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Screening of high risk infants for detection and evaluation of retinopathy of prematurity

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Introduction

Premature birth can be associated with many health risks to newborn infants such as sepsis, hypoxia, jaundice and Retinopathy of prematurity (ROP). Retinopathy of prematurity assumes special importance because if not detected early, the child may become visually handicap. It can often be treated successfully, if it is diagnosed in time. Its prevention requires identification of various risk factors associated with ROP.

ROP is unique in that the vascular disease is found only in infants with an immature incompletely vascularised retina, hence its connection with premature infants. The spectrum of outcome findings in ROP extends from the most minimal sequelae without affecting vision in the mild cases to bilateral irreversible and total blindness in more advanced cases.

Aims and objectives

1. To screen the high risk term and preterm babies for ROP.
2. To find the incidence of ROP based on the data generated in the study.
3. To evaluate the risk factors associated with ROP.

Materials & Methods

Study Design :It is a cross sectional observational epidemiological study. 200 preterm and high-risk term infants were selected by sequential sampling technique. The study was conducted at MY Hospital MGMMC, Indore, Madhya Pradesh, India from May 2012-June 2013.

Inclusion Criteria

- All babies < 1500 gm birth weight (BW)
- All babies < 34 weeks of gestational age (GA)
- All babies >34 weeks of GA and or BW >1500 gms with unstable clinical course or the risk factors mentioned in the table below.[1-3]

Low birth weight	Intraventricular hemorrhage
Oxygen exposure >30 days	Congenital heart disease
Antenatal h/o of steroids/NSAIDS	Hyperbilirubinemia

Phototherapy exposure	Birth trauma
Erythropoietin in high doses	Neonatal asphyxia
Septicemia	Blood transfusion
Lactic acidosis	Intra uterine growth retardation
Respiratory distress syndrome	Antenatal H/O:
Genitourinary infection	Placental insufficiency
Viral infection	Premature rupture of membrane
Multiple pregnancy	

Method

After detailed Antenatal, birth and postnatal infant history, Ocular examination of anterior segment and Posterior segment examination by indirect ophthalmoscopy in full mydriasis was performed, followed by systemic examination and evaluation of other systemic risk factors.

Procedure

- Informed consent of parents were taken
- Preparation for fundus examination:
- The pupil were dilated with Mydriatic drop (tropicamide 1%+ phenylephrine 2.5%) instilled at 10 min interval about 1 hour before the scheduled examination .
- Baby shouldn't be fed immediately before the examination as the child may vomit or aspirate.
- Antenatal & infants history recorded

Fundus examination with indirect ophthalmoscope

- The initial examination for ROP should be done in the nursery in dim illuminated room.
- The neonate is wrapped in a towel so that a single assistant can hold the head steady for examination.
- Apply pediatric eye speculum.
- Posterior segment examination done with indirect ophthalmoscopy with 20D lens.
- Examination of peripheral retina is done with the help of scleral indentor, which in turn stablizes globe.
- All quadrants of retina are examined with gentle head movement.
- Findings are noted in ROP form.
- Topical antibiotic applied
- Stage & severity of ROP was classified according to ICROP.

Precautions

- Avoid excess of phenylephrine.
- Avoid spilling of eye drops.
- Baby shouldn't be fed within 1 hour of examination.
- Periphery of retina should be cautiously examined for the extent of change.
- Globe indentation may give an erroneous impression of plus disease.
- Plus disease should be looked without indentation.

Time of screening[4]

- The initial examination should be at 4-6 weeks postnatal, or between 31 & 33 weeks of gestation.

Follow up schedule[4]

- If retina is immature (retinal vessels not seen up to nasal orra serrata) then baby must be screened every 2 weeks till the retina is mature.
- In eyes with retinal vessels seen only up to the zone 1 at initial visit, weekly evaluation is needed. These eyes can develop rush disease very quickly, and not necessary the classical stages 1-3 before reaching threshold ROP.

- If there are early signs of ROP then the child must be examined every week for any progression or regression of the disease.
- If child develop pre-threshold ROP, then the child should be seen every 3-7 days for progression.
- In case of threshold ROP, urgent peripheral retinal laser/cryo-ablation should be done within 48-72 hours.
- In eyes with ROP stage 4/5, early surgical treatment such as belt buckling / vitreous surgery can help save some vision, though the majority have a dismal prognosis.
- In case of doubt examination should be conducted weekly or bi-weekly, at least till the child is 38-40 weeks.

Follow-up examinations on the basis of retinal findings classified according to the international classification[4]

1-week or less follow-up - Stage 1 or 2 ROP: zone I, Stage 3 ROP: zone II

1- to 2-week follow-up - Immature vascularization: zone I—no ROP, Stage 2 ROP: zone II , Regressing ROP: zone I

2-week follow-up - Stage 1 ROP: zone II, Regressing ROP: zone II

2- to 3-week follow-up- Immature vascularization: zone II—no ROP, Stage 1 or 2 ROP: zone III ROP, Regressing ROP: zone III

The presence of plus disease (defined as dilation and tortuosity of the posterior retinal blood vessels) in zones I or II suggests that peripheral ablation, rather than observation, is appropriate.

ROP–Classification [5]

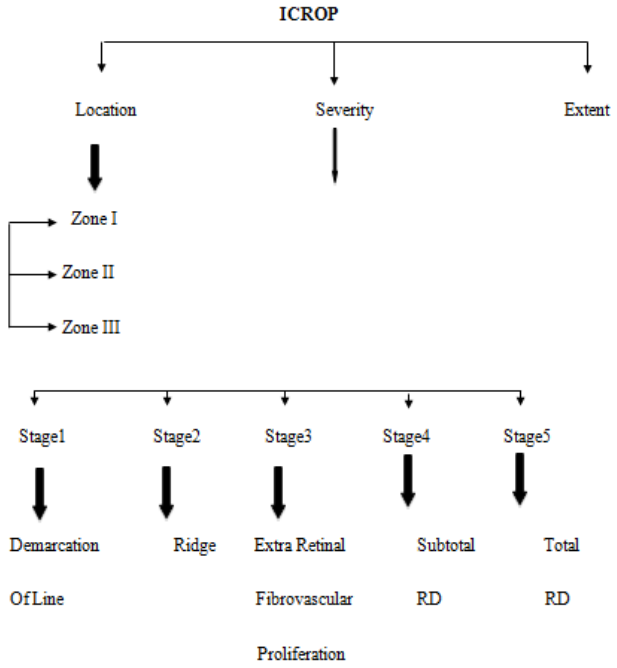


Figure 1: ROP classification on the basis of severity

Stage Description

STAGE I : Demarcation line.

STAGE II : Ridge.

STAGE III: Ridge with extra retinal moderate to severe fibrovascular proliferation.

STAGE IV : Subtotal retinal detachment

a) Macula on b) Macula off

STAGE V : Total retinal detachment

RD Classified On The Basis Of Funnel Configuration

Anterior	**Posterior**
Open	Open
Open	Narrow
Narrow	Open
Narrow	Narrow

The overall status of the eye will have either:

1. Immature 2. Mature 3. ROP

Immature

Signifies that though there is no ROP, yet the vasculature has not matured fully . Immature

vasculature is defined as vessels which are short of 1 DD of the nasal or temporal ora. Thus they could terminate in zones I/II/III and are designated accordingly immature I, II, III. A potential for developing ROP exists till the vessels are still immature. Regular follow-up is required for such neonates till both nasal and temporal ora serrata matures (40-45 weeks).

Mature

Signifies that the vessels have now reached at or within 1 DD of both nasal and temporal ora-serrata. This child does not require further follow-up.

2.

ROP

Presence of ROP is to be recorded meticulously in relation to

a. Zone and stage of ROP in each clock hour
b. Presence or absence of plus disease

Prethreshold ROP

1. Any stage of ROP in zone 1 with plus disease.

2. ROP stage 3 with plus disease with 3 contiguous or 5 interrupted clock hours of involvement of retina in zone 2 but less than threshold.

Threshold Disease

Zone 1 or 2 ROP stage 3 more than 5 contiguous or 8 cumulative clock hours with plus disease.

Plus Disease

When the vascular changes are so enhanced that the posterior pole vessels are dilated & tortuous and disease is labeled as Plus disease.

Rush Disease

Any ROP in Zone 1 with presence of plus disease is termed as Rush disease.

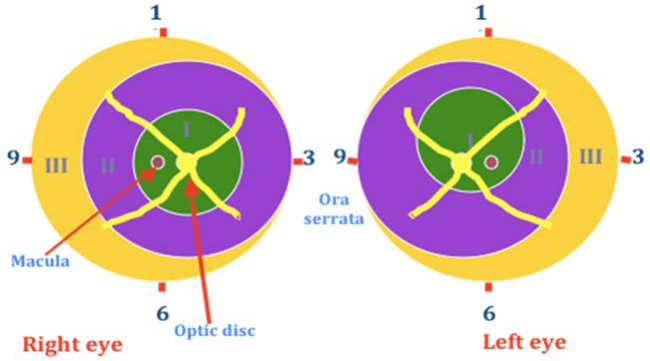


Figure 2: ICROP Zone Scheme for Locating ROP[5]

Observations

Table 1: Incidence of ROP

1	High Risk Infants Screened	200
2	Diagnosed ROP	37
3	Incidence of ROP	18.5%

Table 2 Incidence of ROP In Term And Preterm Infants

Incidence of ROP In Term And Preterm Infants	Total Infants Screened	ROP Developed	Percent
Preterm	161	35	21.74% (33/161)
Term	39	2	5.13% (4/39)
Total	200	37	18.5% (37/200)

Table 3: Sex Wise Distribution of ROP

	High Risk Infants Screened	ROP	
		No. OF ROP	Percentage
Male	101	20	54.05 % (20/37)
Female	99	17	45.94 % (17/37)
Total	200	37	

Table 4: Incidence of ROP In Relation To Gestational Age

Gestational Age	High Risk Infants Screened	Diagnosed ROP	
		NO. OF ROP	Percentage
≤28WEEKS	26	10	26.9 % (10/26)
28-37WEEKS	140	25	20.28 % (25/140)
≥37WEEKS	34	2	5.55% (2/34)
Total	200	37	

Table 5: Incidence In Relation To Birth Weight

Birth Weight(KGMS)	High Risk Infants Screened	Diagnosed ROP		
		NO. OF ROP	%	As fractional percentage of overall incidence
≤ 1	16	8	50%	4%
1 – 1.5	111	20	18.02%	10%
1.5-2	43	6	13.95%	3%
2-2.5	15	0	0	-
≥ 2.5	15	3	20%	1.5%
Total	200	37	100%	18.5 %

Table 6: Stage wise Distribution of Cases of ROP

Stage of ROP	Diagnosed ROP	Percentage
Stage I	13	35.14%
Stage II	20	54.05%
Stage III	4	10.81%1
Stage IV	-	-
Stage V	-	-
Plus disease	-	-
Threshold disease	-	-
Total ROP	37	100%

Table 7: Incidence of Stages of ROP In Relation To Gestational Age

Stages of ROP	Gestational age						Total
	≤ 28 Weeks		28-37 Weeks		≥ 37 Weeks		
	No.	%	No.	%	No.	%	
Stage I	2	20% (2/10)	11	44% (11/25)	-		
Stage II	6	60% (6/10)	12	48% (12/25)	2	100% (2/2)	
Stage III	2	20% (2/10)	2	8% (2/25)	-	-	
Stage IV	-	-	-	-	-	-	
Stage V	-	-	-	-	-	-	
Plus disease	-	-	-	-	-	-	
Prethreshold	-	-	-	-	-	-	
Threshold	-	-	-	-	-	-	
Total	10		25		2		37

Probability of various risk factors being of significance for development of ROP calculated by CHI - SQUARE TESTS is as follows

$$\chi^2 = \Sigma \text{ OBSERVED VALUE} - \Sigma \text{ EXPECTED VALUE} / \Sigma \text{ EXPECTED VALUE}$$

For $\chi^2 \geq 4$, $P<0.5$ which is statistically significant and hence probability of the risk factor being associated with ROP.

Table 8: Probability of Septicemia Being a Significant Risk Factor for Development OF ROP

	ROP +	ROP-	TOTAL	p value
Septicemia +	21	54	75	-
Septicemia -	16	109	125	-
Total	37	163	200	0.0074

The association between rows (septicemia) and columns (ROP) is considered to be statistically significant

Table 9: Probability of gestational age <34 weeks being a significant risk factor for development of ROP

	ROP +	ROP -	TOTAL	p value
Gestational Age < 34 Weeks	31	84	115	-
Gestational Age ≥ 34 Weeks	6	79	85	-
Total	37	163	200	0.0003

The association between rows (gestational age < 34 weeks) and columns (ROP) is considered to be statistically significant.

Table 10: Probability of birth weight < 1.5 kgs being a significant risk factor for development of ROP

Birth Weight (BW)	ROP +	ROP -	TOTAL	p value
BW < 1.5 Kgs	32	95	127	-

BW ≥ 1.5 Kgs	5	68	73	-
TOTAL	37	163	200	0.0013

The association between rows (BW < 1.5 Kgs) and columns (ROP) is considered to be very statistically significant.

Table 11: Probability of prolonged o_2 exposure being a significant risk factor for development of ROP

	ROP +	ROP -	TOTAL	p value
O_2 Exposure +	19	43	62	-
O_2 Exposure -	18	120	138	-
TOTAL	37	163	200	0.003

The association between rows (PROLONGED O_2 EXPOSURE) and columns (ROP) is considered to be very statistically significant.

Note: prolonged O_2 exposure is >15 days of O_2 exposure at >80mm Hg .

Table 12: probability of phototherapy being a significant risk factor for development of ROP

	ROP +	ROP -	TOTAL	p value
H/O Phototherapy +	11	19	30	-
H/O Phototherapy -	26	144	170	-
TOTAL	37	163	200	0.0054

The association between rows (H/O PHOTOTHERAPY) and columns (ROP) is considered to be statistically significant.

Table 13: probability of blood transfusions being a significant risk factor for development of ROP

	ROP +	ROP -	TOTAL	p value
H/O BT +	8	12	20	-
H/O BT -	29	151	180	-
TOTAL	37	163	200	0.009

The association between rows (H/O BT) and columns (ROP) is considered to be very statistically significant.

Table 14: probability of intrauterine growth retardation (IUGR) being a significant risk factor for development of ROP

	ROP +	ROP -	TOTAL	p value
IUGR +	12	27	39	-
IUGR -	25	136	161	-
TOTAL	37	163	200	0.0279

The association between rows (IUGR) and columns (ROP) is considered to be statistically significant.

Table 15: probability of twin delivery being a significant risk factor for development of ROP

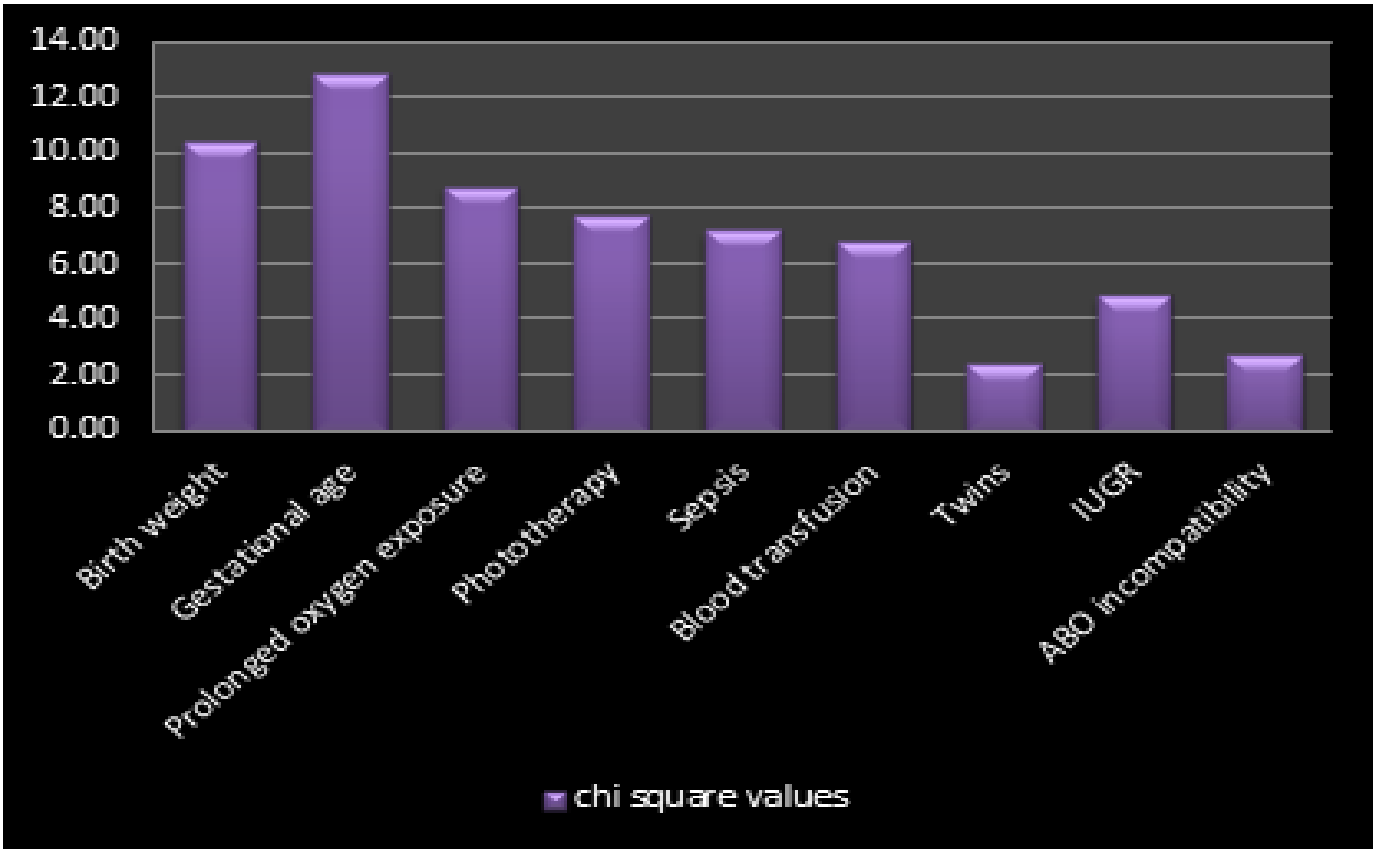
H/O Twins	ROP +	ROP -	Total	P value
+	6	13	19	-
-	31	150	181	-
Total	37	163	200	0.1227

The association between rows (H/O TWIN DELIVERY) and columns (ROP) is considered to be statistically insignificant.

Table 16: Probability of abo incompatibility being a significant risk factor for development of ROP

H/O ABO Incompatibility	ROP +	ROP -	TOTAL	p value
+	2	2	4	-
-	35	161	196	-
TOTAL	37	163	200	0.1012

The association between rows (ABO INCOMPATIBILITY) and columns (ROP) is considered to be statistically insignificant.



<4 – statistically insignificant

≥4 – statistically significant

Figure 3: Relation of ROP with various risk factors

Incidence of ROP in high risk infants

- The incidence of ROP varied according to the screening time & protocol. The incidence of ROP in various studies has been reported to vary from 0.3% to 65%.[6-12]
- ROP in Infants with Birth Weight Above 1500 Grams - Incidence of ROP 19.1%. ROP may occur in newborn infants of larger birth weight but with good prognosis, and oxygen therapy seems to predispose to the disease.[13]

- In our study we found the incidence of ROP was 18.5%. Incidence in preterm was 21.74% & in term was found to be 5.13%.

Sex wise distribution of ROP

- Bradley T Smith and William S Tasman studied 33 patients, of which (70.2%) were females and 14 were males (29.8%), suggesting that females may have had a greater tendency to survive than males . However, this observation was statistically not significant.[14]
- According to screening criteria of our study total 200 high risk term and preterm infants were examined: - 54.05% of diagnosed ROP were males & 45.94% being females.

Incidence in relation to gestational age (GA) and birth weight

- Incidence and severity are inversely proportional to birth weight and gestational age.
- Maximum no. of incidence of ROP with GA <= 31 wks.[15]
- In our study the maximum incidence of ROP was found in GA between ≤28-37 wks i.e 21.08% . 94.6 % of the total children diagnosed ROP belonged to this gestational age group. As per literature babies with lesser G.A at birth had a higher incidence of ROP. Survival rate of babies <28weeks is very low in the setting of developing state, therefore incidence of ROP is more in babies of G.A between 28-37weeks than <28weeks babies.
- The incidence of ROP among Extremely Low Birth Weight (ELBW) babies was 48.9% and 18.2% for Very Low Birth Weight (VLBW) babies. [16]
- In our study we got maximum no. of ROP cases in BW <1 kg (ELBW) was 50 % & 18.02% for children weighing between 1-1.5 kgs(VLBW) which is in accordance with the above mentioned study.
- The incidence of ROP is increasing due to increased survival of low-birth weight babies. This is called second epidemic**.**

Incidence of stages of ROP

- Incidence of ROP according to stage of disease was found to be 5.3 , 4.3 ,9.6 ,1.6 ,7 ,9.1 for stages 1, 2, 3, 4, 5 and plus disease respectively.[17] In another study Incidence of stage 1 was 16.97%, stage 2 was 17.58%, stage 3 was 11.52% and stage 4b was 1.21%.[3]
- In our study percentages of stage 1,2,3 were 6.5% , 10% & 2% respectively.
- In our study maximum incidence was found to be of stage 2 followed by stage 1 that is 10% & 6.5% respectively.

Incidence of stages in relation to G.A:

- Incidence of ROP in G.A < 28wks of Stage I in is 20%, Stage II is 60%, Stage III is 20%. Incidence between 28-37 wks of Stage I in G.A is 44%, Stage II is 48%, Stage III is 8%. Only stage II was found in G.A ≥ 37 weeks

Study of risk factors

- Risk factors for ROP: Oxygen exposure frequent apneic spells, bronchopulmonary dysplasia, sepsis, low Apgar score, intraventricular hemorrhage, exchange transfusion, patent ductus arteriosus, in the neonate were associated with significantly higher rates**.** [18]
- Blood transfusion(OR=9.86, p<0.005), sepsis (OR=11.31, p<0.001) and Hyaline membrane disease (OR=6.23, p<0.05) were determined as retinopathy developing risk factors. Increasing duration of phototherapy(p<0.05) and mean PaO

($p<0.05$) related to increasing the probability of ROP [19]

- In our study, out of 200 cases screened 62 had a history of oxygen therapy, of these 19 (30.64%) developed ROP, 30 had been given phototherapy out of which 11 developed ROP (36.66%), 20 were given blood transfusions & 8 of them developed ROP (40%), 39 infants were IUGR babies and 12 of them developed ROP (30.77%)and out of 75 cases of septicemia, 21 developed ROP (28 %).

  In Preterm Infants and Term Infants Risk Factors Associated (Maximum) were:

  Gestational age , birth weight, O_2 exposure, phototherapy, sepsis, IUGR.

Summary

- The incidence of ROP is increasing due to increased survival of low-birth weight babies. Screening of high risk infants is essential to detect ROP.
- In our study we found the incidence of ROP was 18.5%.
- Incidence ROP in preterm – 21.74% (total sample of preterm 161)& in term – 5.13% (total sample of term 39).
- Most commonly detected stage of ROP is stage II followed by stage I.
- In our study the maximum incidence of ROP (26.9%) was found in gestational age ≤ 28 weeks.
- In our study the maximum incidence of ROP (50%) was found in birth weight <1kgms.
- Risk factors associated with ROP in order of frequency:

  Lower gestational age > Birth weight > Duration of oxygen exposure > Phototherapy > Sepsis > Blood transfusions > Intra uterine growth retardation (IUGR)

Conclusion

Thus we can say that low birth weight and young gestational age are the most important risk factors in the development of ROP, apart from this oxygen therapy for more than 30 days, sepsis, phototherapy, sepsis, blood transfusion and IUGR were also found to be associated with development of ROP. ABO incompatibility and twin gestation are not associated with increased risk of development of ROP. The analysis for incidence and risk factors will be helpful in understanding and prediction of ROP formation in high risk neonates. The timely screening of high risk infants is important to prevent the development of advanced ROP.

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