Prospective Clinical Study on Incidence, Risk Factors and Management of Retinopathy of Prematurity in Preterm Babies Admitted in NICU, GGH, Kakinada

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Abstract

This study was done to study the incidence, risk factors, severity and interventions done for ROP in preterm babies. This was a Hospital based prospective study done in Neonatal intensive care unit for a period of 18 months. Inclusion criteria, exclusion criteria and timing of screening were taken according to NNF guidelines. ROP screening was done using RETCAM and timely intervention was done whenever needed with laser and/or intravitreal bevacizumab. Out of 576 screened preterm babies, 124 (21.4%) had ROP and among them 64 (51%) babies had type1 ROP, 48 (38%) had type2, 12 (9.6%) had Aggressive posterior ROP. ROP incidence was higher in babies with birth weight <1000gms (75%), 1001-1250gms (63%), 1250-1500gms (35%) with mean weight being 1310gms. 90% of babies with ROP were of < 34 weeks of gestation with mean GA of 31weeks. Most common risk factors identified on univariate analysis apart from birth weight and gestational age were oxygen therapy, CPAP, RDS, sepsis, duration of stay, apnea and hyperbilirubinemia (with p values < 0.0001). Multivariate analysis showed oxygen therapy, CPAP, RDS, sepsis and hyperbilirubinemia were significantly associated with ROP. Among 29 babies with blood transfusion, 44.8% had ROP and of which 77% had severe ROP (type 1 ROP or APROP). Laser treatment was given for 43 (56.6%) babies and intravitreal bevacizumab for 28 (36.8%) babies and 5(6.6%) babies received both. This study identified increased incidence of APROP. Severe ROP higher among babies who received blood transfusion.

Keywords: retinopathy of prematurity, special new born care unit, national neonatal forum, aggressive posterior ROP, vascularized retina.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder that affects the developing retinal vessels of premature infants. Premature retina exposed to high oxygen concentration, followed by abrupt withdrawal, easily undergoes uncontrolled vascular proliferation, fibrosis and eventually results in retinal detachment. In 1942, Terry [1] first described retrolental fibroplasia with implication of oxygen therapy as the causative agent [2, 3].

The aim of the present study was to identify the incidence, risk factors and severity of ROP in at risk preterm babies and refer them for early intervention whenever needed.

MATERIALS AND METHODS

This was a hospital based prospective study done in Neonatal Intensive Care Unit, Department of Pediatrics, Government General Hospital, Kakinada for a period of 18 months from January 2017 to June 2018. As per National Neonatal Forum guidelines babies born <34weeks gestational age and/or <1750 grams birth weight and infants between 34 to 36 6/7 weeks gestational age or a birth weight between 1750 and 2000 grams with risk factors for ROP were screened.

The first retinal examination was done at 4 weeks of postnatal age or 30 days of life in infants born ≥ 28 weeks of gestational age. Smaller babies born <28 weeks of gestational age or < 1200 grams birth weight were screened early at 2-3 weeks of age.
All the eligible preterm babies admitted in NICU were enrolled in this study, of which babies who died before the scheduled time of screening and babies with > 34 weeks gestational age and/or >1750 grams of birth weight without risk factors for ROP were excluded.

A predesigned proforma was used to collect data for risk factors such as birth weight, gestational age, multiple gestations, gender, duration of hospital stay, duration of oxygen given with hood or nasal prongs, duration of CPAP, duration of mechanical ventilation, blood transfusions, complications during hospital stay like jaundice, apnea, sepsis, hypoglycemia, polycythemia and interventions done like phototherapy and exchange transfusion.

Ethical clearance was obtained from the hospital ethics committee and informed consent of the parents was also obtained.

**PROCEDURE OF SCREENING**

An hour before screening, pupils of babies were dilated with 0.5% tropicamide + 1.25% phenylephrine drops one drop in each eye, 3 times 10 minutes apart. Screening was done in NICU by technician by using RETCAM. Images were interpreted by retina specialist. Retinopathy was graded into stages and zones as per the ICROP classification [12].

Infants with fully vascularized retina were not examined again. Those babies with zone I - stage 1 or 2 and zone II - stage 3 were reviewed after one week.

Babies were followed till complete vascularization. Babies with zone I – stage 3 or any stage with plus disease and zone II – stage 2 or 3 with plus disease and APROP were treated with laser or intravitreal bevacizumab within 48 hours under local anesthesia. All the treated babies were reviewed after 3 days and then weekly for regression.

**STATISTICAL ANALYSIS**

Analysis was performed using SPSS version 24. Univariate analysis was conducted using Chi square test and odds ratio. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables which were significant in the univariate analysis.

**RESULTS**

As per NNF guidelines 690 babies were eligible for screening of which 42 did not come for screening even for the first time. Of the remaining, 72 did not come for subsequent follow up in spite of repeated reminders. A total of 576 babies completed their screening. Out of the 576 screened preterm babies, 124 had ROP and the incidence of ROP was 21.6%.

The incidence of ROP according to gestational age is shown in Table 1. Mean gestational age of babies with ROP was 31 weeks gestation. As the gestational age decreased, the incidence of ROP increased.

**Table-2: Distribution of study population based on birth weight**

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>ROP+</th>
<th>ROP-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000gms</td>
<td>6(75%)</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>1000-1249gms</td>
<td>45(63%)</td>
<td>26</td>
<td>71</td>
</tr>
<tr>
<td>1250-1499gms</td>
<td>44(35%)</td>
<td>80</td>
<td>124</td>
</tr>
<tr>
<td>1500-1749gms</td>
<td>21(8.5%)</td>
<td>225</td>
<td>246</td>
</tr>
<tr>
<td>1750-2000gms</td>
<td>8(6%)</td>
<td>119</td>
<td>127</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>452</td>
<td>576</td>
</tr>
</tbody>
</table>

The chi-square value is 140.9577. The p-value is < 0.00001.

The incidence of ROP according to birth weight is shown in Table 2. Mean birth weight of babies with lower birth weight had higher chances of getting ROP.

**Table-2: Distribution of study population based on birth weight**

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>ROP+</th>
<th>ROP-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000gms</td>
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</tr>
</tbody>
</table>

The chi-square value is 140.9577. The p-value is < 0.00001.

A univariate analysis was initially done taking each risk factor. Chi square values were calculated for duration of oxygen therapy (Chi: 305.3464), duration of hospital stay (Chi: 239.8715) and odds ratios were calculated for RDS (OR: 15.2062, CI: 9.2328 to 25.0441), sepsis (OR: 19.0189, CI: 6.3061 to 57.3602) hyperbilirubinemia (OR: 11.7191, CI: 6.6134 to 20.7665) and apnea (OR: 9.6667, CI: 5.1748 to 18.0576) showed statically significant association with incidence of ROP with p values < 0.0001. Babies who received Oxygen for longer duration had higher incidence of ROP as shown in Table 3. None of the babies (261) who did not receive oxygen, developed ROP.

**Table-3: Relation between duration of oxygen and ROP**

<table>
<thead>
<tr>
<th>Duration of oxygen</th>
<th>ROP+</th>
<th>ROP-</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 days</td>
<td>13(8.6%)</td>
<td>139</td>
<td>152</td>
</tr>
<tr>
<td>4-7 days</td>
<td>87(63%)</td>
<td>52</td>
<td>139</td>
</tr>
<tr>
<td>8-14 days</td>
<td>24(100%)</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>No oxygen</td>
<td>0</td>
<td>261</td>
<td>261</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>452</td>
<td>576</td>
</tr>
</tbody>
</table>

The chi-square value 305.3464. The p-value is < 0.00001.
Multiple regression analysis showed oxygen therapy (OR: 0.060, p: .007), CPAP (OR: 0.0236, p: .000), RDS (OR: 0.310, p: .000), sepsis (OR: 0.15, p: .000) and hyperbilirubinemia (OR: 0.337, p: 0.004) to be significantly associated with ROP as depicted in Table 4.

<table>
<thead>
<tr>
<th>Risk factors of ROP</th>
<th>ROP +Ve (n=124) %</th>
<th>ROP -Ve (n=452) %</th>
<th>P Value</th>
<th>Multi variant Analysis Odds ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2(315)</td>
<td>124(39.3%)</td>
<td>191(60.7%)</td>
<td>.007</td>
<td>0.060</td>
</tr>
<tr>
<td>CPAP(112)</td>
<td>78(58%)</td>
<td>42(8.8%)</td>
<td>.000</td>
<td>0.236</td>
</tr>
<tr>
<td>RDS(197)</td>
<td>100(50%)</td>
<td>97(50%)</td>
<td>.000</td>
<td>0.310</td>
</tr>
<tr>
<td>SEPSIS (509)</td>
<td>115(22.7%)</td>
<td>394(77.4%)</td>
<td>.000</td>
<td>0.159</td>
</tr>
<tr>
<td>NNJ(282)</td>
<td>109(38.6%)</td>
<td>173(61.4%)</td>
<td>.004</td>
<td>0.337</td>
</tr>
<tr>
<td>APNEA(51)</td>
<td>34(66.6%)</td>
<td>17(33.4%)</td>
<td>.010</td>
<td>0.346</td>
</tr>
</tbody>
</table>

Both eyes were affected in all infants having ROP. Zones and stages were shown in the Figure 1 and 2.

Out of 124 babies with ROP, laser photocoagulation was done in 43(56.6%) babies and intravitreal bevacizumab was instilled in 28 (36.8%) babies and 5 (6.6%) babies received both. All babies withstood the procedure well and there were no post-laser complications other than reddening of the conjunctiva, which disappeared in 2-3 days.

**DISCUSSION**

In the present study all babies having birth weight <1750g, gestation ≤34 weeks were screened. Infants with birth weight between 1750 to 2000 gms, gestation 34 to 36 6/7 weeks were screened only if they had additional risk factors [4-6,13]. As reported by Palmer, et al. [15], incidence and severity of ROP was closely related to lower birth weight and lower gestational age, as was seen in the present study. The incidence of ROP of 21.4% in this study was much lower than that reported by Gopal, et al. [16] in 1995. In more recent studies, incidence of ROP reported is similar to the present study incidence [17, 18].

There are varying screening criteria described by different authors. Maheshwari, et al. in 1994 [19] and Gupta, et al. in 2004 [18] screened all babies ≤1500g and/or gestational age ≤35 weeks. Vinekar, et al in 2007[20] suggested that the scenario in developing countries is quite different. Larger and gestationally ‘older’ infants are more likely to develop ROP compared to their counterparts in Western countries. Hence, the application of Western screening guidelines for developing countries has been questioned by Jalali, et al. in 2003[21]. As a higher cutoff limit, they recommended screening babies born at <37weeks gestation and/or birth weight <2000g in the presence of a high sickness score, in order to prevent missing any infant with threshold ROP. Based on these studies present criteria of ROP screening was recommended by NNF in 2011.Goble, et al. from England [22] felt that they were screening too many babies for ROP and recommended that babies with birth weight above 1250g should not be screened. In present study, we would have missed 29 cases of ROP needing laser or intravitreal bevacizumab if we had used <1500 as
criteria, as per American Academy of Pediatrics (AAP) updated recommendations [16].

Many risk factors have been reported to predispose to the development of ROP. Oxygen therapy, anemia, packed cell volume transfusion [9], septicemia, anemia and clinical sepsis [10,11] are important risk factors [17, 20, 24, 25]. In present study, oxygen administration, septicemia, hyperbilirubinemia, CPAP and anemia were found to be significant risk factors. Vinekar, et al. [20] also found that septicemia was a significant risk factor. Aggarwal, et al. [17] found anemia, clinical sepsis and male sex to be significant risk factors [7,8].

Of the 690 eligible preterm babies, 42 did not come for screening even for the first time. Of the remaining 72 did not come for follow up in spite of repeated reminders, and many of these babies had incompletely vascularized retina. There is a possibility that these neonates might develop ROP in case normal complete retinal vascularization did not take place.

**CONCLUSION**

NNF guidelines are appropriate for screening of ROP in developing countries unlike western world. In the present study 8 preterm babies with birth weight 1750 to 2000 grams and 21 preterm babies with birth weight 1500-2000 developed ROP.

Higher duration of NICU stay, sepsis, hyperbilirubinemia, anemia were some of the risk factors for ROP in the present study.

In the present study all babies who received oxygen for > 7days had ROP whereas all preterm babies who were not given oxygen did not develop ROP. Hence oxygen should be used as a drug only for minimal possible duration, with least possible FiO2.

Due to repeated blood samplings these tiny babies are more likely to become anemic requiring blood transfusion. So, it is important to limit the blood investigations as and when required only, which in turn decreases risk of ROP.

As of now ROP screening is included in the RBSK. Screening rates are increasing all over the country. So, measures to decrease the incidence of ROP now take prime importance. In the present study dropout rate for follow up screening of ROP was 19%. This shows the need to emphasize on the parent counseling periodically during hospital stay for regular follow ups till complete vascularization of retina. Predesigned software that can remind the parents and local ANM/ASHA workers regarding ROP screening similar to POSHAN scheme and immunize India may decrease the dropouts.

**ACKNOWLEDGMENT**

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