30,9.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUGR</td>
<td>00 (0)</td>
<td>05 (22.7)</td>
<td>05 25</td>
<td>27.7 (1.30,9.89)</td>
<td></td>
</tr>
</tbody>
</table>

**Discussion**

- In this study we found Low-Gestational Age is significantly associated with occurrence of ROP, it is the most important risk factor in ROP. Similar observations made by Shah et al
11, Karna et al 12 and Fortes et al 13 in their respective studies. This was explained by immaturity of retinal neural and vascular development at birth in preterms and therefore retinal vulnerability to oxidative damage and to a number of perinatal factors which include Hyperoxia and Hypoxia, Blood Transfusions, and Sepsis.

- Oxygen Therapy was an independent risk factor for the development of ROP. We found a significant relationship between the occurrence of ROP and use of Oxygen. In our study we found that duration of oxygen therapy is insignificant for development of ROP which was in agreement with the results of Dutta et al 14 However few studies reported that a duration of oxygen therapy was a significant risk factor for development of ROP. This could be because of change of setting and other Perinatal and Postnatal factors.

- Low Gestational Age and Mechanical Ventilation were associated with severity of ROP which was in agreement with results of Wang et al 15, Mojgan Bayat-Mokhtari et al. 16

- In this study, we found that Sepsis was significantly associated with the development of ROP. This was in agreement with Shah et al 11 and Vinekar et al 17, which may be due to the effect of endotoxins on retinal blood vessels. On the other hand, this was in disagreement with the results of Chaudhari et al 18, and Smith et al 19.

Conclusion

- Survival of High Risk Newborn is at most priority of Pediatrician. However clinicians should be aware of the presence of the additional risk factors while managing and monitoring of preterm infants. The analysis of risk factors for ROP development will help clinicians to predict it in high risk infants.

- Regular Follow Up and timely Retinal Screening of High-Risk Preterm infants is important to identify ROP in earlier stages. It will prevent the development of advanced ROP by adequate intervention.

- Since ROP may produce serious sequelae including complete blindness, all efforts must be made to prevent the development of advanced ROP through changes in the neonatal care, control of sepsis, judicious use of oxygen therapy and improvement in detection of threatening ROP markers.

Limitation

This is a time bound study and conducted on a relatively small sample size. In future, these limitations can be overcome by planning a Multi-Centric study with larger sample size.

Acknowledgement

We sincerely acknowledge our Dean for her continuous guidance and support in conducting this study.

Bibliography

8. Zia Chaudhary, M Vanathi authors: Paediatric Ophthalmology.


15. Zong-Hua Wang, Yao-yuli and Zhi-Min Liu authors. Birth weight and gestational age on ROP in Discordant twins in China.


