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Original Research Article

Retinopathy of Prematurity: Analysis of Demographic and Clinical Profiles, Incidence, Risk Factors and Treatment Outcome

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Abstract

This is a prospective, unmasked and interventional study. The 207 premature babies were examined for incidence of retinopathy of prematurity (ROP), foetal and maternal risk factors to design an effective screening program for ROP. Further, the efficacy of the modes of treatment were evaluated. Preterm neonates with birth weight ≤ 1500 grams and/or gestation age ≤ 32 weeks; and selected patients with birth weight between 1500 to 2000 grams, or gestational age > 32 weeks but ≤ 35 weeks with unstable clinical course were included in the study. The incidence of any stage of ROP in this study was 21.26%. Majority of patients (84.1%) with ROP developed mild forms of ROP (stage 1 and 2) without plus disease and regressed spontaneous during observation. On univariate analysis, the significant risk factors predisposing to ROP were low gestation age, low birth weight, respiratory distress, unmonitored oxygen supplementation, sepsis, blood transfusion, surfactant use and metabolic acidosis. Maternal risk factor was pregnancy induced hypertension. On multivariate analysis, unmonitored oxygen exposure was the only independent risk factor for ROP. The 15.9% of ROP cases required treatment, and the majority were treated with Diode laser photocoagulation to avascular retina. Intravitreal Bevacizumab was used in 2 cases of AP-ROP in zone 1. Retinopathy in all the five patients regressed.

Key words: Diode laser, Low birth weight, Low gestation age, Oxygen supplementation, Preterm neonate, Respiratory distress, Pregnancy induced hypertension.

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of blindness and marked visual impairment among premature and low birth weight neonates. The rate of blindness caused by ROP varies greatly among countries and different regions within countries, depending on their level of development, standard of neonatal care, neonatal survival rate in preterm infants and whether effective screening and treatment programs exist. That is why; screening guidelines must 'not be generalized' and must take into account 'regional differences'. As screening criteria differ across different ROP units and time-periods, overall incidence of ROP varies from 20% to 52% with more recent studies reporting lower rates of ROP ranging from 20% to 30 % [1-5]. An important lesson is learnt from units reporting incidence of ROP in different time periods. Initial low incidence of ROP rises with better screening protocols, availability of assisted ventilation services and survival of sicker, smaller neonates. In this phase even sick but relatively mature (late preterm) neonates have been reported to develop ROP. This period is followed by gradual decline in incidence of ROP especially of more severe variety [5-7].

Treatment includes Diode/green laser photocoagulation; or cryotherapy, where laser is not available, of avascular retina for ROP at prethreshold stage. Recently, intravitreal injections of anti-VEGF agents were used as a "rescue- therapy " when laser therapy was not possible due to hazy media, and in some cases of aggressive posterior ROP (AP-ROP) in zone I. Vitreoretinal surgery is done in the advanced stages (stage 4 and 5) of ROP with invariably poor visual outcomes. Threrefore, scrrening of ROP and treatment at the prethreshold stage carries the best prognosis [4-7].

Considering so much of diversity in incidence, risk factors and treatment outcomes of this disease, we realised that guidelines and screening programs that take into consideration the characteristics of local populations should be designed. So, we decided to conduct a prospective study in our region, in order to design a better and more efficient screening program and analyse risk factors and efficacy of treatment modalities.

MATERIALS AND METHODS

This prospective, unmasked and inertrventional study was conducted in a Regional Institute of Ophthalmology in northern India among the premature neonates admitted in Neonatal Intensive Care Units (NICU), between May, 2017 to April, 2018. Patients with birth weight ≤ 1500 grams (g) and/or Gestational age ≤ 32 weeks (wk); and selected patients with birth weight between 1500 and 2000 g, or gestational age > 32 wk but ≤ 35 wk with unstable clinical course or neonatologist's concern over exposure to high risk factors, were included in the study. Infants with major congenital malformations, chromosomal anomalies, ocular anomalies and patients who died or lost to follow up were excluded from the study. A detailed history was taken in each case from parents and available records. Standard procedures and precautions described in literature were employed for fundus dilatation, topical anaesthesia and examination. Binocular indirect ophthalmoscopy was done using Alfonso ROP speculum and Pan Retinal lens and scleral indentation using a small muscle hook. Early treatment of retinopathy (ETROP) study recommendations was adhered to whenever treatment was necessary.

For each infant with ROP, the age at which it was first detected, the location (zones), severity (stage), extent of ROP (in clock hours) and exposure to any risk factor were recorded on a prescribe format. The data was entered in to Microsoft excel spread sheet and statistical analysis was performed with SPSS (Staitiscal Package for the Social Sciences) software version 21.0 (SPSS Inc., Chicago, IL). Clinical data were expressed as mean ± standard deviation (SD) and percentage (%). Univariate analysis for putative risk factors was performed. Student's 't' test (two sided) was used to compare normally distributed numerical variables, Mann-Whitney 'U' test for numerically variables with skewed distribution and Pearson's Chi Square test for categorical variables. The difference was considered significant when the p value was < 0.05. Multivariate binary logistical regression analysis was performed to identify independent risk factors of ROP.

RESULTS AND ANALYSIS

The demographical details of the study were as shown in table 1.

Table-1: Demographic details of the study group (n = 207)

Demographic details	
Total number of patients: n (%)	207 (100 %)
Number of males: n (%)	101 (48.79 %)
Number of females: n (%)	106 (51.21 %)
Mean birth weight (g.): mean ± SD	1372 ± 197.69
Mean gestational age (wk.): mean ± SD	31.97 ± 1.67
Singleton: n (%)	168 (81.11 %)
Twins: n (%)	36 (17.39%)
Triplets: n (%)	3 (1.44 %)

In total, 207 surviving preterm neonates who met inclusion criteria were screened. Subjects were divided in two groups.

In group I: ROP was present (44 babies).

In group II: ROP was absent (163 babies).

At the completion of follow-up, 21.26% babies were diagnosed to have developed some stage of ROP in at least one eye on at least one occasion. Thus, the incidence of ROP in the present study was 21.26%.

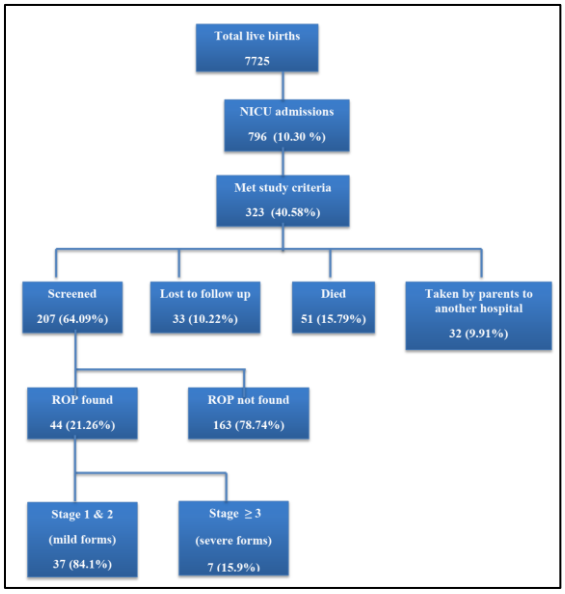

Fig-1: Schematic diagram of demographical and clinical profile of the infants in the present study

Of all the neonates in the present study, 48.8% were males and 51.2% were females. Gender was not found to significantly influence the incidence of ROP in the present study using Pearson's chi square test (p=0.130) as shown in table 2.

Table-2: Sex ratio between the two groups

Sex	ROP-group (I) n (%)	No- ROP group (II) n (%)	Total n (%)	p value
Males	26 (59.09)	75 (46.01)	101 (48.79)	=0.130 NS*
Females	18 (40.91)	88 (53.99)	106 (51.21)	
Total	44 (21.26)	163 (78.74)	207 (100)	

NS*= Not Significant

The mean birth weight (BW) of the entire group was 1372±197.692 g (range: 850-1800 g). The mean BW of group I was 1284.66±197.692 g, and in group II 1396.04±188.237g. This difference was statistically significant (table 3).

Table-3: Birth weight (BW) in the two groups.

BW (g)	ROP-group (I)	No-ROP group (II)	Independent Sample-test (p value)
Mean ± SD	1284.66±209.144	1396.04±188.237	0.001 Sig.*

Sig.*= Significant

The effect of BW on incidence and severity of ROP was as shown in table 4. The maximum number of cases (82.2 %) had mean BW of ≤ 1500 g. Out of these, 41 (24.1%) neonates developed ROP. Of these 41 cases, 87.8% developed mild form of ROP and rest severe form (table 4).

Table-4: Incidence and severity of ROP in relation to BW

BW(g)	No. of infants			Stage of ROP			
	Sub total	With ROP n (%)	Cumulative %	1	2	3	4-5
≤ 1000	7	4 (57.1)	57.10	2	1	1	0
1001-1250	52	18 (34.61)	37.30	6	9	1	2
1251-1500	111	19 (17.11)	22.30	13	5	1	0
>1500	37	3 (8.10)	21.26	2	1	0	0
Total (%)	207	44 (21.25)	21.26	23	16	3	2

The difference in incidence of ROP in neonates of birth weight ≤ 1000 g (Extremly low birth weight: ELBW) and BW≥ 1000 gms was statistically significant (p < 0.038), as shown in table 5.

Table-5: Effect of ELBW on development of ROP

BW(g)	No. of infants		p value
	Subtotal	With ROP (%)	
≤ 1000	7 (3.4)	4 (57.1)	<0.038 Sig.
> 1000	200 (96.6)	40 (20.0)	

Although, 37.3 % of neonates with birth weight of ≤ 1250 g (very low birth weight: VLBW) developed ROP, only 14.9% of neonates with birth weight > 1250 g developed ROP. This was statistically significant (p=0.001), as shown in table 6.

Table-6: Effect of VLBW on development of ROP.

BW (g)	No. of infants		p value
	Subtotal	With ROP (%)	
≤ 1250	59	22 (37.3)	=0.001 Sig.
> 1250	148	22 (14.9)	

The incidence of ROP between neonates with birth weight ≤ 1500 g (LBW) and those with birth weight of >1500 g was also statistically significant (p < 0.001), as depicted in table 7.

Table-7: Effect of LBW on development of ROP in different weight groups.

BW(g)	No. of infants		p value
	Subtotal	With ROP (%)	
≤ 1500	170 (82.1)	41 (24.1)	<0.001 Sig.
> 1500	37 (17.9)	3 (8.1)	

The mean period of gestation of the entire group was 31.971±1.674 wk. In group I, it was 31.095±1.856 wk and in group II it was 32.207±1.545 wk. This difference was statistically significant (p = 0.001), as shown in table 8.

Table-8: Incidence and severity of ROP in relation to GA

GA(wk.)	No. of infants			Stage of ROP				p value
	Sub total	With ROP n (%)	Cumulative %	1	2	3	4-5	
≤ 28	7	5 (71.4)	71.4	1	3	1	1	=0.001 Sig.
29-32	110	30 (27.3)	29.9	17	9	2	1	
>32	90	9 (10.0)	21.3	5	4	0	0	
Total (%)	207	44 (21.25)	21.26	23	16	3	2	

Retinopathy of prematurity was found in 71.4% of neonates with GA of ≤ 28 wk as compared to 19.5% neonates with GA of >28 wk. This difference was statistically significant (p=0.005), as depicted in table 9.

Table-9: Effect of GA on incidence of ROP in different GA groups

GA (wk)	No. of infants		p value
	Subtotal	With ROP (%)	
≤ 28	7 (3.4)	5 (71.4)	= 0.005 Sig.
> 28	200 (99.6)	39 (19.5)	

The incidence of of ROP was higher (29.9%) in neonates with GA of ≤ 32 wk compared to (10%) neonates with a GA>32 wk ((P=0.001), as shown in table 10.

Table-10: Effect of GA on incidence of ROP in different GA groups

GA (wk)	No. of infants		p value
	Subtotal	With ROP (%)	
≤ 32	117 (56.5)	35 (29.9)	=0.001 Sig.
> 32	90 (43.5)	9 (10.0)	

So, the incidence of ROP was found to be inversely correlated with BW and GA. In order to find the effect of BW and GA on severity of ROP, the neonates with ROP were divided into mild forms and severe forms.

The mean BW was 1296±209.461 g for mild forms, and 1196.00±205.743 g for the severe forms. However, when analysed for significance related to BW, this was not statistically significant (p=0.320). The mean GA was 31.31±1.692 wk for mild disease and 29.40±2.408 wk for severe disease. This difference was significant (p = 0.028).

Mean maternal age of the entire group was 24 ± 3.38 years (range 19-35 years). In group I, the mean age was 24.80± 3.695 years (yr), and in group II it was 24 ± 3.303 yr. This difference was statistically insignificant using student's t test (p = 0.952).

Table-11: Maternal age and its effect on development of ROP

Maternal age (yr)	ROP- group (I)	NO-ROP group (II)	P value
Mean ± SD	24.80 ±3.69	24.76 ± 3.30	0.952 NS

Overall, 25 mothers (12.07%) suffered from pregnancy induced hypertension (PIH). Of these, 22.72% mothers in group I and 9.2% in group II had PIH. This difference was significant using Pearson's chi square test (p = 0.015) as shown in table 12.

Table-12: Effect of PIH on development of ROP

PIH	ROP- group (I) n (%)	No- ROP group (II) n (%)	Total n (%)	p value
Absent	34 (77.3)	148 (90.8)	182 (87.9)	=0.015 Sig.
Present	10 (22.7)	15 (9.2)	25 (12.1)	
Total	44	163	207 (100)	

Of 207 babies, 168 were single, 36 twins and 3 triplet. In group I, 25% babies were born out of multiple births (MB), and in group II there were 17.17% such infants. When analysed statistically, presence of multiple births was not a significant risk factor (Table 13).

Table-13: Influence of multiple births on development of ROP

MB	ROP- group (I) n (%)	No -ROP group (II) n (%)	Total n (%)	p value
Absent	33 (75)	135 (82.8)	168 (81.2)	>0.391 NS
Present	11 (25)	28 (17.2)	39 (18.8)	
Total	44	163	207 (100)	

Overall, 12.07% mothers suffered from antepartum haemorrhage (APH). Of these, 15.90% mothers in group I and 11% in group II suffered from APH. This was not significant using chi square test (p=0.379) as shown in table 14.

Table-14: Effect of antepartum haemorrhage (APH) on development of ROP

APH	ROP- group (I) n (%)	No -ROP group (II) n (%)	Total n (%)	p value
Absent	37 (84.1)	145 (89.0)	182 (87.9)	p=0.379 NS
Present	7 (15.9)	18 (11.0))	25 (12.1)	
Total	44	163	207 (100)	

In the present study, none of the mother suffered from daibetes mellitus and no mother gave history of substance abuse or smoking during antenatal period or pregnancy.

Mean APGAR score in group I and II were as shown in table 15. The difference in the two groups was statistically significant using Mann-Whitney 'U' test (table 15).

Table-15: APGAR score at I and 5 minutes and its effect on development of ROP

APGAR score	ROP- group (I) (mean ± SD) (out of 10)	No- ROP group (II) (mean ± SD) (out of 10)	p value
1 minute	5.34 ± 1.010	5.77 ± 1.022	0.003 Sig.
5 minute	7.23 ± 0.886	7.67 ± 0.832	0.001 Sig.

The mean duration of oxygen exposure in the present study was 8.73 ± 5.869 days (range: 0-28 days). In group I, it was 13.89 ± 6.127 days and in group II 7.34 ± 4.967 days. This difference was highly significant (p < 0.001).

Table-16: Comparison of duration of oxygen exposure in the two groups

Duration of Oxygen exposure	ROP -group (I)	No- ROP group (II)	P value
Days (mean ± SD)	13.89 ± 6.13	7.34 ± 4.97	< 0.001

The mean duration of oxygen exposure was 13.46 ± 5.817 days for mild forms of ROP and 17.20 ± 8.167 dyas for severe forms. However, when analysed this difference was not statistically significant (p = 0.203) as shown in table 17.

Table-17: Relationship of duration of oxygen exposure to severity of ROP

Severity of ROP (Stage)	Duration of oxygen exposure Days (mean ± SD)	p value
1 & 2 (mild forms)	13.46 ± 5.82	=0.203 NS
3 & above (severe forms)	17.20 ± 8.17	

NS= Not Significant

Overall, 135 babies (65.21%) developed respiratory distress syndrome (RDS). Of these, 84.09% infants developed ROP and 60.12% did not. This difference was significant (Pearson's chi square test: p = 0.003) as depicted in table 18.

Table-18: Effect of respiratory distress syndrome (RDS) on development of ROP

RDS	ROP- group (I) n (%)	No -ROP group (II) n (%)	Total n (%)	P value
Absent	7 (15.9)	65 (39.9)	72 (34.8)	=0.003 Sig.
Present	37 (84.1)	98 (60.1)	135 (65.2)	
Total	44	163	207 (100)	

Seveny six babies (36.71%) needed surfactant in the present study. The 52.27% neonates in group I needed surfactant as compared 32.52% in group II. This difference was significant (p = 0.003) as shown in table 19.

Table-19: Effect of use of surfactant on development of ROP

Surfactant	ROP- group (I) n (%)	No- ROP group (II)n (%)	Total n (%)	p value
Not given	21 (47.7)	110 (67.5)	131 (63.4)	=0.003 Sig.
Given	23 (52.3)	53 (32.5)	76 (46.6)	
Total	44	163	207 (100)	

Overall, 22.22% babies were detected to have sepsis. Of these, 36.36% developed ROP and 18.40% did not. This difference was significant (Pearson's chi square test: p = 0.011) as depicted in table 20.

Table-20: Effect of sepsis (positive on screen / culture) on development of ROP

Sepsis	ROP- group (I) n (%)	No- ROP group (II) n (%)	Total n (%)	p value
Absent	28 (63.6)	133 (81.6)	161 (77.8)	=0.011 Sig.
Present	16 (36.4)	30 (18.4)	46 (22.2)	
Total	44	163	207 (100)	

In total, blood transfusion (BT) was given to 20 babies (9.66%). Of these,18.18% developed ROP and 7.36% did not. This difference was significant using Pearson's chi square test (p = 0.031) as shown in table 21.

Table-21: Effect of blood transfusion on development of ROP

BT	ROP- group (I) n (%)	No-ROP group (II) n (%)	Total n (%)	p value
Not done	36 (81.8)	151 (92.6)	187 (90.3)	=0.031 Sig.
Done	8 (18.2)	12 (7.4)	20 (9.7)	
Total	44	163	207 (100)	

In group one 52.27%, and in group two 22.09% neonates developed metabolic acidosis. This difference was highly significant (p < 0.001) as depicted in table 22.

Table-22: Effect of metabolic acidosis on development of ROP

Metabolic acidosis	ROP- group (I) n (%)	No- ROP group (II) n (%)	Total n (%)	p value
Absent	21 (47.7)	127 (77.9)	148 (71.5)	<0.001 Sig.
Present	23 (52.3)	36 (22.1)	59 (28.5)	
Total	44	163	207 (100)	

The incidence of apnoea in the whole group was 19.80%. In group one 27.3% infants, and in group two 17.8% infants developed apnoea. This difference was not significant (table 23).

Table-23: Incidence of apnoea and its effect on development of ROP

Apnoea	ROP- group (I) n (%)	No-ROP group (II) n (%)	Total n (%)	p value
Absent	32 (72.7)	134 (82.2)	166 (80.2)	>.0.479 NS
Present	12 (27.3)	29 (17.8)	41 (19.8)	
Total	44	163	207 (100)	

The incidence of neonatal seizures in this study was 7.25%. In group one 9.09%, and in group two 6.74% infants had neonatal seizures this difference was not significant (table 24).

Table-24: Effect of neonatal seizures on development of ROP

Seizures	ROP- group (I) n (%)	No-ROP group (II) n (%)	Total n (%)	p value
Absent	40 (90.9)	152 (93.2)	192 (92.7)	>0.678 NS
Present	4 (9.1)	11 (6.8)	15 (7.3)	
Total	44	163	207 (100)	

Overall, 42.03% babies developed neonatal jaundice (NNJ). The 45.45% infants developed ROP and 41.10% did not. This difference was not significant (table 25).

Table-25: Effect of neonatal jaundice (NNJ) on development of ROP

NNJ	ROP- group (I) n (%)	No-ROP group (II) n (%)	Total n (%)	p value
Absent	24 (54.5)	96 (58.9)	120 (58.0)	=0.589 NS
Present	20 (45.5)	67 (41.1)	87 (42.0)	
Total	44	163	207(100)	

Only 1 case of necrotizing enterocolitis was found in the present study. This neonate developed ROP. This was not significant using Pearson's chi square test (p = 0.604).

In the present study, 11 risk factors predisposing to development of ROP were found on univariate analysis (table 26).

Table-26: Significant infantile risk factors on univariate analysis

Risk factor	ROP- group (I)	Non-ROP group (II)	P value
Birth weight (grams)	1284±209.14	1396±188.24	0.001
Period of gestation (weeks)	31.095±1.55	32.21±1.55	<0.001
Pregnancy induced hypertension	22.72 %	6.74 %	0.015
Apgar score at 1 min	5.34±1.01	5.77±1.02	0.003
Apgar score at 5 min	7.23±0.89	7.67±0.83	0.001
Oxygen exposure	13.89±6.13	7.34±4.97	<0.001
Respiratory distress	84.09 %	60.12 %	0.003
Surfactant	52.27 %	32.52 %	0.016
Blood transfusion	18.18 %	7.36 %	0.031
Sepsis	36.36 %	18.40 %	0.011
Metabolic acidosis	52.27 %	22.09 %	<0.001

On analysis, the significant maternal factors predisposing to development of ROP were noted (table 27).

Table-27: Significant maternal risk factors on univariate analysis

Risk factor	Non- ROP group (I)	ROP-group (II)	P value
PIH	9.80%	23.91%	<0.001

We applied stepwise multiple logistic regression analysis on all the risk factors that were significant on univariate analysis. On multivariate analysis only oxygen exposure was found to be independet risk factor for development of ROP (table 28).

Table 28: Independent risk factors after stepwise multiple logistic regression analysis

Variable	Beta	Standard error	Wald	95% confidence interval	P value
Oxygen	-0.206	0.036	33.038	0.759-0.873	0.001

Among the 44 ROP cases, 2 (4.54%) cases of ROP with prominent plus disease in zone I (AP-ROP), and 3 (6.82%) cases of stage 3 prethreshold ROP in zone II, one case (2.27%) each of stage 4a and stage 5 were observed.

Three (6.82%) cases with prethreshold ROP were treated with Diode laser ablation of avascular retina, starting anterior to the ridge upto ora, in confluent manner using laser indirect ophthalmoscope (LIO) under topical anesthesia. The 2 (4.54%) cases of AP-ROP were treated with intravitreal injection of 0.625 mg (0.025 cc) of Bevacizumab (Avastin; Zenentech, South San Francisco, Calif.) once. Regression occurred in all cases.

One case each of stage 4a and stage 5 ROP were referred for vitreoretinal surgery to advanced center, as facities for surgery for these cases was not available in our center.

We observed 37 cases (84.1%) of stage 1 and stage 2 ROP without plus disease occurring in zone II and zone III without any intervention. All of these cases regressed without any treatment during the observation period.

DISCUSSION

Retinopathy of prematurity (ROP) continues to be one of the leading causes of childhood blindness and marked visual impairment among premature and LBW neonates the world over. The incidence and severity of ROP correlates strongly with LBW and low GA. The rate of blindness caused by ROP varies greatly among countries and different regions within countries depending on their level of development, standard of neonatal care, neonatal survival outcomes and whether effective screening and treatment programs exist. That is why; screening guidelines must 'not be generalized' and must take into account 'regional differences'.

The present work comprised of a one year prospective, unmasked and interventional study conducted in a Regional Institute of Ophthalmology in northern India. Of the 207 preterm babies who fulfilled the inclusion criteria, 21.26% babies developed ROP. Thus, the incidence of ROP in the present study was 21.26%. Incidence of ROP in various Indian studies published in chronological order are 38%, 47.2%, 46.0%, 52.0%, 32.0%, 21.7% and 22.3% respectively [1,3-5,8-10]. As screening criteria differ across different ROP units and time-periods, overall incidence of ROP varies from 20% to 52%, with more recent studies reporting lower rates of ROP ranging from 20% to 30 % [1-5]. The incidence of ROP in the present study is similar to that reported in the recent studies.

Of these 44 babies who developed ROP, the various stages observed were stage 1 in 52.3%, stage 2 in 36.4%, stage 3 with plus disease (prethreshold disease) in 13.62%, stage 4a and stage 5 in 2.27% cases each. The aggressive posterior ROP (AP-ROP) was seen in 4.54% cases. Thus, the maximum number of ROP patients (88.7%) were having mild forms (stage 1 and 2) of the disease

The mother's age did not significantly influence the incidence of ROP. No study in the availalable literature was found in this regard. Similarly, gender also did not significantly influence the incidence of ROP in the present study. Previously, male gender has been noted to be a risk factor by Darlow *et al*. [11]. Yang et al. reported male gender and non-black race to be predictors for ROP. In their study, this bias towards male gender could not be expalineed [12].

The mean BW in babies developing ROP was 1285 gms and it was 1396 gms in those in which ROP was not observed. This difference was statistically significant. The incidence of ROP in neonates with BW $\leq$ 1000 gm was significantly higher than in those with BW > 1000 gms. Further, the incidence of ROP in baies with mean BW $\leq$ 1250 gm. was singnificantly higher than in those with BW > 1250 gm. Similarly, the rate of ROP in neonates with BW $\leq$ 1500 gs was significantly higher than in those with BW > 1500 gm.The mean BW in neonates with severe form of ROP was lower than in those with mild form of ROP, but this differnce was not significant statistically. This compares favorably with other studies [7,12].

Mean period of gestation of 31.1 weeks in ROP group was found to be significantly lower than in those who did not develop ROP (32.2 weeks). The GA in those with severe forms of ROP was significantly lower than in those with mild forms of ROP. Incidence of ROP in babies with GA of $\leq$ 28weaks was significantly higher than in those with GA of > 28 weeks. Further, the rate of ROP in babies with GA of $\leq$ 32 weaks was significantly higher than in those with GA of > 32 weeks.

Several studies have found that LBW and short GA were the most significant factors for development and progression of ROP [7, 9]. Gilbert *et al*. in their recent study have shown that mean BW of infants with severe forms of ROP in highly developed countries was

< 800 gm and mean GA < 26 weeks; whereas, in moderately developed countries thes values were > 1000 gms and > 26.3-33.5 weeks respectively [13]. Accordingly, the mean BW and mean GA in severe forms of ROP in our study were comparable to results of moderately or poorly developed countries.

Recently, Yanovitch *et al*. suggested that BW > 1500 gms and presence of ≥ 2 risk factors could be used as a screening score and the benefit would be $ 587.75 per infant screened [7].

Our incidence of 14.9% in babies with birth weight >1250 gm is greater than a report from USA, in which Yanovitch *et al*. found an incidence of 4.2% in babies weighing between 1250 – 1800 grams [7]. Keith *et al*. [14] found an incidence of 6.40% of ROP in babies in BW group 1250-1499, which is lower than 14.90% found in the present study. The incidence of severe ROP was 0.8% in the 'heavy' cohort, this corroborates with our finidng of 0.9%.

Our study has revealed 11 significant risk factors on univariate analysis that portend the development of ROP in preterm babies in our region. These include LBW, low GA, PIH, low APGAR score, longer duration of oxygen exposure, respiratory distress, and use of surfactant, sepsis, blood transfusion and metabolic acidosis. This is comparable to other studies [2, 8, 10].

When these significant risk factors were analysed using multivariate logistic regression, it was found that oxygen exposure was the only independent risk factor in the present study. This analysis confirmed that oxygen therapy using mechanical ventilation, controlle positive assisted pressure (CPAP) ventilation and free flow oxygen therapy was an independent risk factor in our study. This is a well-established risk factor in the development of ROP including severe ROP in VLBW and LBW babies [8, 15].

The relationship between blood transfusion and increased incidence of ROP was reported previously [2, 7, 9, 11]. Our study found it to be a significant risk factor, though not independent, for the development of ROP. Sepsis has been found to be a significant risk factor in a study by other investigator [2] as in our study.

Respiratory distress syndrome (RDS) was noted to be a significant risk factor in our study. Prenatal treatment treatment with haloginated corticosteroids and/or post natal surfactant therapy, oxygen supplimentation are still the mainstay of prevention and treatment of RDS [16].

In the present study, use of surfactant for treatment of RDS showed a significant increase of ROP incidence. One study showed no significant association between prophylactic surfactant therapy and incidence of ROP [17], other study reported that use of surfactant increaesd the risk of developing ROP [18].

The maternal PIH was found to be a significant risk factor in the present study. We did not found any other maternal disease in our study. Purohit *et al*. in his study on babies weighing > 1500 gms found that toxemia in pregnancy was a risk factor [19]. In the same study and other studies, other maternal factors were also found to be significant [19-21]. Similarly, in a cohort of VLBW babies Shah *et al*. Found preeclampsia and prenatal betamethasone to be significant risk factors on univariate anlysis [22]. Maternal PIH and toxemia has been known to cause placental infarcts and compromised fetal blood flow, hence compromising fetal nutrition and growth and resulting in intrauterine growth retardation (IUGR). Weather, PIH is a surrogate risk factor for prematurity and low birth weight or an independent risk factor causing ROP requires further studies.

The significant risk factors found on univariate analysis were compared with other studies (table 28).

Table-28: Significant risk factors on univariate analysis: Comparative analysis with other studies

STUDY	SIGNIFICANT RISK FACTORS	COMMON WITH PRESENT STUDY
Maheshwari [2]	Blood transfusion, Sepsis	Blood transfusion, Sepsis
Yanovitch [7]	Sepsis, Antibiotic, Ventilation, Blood transfusion	Sepsis, Blood transfusion
Rekha [9]	Anaemia, Blood transfusion Apnoea	Blood transfusion
Darlow [11]	Male gender, IUGR	None
Yang [12]	Male gender, Non-black	None
Fang PC [15]	Oxygen, Blood transfusion	Oxygen, Blood transfusion
Purohit [19]	Apnoea, BDP, Sepsis	Sepsis
Charles [23]	IVH, RDS, Sepsis, Hispanic	RDS, Sepsis
Jandeck [24]	GA, Blood loss, Acidosis, Asphyxia	GA, Acidosis, Asphyxia

The significant maternal risk factors found on univariate analysis were compared with other studies published in the literature (table 29).

Table-29: Significant maternal risk factors on univariate analysis: Comparative analysis with other studies

STUDY	SIGNIFICANT RISK FACTORS	COMMON WITH PRESENT STUDY
Purohit [19]	Diabetes, PIH, Antihistamine	PIH
Shah [22]	PIH, Betamethasone	PIH

The number of ROP patients requiring treatment in the present study was 15.9%. The BW of neonates requiring treatment in the present study were 800, 1250, 1500 gm in babies with prethreshold disease, 680 and 800 gm in infants of AP-ROP, 1080 gm in stage 4a and 1200 gms. In stage 5 ROP. A recent study in India with similar screening criteria and similar overall incidence (22.3%) found that 33.6 % babies with ROP required treatment [5]. This was greater than that found in our study. This difference may be explained by better NICU facilities and screening startegy in our institute.

Though the incidence of ROP is significantly greater in BW < 1500 gms, but the fact that 8.1% of high risk babies weighing >1500 grams have ROP cannot be ignored. So, the need of the hour is to establish 'sickness criteria' so that those with significant risk factors in the heavy cohort are also screened.

Our study had some limitations. First, the sample size is small. Second, our final study population was 60% of of all neonates intended for study. The loss of cases due to death, transfer to other hospitals, lost to follow-up and incomplete chart retrieval was unavoidable. And the high ratio of excluded group may affect the results of the analysis. Third, this study was a single centric study, and the data provided may not be representive of other regions in our country. Therfore, the multicentric trials with larger sample size and longer duration may be helpful for generalising the results of the present study.

CONCLUSION

Incidence of ROP in the present study was 21.26%, and the incidece of ROP was inversely correlated with low birth weight and gestation age. The mean BW in neonates with severe form of ROP was lower than in those with mild form of ROP, but this differnce was not significant statistically. The mean period of gestation in ROP group was found to be significantly lower than in those in who did not develop ROP. The GA in those with severe forms of ROP was significantly lower than in those with mild forms of ROP.

Regarding risk factors: LBW, short GA, low APGAR score, longer duration of unmonitored oxygen supplimentation, presence of RDS, use of surfsctant, need for blood transfusion, presence of sepsis and metabolic acidosis had significant effect on development of ROP on univariate analysis. But on multivariate analysis, using stepwise multiple logistic regressions, only oxygen exposure was found to be an independent risk factor.

The 15.9% cases of ROP needed treatment. The 6.8% cases with prethreshold ROP were treated with Diode laser ablation of avascular retina, and 4.5% of AP-ROP was treated with intravitreal injection of Bevacizumab. Regression occurred in all cases. One case each of stage 4a ROP and stage 5 ROP were referred for vitreoretinal surgery to advanced center. The rest (84.1) of ROP cases regressed without any intervention during the observation period.

The incidence of 8.1% ROP in high risk babies weighing > 1500 gm is a considerable figure. So, babies with birth weight > 1500 gms, with exposure to high risk factors, should also be screened. The population of infants who develop severe ROP in developed countries differs from those in developing countries. That's why the screening guidelines must 'not be generalized' but should take into account 'regional differences'.

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