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Original Research Article

SCRUTINIZING THE CURRENT RISK FACTORS OF RETINOPATHY OF PREMATURITY IN NEWBORN BABIES

Dr. Priya Singh[1] (PG Resident), Dr. V. Bhaisare[2] (Prof.) & Dr. S. Arya[3] (Prof.)

Dept. of Ophthalmology, M.G.M. Medical College & M.Y. Hospital, Indore (M.P.)[1,2&3]

Corresponding Author: Dr. Priya Singh

Abstract

Background & Methods: To find the trend of current risk factors of retinopathy of prematurity in newborn babies, so that preventive and curative measures can be undertaken to avert the progression of complications, leading to blindness.

This is an observational study which included 70 newborn babies who are sick or preterm admitted at NICU, SNCU, and presenting to our tertiary eye care center for the duration of 2 months. All the premature babies with risk factors of ROP or diagnosed for the same, whose guardians gave consent for the examination was included in this study. Babies with gestation less than 28 weeks or birth weight less than 1200 grams were screened by 2-3 weeks' time and with gestation 28-34 weeks or birth weight less than 2000 grams were screened not later than 4 weeks, according to NFF guidelines. Instrument used was indirect ophthalmoscope with 20D lens for examination of fundus on every visit with pediatric eye speculum, mydriatic eye drops. Findings of the examination were recorded on a ROP chart noting the stages. The ROP chart contained patient's name, gender, gestational age, birth weight and other risk factors such as prolonged oxygen exposure, IUGR, respiratory distress, twins, sepsis, anemia, blood transfusion, phototherapy, ABO in compatibility and with unstable clinical course .

Results: 70 newborn babies were screened for ROP and the incidence of ROP in this study was 28.5%. The mean birth weight of the ROP babies was 1356 gm, and the mean gestational age of the ROP was 31 weeks. On multivariate analysis, risk factors predisposing to ROP ($P<0.05$) were Sepsis, long term oxygen exposure, respiratory distress syndrome, multiple births and IUGR.

Conclusion: The babies with premature birth, low birth weight proved to be with most common risk but sepsis being the immerging trend currently along with long term oxygen exposure, RDS, IUGR thus should be monitored early with meticulous care to curb the progression of blindness. Also the occurrence of ROP is trending towards a rise including newborns with higher birth weight and gestational age in developing countries; hence necessitating to use different guideline for Screening of Newborns in these developing countries.

Keywords: Risk factors, low birth weight, blindness, retinopathy of prematurity.

Study Design: Observational Study.

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1. Introduction

Retinopathy of Prematurity is a neovascularising disease of premature retina that in it's most severe form can lead to retinal detachment and subsequent blindness. ROP is a multifactorial vasoproliferative disorder of retina, that increases in incidence with decreasing gestational age and birth weight[1]. Approximately 65% of infants with a birth weight of <1250 gm, and 80% of infants with a birth weight <1000 gm, will develop some degree of ROP.

Beginning at 16 weeks, retinal angiogenesis normally proceeds from the optic disc to periphery reaching the outer rim of the retina nasally at about 36 weeks and extending temporally by approximately 40 weeks20.

Injury to this process may result in pathological changes in the growing retina. Initially it causes cessation of vasculogenesis followed by abrupt termination of vessels marked by a thin line in the retina which then grows into an ridge made up of mesenchymal and endothelial cells[3].

Sometimes, abnormal proliferation of vessels out of the plane of the retina, into the vitreous and over the surface of the retina may occur[4]. Then it is followed by cicatrization and traction on the retina may occur and which can lead to retinal detachment, thus leading to blindness.

Over one-fourth of the world's blind children live in India. Childhood blindness in India accounts for a serious health problem. Over 22% of childhood blindness in India is attributable to Retinal aetiologias and "Retinopathy of Prematurity - ROP" is the commonest, and more preventable of these causes. In fact the WHO now suggests that India and other middle-income countries are suffering from the 'third epidemic' of this disease.

The Major risk factors associated with ROP are prematurity, LBW, oxygenation, respiratory distress, apnea, bradycardia, heart Disease infection, hypercarbia, acidosis, anemia and the need for transfusion. Generally, the lower the gestational age, the lower the birth weight, and the sicker the infant are, the greater the risk is for ROP[5].

Earlier studies had been done mostly on babies <1500 grams and <32 weeks. So, present study has been taken to find the incidence of ROP in babies >1500 grams and >32 weeks.

METHODS

Aim & Objective

1. To identify the current risk factors of Retinopathy of prematurity in new born babies at our tertiary care centre.
2. To analyse the incidence of babies with increasing birth weight and gestational age presenting with risk factors.

2. Material and Methods

Study population

Present Study was conducted at Mahatma Gandhi Memorial Medical College, Indore (MP) from December 2022 to January 2023 and 20 neonates who fulfilled the inclusion criteria were screened for the presence of ROP after the approval from the Ethics committee and scientific committee.

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Neonates, infants admitted at NICU, SNCU, referred from periphery and other centers to the outpatient department in dept. of ophthalmology at MGMMC AND MYH, Indore. Sick preterm baby treated for respiratory distress syndrome/pneumonitis by supplementary oxygen will be screened.Other co-morbid conditions such as neonatal hyper bilirubinemia treated by phototherapy or multiple blood transfusions will be included in the study.

Inclusion Criteria:

• Birth weight less than 2000 grams
• Gestational age less than 34 weeks
• Gestational age between 34 to 36 weeks but with
risk factors such as:
Cardio-respiratory support, Prolonged oxygen therapy, Respiratory distress syndrome, Chronic lung disease, Fetal haemorrhage, Blood transfusion, Neonatal sepsis, Exchange transfusion, Intraventricular haemorrhage, Apnea.

Exclusion criteria

• Babies born at >34 weeks of gestational age and
>2000 grams without risk factors.
• Patients/Guardians who will not give consent for the study

STUDY PROCEDURE

The neonates were followed up at 4 weeks of birth for first screening or if <28 week or <1200 grams then at 3 weeks after delivery. The study population was screened for ROP with Indirect Ophthalamoscope after dilatation with Tropicamide plus Phenylephrine eye-drops
After that follow up examination of those neonates done at interval of 2 to 3 weeks based upon retinal findings. Screening was continued regularly until retina was completely vascularized, ROP was fully regressed, there are no signs of risk for visual loss and ROP was progressed to a level of severity where treatment is indicated.

- Anterior segment examination for any anomaly like tunica vasculosalentis remnants of hyaloid artery, congenital cataract and corneal opacity.
- Systemic examination: Associated systemic disease.
- Associated risk factor for development of ROP
- Appropriate statistical test would be applied wherever applicable. Pearson's chi-square test was used to check association between qualitative variables.

3. Result

In present study 70 newborn babies were screened for ROP who fulfilled the screening criteria. Out of 70 babies, 16 cases were positive for retinopathy of prematurity. Hence incidence of ROP in this study babies is 28.5%. Out of total 70 cases, 39 were males and 31 were females. From 39 males, 10(25.6%) have ROP and from 31 females, 6 (19.35%) have ROP.
The mean birth weight of the ROP babies was 1356 gms, And the mean gestational age of the ROP babies was 31 weeks.

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Out of 16 cases of ROP, 8 (50%) babies were in stage 1, 7 (43.75%) babies were in stage 2 and 1 (6.25%) baby was in stage 3 ROP. Thus stage 1 was most common out of all stages. No pre plus, plus or APROP cases were noted.
While in zone wise distribution, out of 16 cases of ROP, 4 cases(25%) were in zone 1, 7 cases (43.75%) were in zone 2 and 5 cases (31.25%) were in zone 3. Thus maximum incidence was in zone 2.

From 39 males, 10 (62.5%) were have ROP and from 31 females, 06 (37.5%) were have ROP. There was no statistically significant association between males and females for occurrence of ROP. (P value 0.620882)

Table No. 1: GENDER DISTRIBUTION

PRETERM NEONATES SCREENED	70
DIAGNOSED CASES OF ROP	16

Table No. 2: GENDER DISTRIBUTION

	PRETERM NEONATES SCREENED	**ROP NO OF INFANTS WITH ROP**	**n/N ('n' : No of infants diagnosed as ROP in particular sex category. 'N': Total no of diagnosed ROP)**
MALES	39	10	62.5%
FEMALES	31	06	37.5%

The chi-square statistic is 0.2446. The *p*-value is .620882. The result is *not* significant at $p < .05$.

TABLE 3: COMPARISON OF RISK FACTORS IN PRETERM ROP

Risk factor	**Number of newborn and infants with respective risk factors (N)**	**Number of newborn and infants with risk factors who develop ROP(n)**	**Percentage (n/N)**
O2 exposure	25	8	32%
IUGR	21	4	19.04%
Low birth weight	70	16	22.85%
RDS	24	5	20%

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twins	10	2	20%
Fungal sepsis	17	5	29.41%
Anaemia	16	3	18.75%
Blood transfusion	5	1	20%
phototherapy	11	2	18%
ABO incompatibility	4	1	25%

The chi-square statistic is 120.4991. The *p*-value is < 0.00001. The result is significant at $p < .05$.

Oxygen exposure duration	ROP cases	**%**
</=3 days	3	37.5%
>3 days	5	62.5%

TABLE 4: RELATION OF ROP TO GESTATIONAL AGE

GESTATIONAL AGE	**NEWBORNS SCREENED**		**DIAGNOSED CASES OF ROP**	**DIAGNOSED CASES OF ROP**
		NO OF ROP	INCIDENCE OF ROP	% OF TOTAL NEONATES DIAGNOSED ROP
<28 weeks	2	1	50%	6.25%
28-34 WEEKS	65	15	23.07%	93.75%

TABLE 5: RELATION OF STAGES OF ROP TO GESTATIONAL AGE

	Diagnosed ROP	**Occurrence of ROP(n/N)**
Stage 1	08	50%
stage2	07	43.75%
stage3	01	6.25%
stage4	00	-
stage5	0	-
Plus disease	00	-
total	16	

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The chi-square statistic is 8.8759. The *p*-value is .00289. The result is significant at $p < .05$.

TABLE 6: RELATION OF ROP TO BIRTH WEIGHT

Birth weight (kgs)	High risk (preterm) Newborn screened	Diagnosed ROP: No of ROP	Incidence of ROP in percentage	% of total newborn in the respective B.W. category developing ROP
<1 KG	04	02	50%	12.5%
1-1.4 KG	54	12	22.22%	75%
1.5-2 KG	12	02	16.66%	12.5%
TOTAL	70	16		

The chi-square statistic is 2.8429. The *p*-value is .416483. The result is *not* significant at $p < .05$.

TABLE 7: RATE OF SPONTANEOUS REGRESSION OF ROP
'n' DIAGNOSED ROP IN PARTICULAR STAGE 'N' TOTAL NO OF ROP DIAGNOSED

Stages of ROP	No of diagnosed ROP	No of infants in Regression	Percentage of regression n/N
Stage 1	08	07	**43.75%**
Stage 2	07	05	**31.25%**
Stage 3	01	-	**-**
Stage 4	00		
Stage 5	00		
Plus disease	00		

The chi-square statistic is 0.5303. The *p*-value is .466479. The result is *not* significant at $p < .05$.

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TABLE 8: TREATMENT MODALITIES OF ROP

Treatment modality	No of babies with ROP underwent treatment		% (N/N)
Follow-up	12		75%
Laser Indirect ophthalmoscope for Laser application	-		
Intravitreal anti-VEGF	04		25%
Vitroretinal surgery	-		

4. Discussion

The proportion of blindness as a result of ROP varies greatly among countries and is influenced by both the level of neonatal care and the availability of effective screening and treatment programs [6]. A global perspective of the epidemiological studies of ROP showed that ROP has exhibited three epidemics [7]. The "first epidemic" occurred in the 1940s and 1950s and principally affected premature infants in the USA and Western Europe. At that time unmonitored supplemental oxygen was the principal risk factor. The "second epidemic" began in the 1970s, as a result of the increased survival rates of extremely premature infants in industrialized countries. The low birth weight and low gestational age of infants are risk factors for The "third epidemic" of ROP began in the 2000s due to the increased survival rates of premature infants in middle income countries [8].

In recent Indian studies also there has been a trend to include neonates with higher gestational age and birth weight. A study done by Charan R et al had screened all babies <1700 gm for ROP. Le c et al, retrospectively analysed data of 2910 infants admitted to the NICU between March 2008 and December 2013 and include neonates with ≤1750 g of birth weight. A study carried out at Safdarjung Hospital by Kapoor et al, all babies of <1800 grams were screened irrespective of their gestational age[10]. The present study was an attempt to find incidence for ROP by newer guidelines from Government of India, published under the Rashtriya Bal Swasthya Karyakram (RBSK) which include screening of all newborns <2 kg and in present study it had shown the significant incidence of ROP in >1.5 kg newborns.

In present study incidence of ROP was 28.5% which was similar like in Goyal A et al, (25.4%). In other studies high incidence of ROP were noted, they were Charan R et al (47.2%), Gopal L et al (38%), Rekha S et al (46%), Aggarwal R et al, (32%), Hungi B et al, (41.5%), Padhi TR et al (33.2%) and Maini B et al, (44.6%). High incidence in this studies can be attributed to low sample size and mainly inclusion of <1500 grams and <34 weeks babies. Birth weight usually correlates with maturity of the newborn[11]. Hence in most of the previous studied, incidence of ROP was highest in babies weighing <1500 grams.

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However recent studies show a slightly different pattern. Vinekar et al, suggested that the scenario in developing countries is quite different. Larger and gestational old'infants are more likely to develop ROP compared to their counterparts in Western countries.

Hence, the application of Western screening guidelines for developing countries had been questioned by Jalali et al. Mean birth weight (1356 gms) in present study was higher than mean birth weight of other studies like 1285 grams in Charan R et al, 1355 grams in Gopal L et al, 1282 grams in Aggarwal R et al, 1113 grams in Kumar P et al and 1315 grams in Padhi TR et al. Most of these study screened neonates by following AAP screening guidelines (<1500 grams) or NNF screening guidelines (<1750 grams).8 By following AAP screening guidelines in present study, 2 ROP cases could be missed and by following NNF screening guidelines 1 ROP case could be missed[12].

Hence present study shows that ROP has been reported in larger babies with a birth weight between 1500 to 2000 grams, and mean birth weight of ROP positive cases was increased which was also seen in study of Hungi B et al, Padhi TR et al and Shah PK et al.10,11,15 Prematurity is single most important risk factor for ROP. Both the incidence and severity of ROP are inversely related to gestational age. Mean gestational age (31 weeks) in present study was higher than mean gestational age of other studies like, 30.3 weeks in Aggarwal R et al, 29 weeks in Kumar P et al, 30.7 weeks in Padhi TR et al.

In present study, stage 1 was more common out of all stages. Similar results like in present study were seen in Rekha S et al, Chaudhari S et al and Le c et al. While stage 2 was more common in Charan R et al and Goyal A et al. Stage IV and V were absent in present study as well as in recent studies. Due to increased awareness of ROP screening and early screening of ROP, end stage of ROP were in decreasing trend. Over the years, the causal link between ROP, supplemental oxygen and its duration has been confirmed by various controlled trials and clinical studies[14]. However, a safe level of oxygen usage has not been found. Complete elimination or restriction of oxygen from intensive management of neonate is not feasible. In present study result shows that maximum numbers (62.5%) of ROP cases was in more than 72 hours group and maximum chances (60%) of ROP was in >14 days oxygen supplementation. In multivariate analysis Rekha S et al, Gupta VP et al, Kumar P et al, Chaudhari S et al and Maini B et al, were found similar result that oxygen therapy was a risk factor for ROP occurrence.

Hence the important message would be to do stringent screening of all newborns exposed to oxygen therapy and especially to those who exposed for >72 hours. In present study, Sepsis was found to be a highly significant risk factor ($p<0.001$). It was also found by linear regression that septicemia alone was an independent risk factor in the causation of ROP. Maheshwari R et al, Aggarwal R et al, Gupta VP et al and Chaudhari S et al also found septicemia a significant risk factor in multivariate analysis[15]. Measures to prevent and adequately treat sepsis would go a long way in lowering the incidence of ROP. In our study, Anemia and Blood Transfusion, both were found to be highly significant risk factors ($p<0.001$) for the development of ROP. While on multivariate analysis multiple Blood Transfusions found to be significant independent risk factor. In the study conducted by Maheshwari R et al and Maini B et al blood transfusion emerged as an independent risk factor for severe ROP. Two other Indian studies by Rekha S et al and Chaudhari S et al also

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found blood transfusions as significant risk factor on univariate analysis. Although, the exact role of blood transfusion in ROP is not clear in Indian and western literature, with an apparent trend of more ROP with the association of blood transfusion, the nurseries all over the world are now using blood in a restricted manner. Exposure to blood of adult type, in preterm babies, itself may be causative of ROP in a dose independent manner. In present study, Respiratory Distress Syndrome (RDS) ($p < 0.01$) and phototherapy ($p < 0.001$) both were found to be a highly significant risk factor on univariate and multivariate analysis. Kumar P et al and Kapoor R et al both found Respiratory Distress Syndrome (RDS) as a significant independent risk factor for ROP in multivariate analysis. Multiple birth ($p < 0.012$) was also found as significant independent risk factor on multivariate analysis in present study[16]. The same was also found by Kapoor R et al on multivariate analysis and by Le c et al on univariate analysis. High incidence of prematurity and low birth weight in multiple births may be causative factor for ROP. While other risk factor like Hypoglycemia, Cardiac Defects, Transient Tachypnea Of New Born, Intraventricular Hemorrhage, Shock, Exchange Transfusion, PIH (pregnancy induced hypertension), Anemia In Pregnancy, PROM (Premature Rupture of Membrane) and Assisted Conception were found to have a non-significant causal relation with occurrence of ROP. ($p > 0.05$) In present study, out of 16 ROP cases, 4(25%) cases were required treatment(anti-vegf injections).12 cases regressed on their own.

5. Conclusion

The babies with premature birth, low birth weight proved to be with most common risk but sepsis being the immerging trend currently along with long term oxygen exposure, RDS, IUGR thus should be monitored early with meticulous care to curb the progression of blindness. Early screening is advised in VLBW and ELBW newborns because ROP tends to be asymptomatic in the early stages followed by a fulminant course later in these newborns. Also the occurrence of ROP is trending towards a rise including newborns with higher birth weight and gestational age in developing countries; hence necessitating to use different guideline for Screening of Newborns in these developing countries**.** As Effective screening and timely intervention halted the progression of ROP to end stages.

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