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**Research Article**

# Screening for retinopathy of prematurity in neonates

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## ABSTRACT

**Background:** Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the retina among preterm infants. Neonates born at less than 32 weeks of gestation are at risk of developing ROP. However preterm infants born at 32 weeks or later can also develop severe ROP if they had turbulent NICU course or required prolonged oxygen therapy. Aims of the study were to determine incidence, risk factors of ROP in neonates and to determine the association of birth weight, gestational age and incidence of ROP.
**Methods:** Prospective analytic study done in indoor patients in neonatal intensive care unit at a tertiary care center from June 2015 to May 2016.
**Results:** Overall incidence of retinopathy of prematurity in preterm neonates is 18.4%. Incidence increases with decreasing gestational age. In preterm <28 weeks of gestational age, incidence of ROP is 35%. Incidence also increases with decreasing birth weight. Incidence of ROP in neonates with birth weight less than 1.25kg is 50%. Risk factors include prematurity, oxygen therapy, septicemia, intraventricular hemorrhage, anemia needing blood transfusion. Most patients of ROP have stage-1 disease (76%). The twenty one cases having ROP underwent laser ablative therapy. Earlier detection by screening leads to early intervention and prevention of blindness.
**Conclusions:** The timely retinal screening of high-risk preterm infants is important to prevent the development of advanced ROP. Since ROP may produce serious sequel up to complete blindness, all efforts must be made to prevent the development of advanced ROP through elimination of preterm births, changes in the neonatal care and improvement in detection of threatening ROP markers.

**Keywords:** Birth weight, Blindness, Prematurity, ROP

## INTRODUCTION

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the retina among preterm infants. Neonates born at less than 32 weeks of gestation are at risk of developing ROP. However preterm infants born at 32 weeks or later can also develop severe ROP if they had turbulent NICU course or required prolonged oxygen therapy.[1]

It has mild to severe spectrum. Recent advances in neonatal care in the last decade, have improved the survival rates for premature infants.[2,3] Consequently, the incidence of ROP has increased in parallel. The most important risk factors which predispose to development of ROP include oxygen therapy, prematurity, anemia needing blood transfusion, sepsis and apnea.[2,3]

Very low birth weight neonates, those born at 32 weeks of gestation a timely screening and treatment of ROP can prevent blindness and minimize visual handicaps. Classification of ROP International Classification of ROP (ICROP) is used for classifying ROP. 15 ICROP describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent, (clock hours) (Figure 1 in Appendix and Table 1).

Aggressive posterior ROP (rush disease):

- A rapidly progressing, severe form of ROP; which if untreated, progresses to stage 5 ROP.
- This may not have classical ridge or extra retinal fibro vascular proliferation.
- Most commonly in Zone I, but may also occur in posterior Zone II.

**Table 1: Classification of ROP (ICROP).**

| | | | |
|---|---|---|---|
| | Zone-1 | Circle with optic nerve at its centre and a radius of twice the distance from optic nerve to macula | |
| Location | Zone-2 | Concentric circle from edge of zone 1 to oraserrata nasally and equator temporally | |
| | Zone-3 | Lateral crescent from zone 2 to oraserrata temporally | |
| Severity | | Stage 1 | Presence of thin white demarcation line separating the vascular from avascular retina |
| | | Stage 2 | The line becomes prominent because of lifting of retina to form a ridge having height and width |
| | | Stage 3 | Presence of extra retinal fibro-vascular proliferation with abnormal vessels and fibrous tissue arising from the ridge and extending into vitreous |
| | | Stage 4 | Partial retinal detachment; not involving macula (4A) or involving macula (4B) |
| | | Stage5 | Complete retinal detachment |
| Plus disease | | | Presence of dilatation and tortuosity of posterior retinal vessels. Associated with vitreous haze, pupillary rigidity |
| Extent | | | Extent of involvement of the retina as expressed as clock hours (30 degree sectors) |
| Pre-plus disease | | | Vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal |

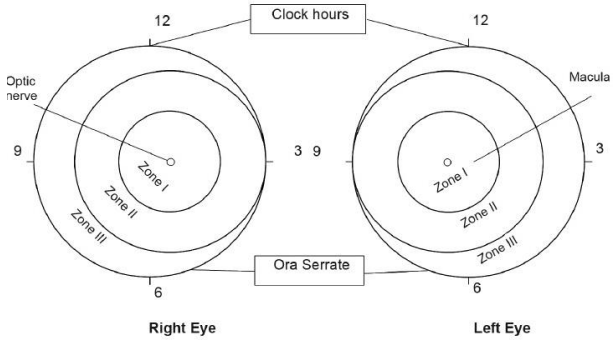


**Figure 1: Aggressive posterior ROP.**

## METHODS

It was a prospective observational study, which was conducted from July 2015 to June 2016. In which 630 preterm newborns born at less than 37 weeks of gestational age admitted in NICU of civil hospital, Ahmedabad, Gujarat, India was taken.

### *Inclusion criteria*

- Birth weight <1.5 kgs.
- Gestational age <or= 34 weeks.
- Birth weight 1.5-2 kg or age 34-37wks of gestational age; if risk factors are present.

a) Prolonged oxygen therapy
b) Respiratory distress syndrome.
c) Sepsis.
d) Multiple blood transfusions.
e) Apneic episodes.
f) Intra ventricular hemorrhage.

**Table 2: Timing of first examination.**

| Gestational age | First screening at |
|---|---|
| >28 weeks | 3-4 weeks of post natal age (not later than 4 weeks) |
| <28 weeks or <1200 grams birth weight | 31 weeks of gestational age |

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings.[5]

### *Procedure*

Pupils are dilated with Phenylephrine 2.5% and Tropicamide 0.5%. Screening of ROP involves indirect

ophthalmoscopy using 20 D or 28/30 D lens by an experienced ophthalmologist. After dilatation of pupils; screening is done using Ret Cam shuttle. Images taken are analyzed by expert ophthalmologist. The degree of ROP (stage, zone extent and presence of plus disease) is determined. Patients are followed up as per requirement for further evaluation. The ones requiring treatment are treated by expert ophthalmologist.

**Table 3: Follow-up examinations recommended by the examining ophthalmologist on the basis of retinal findings.**

| Zone of retinal findings | Stage of retinal findings | Follow up interval |
|---|---|---|
| Zone-1 | Immature vascularisation | 1-2 weeks |
| | Stage 1/2 | 1 week or less |
| | Regressing ROP | 1-2 weeks |
| Zone-2 | Immature vascularisation | 2-3 weeks |
| | Stage 1 | 2 weeks |
| | Stage 2 | 1-2 weeks |
| | Stage 3 | 1 week or less |
| | Regressing ROP | 1-2 weeks |
| Zone-3 | Stage 1/2 | 2-3 weeks |
| | Regressing ROP | 2-3 weeks |

## RESULTS

The study population included 630 neonates; all preterms with a gestational age of 32 weeks or less at birth and a birth weight of 1500 g or less and preterm infants whom gestational age was >32 weeks or birth weight was >1500 g with risk factor, during the duration from June 2015 to June 2016. The birth weights ranged from 940 to 2010 g with a mean of 1510±245 g. Seventy-two cases (41.9%) were delivered vaginally and 100 (58.1%) cases were delivered by Cesarean section.

**Table 4: Incidence.**

| Total preterm neonates | Neonates with retinopathy of prematurity | Incidence |
|---|---|---|
| 630 | 116 | 18.4% |

**Table 5: Sex incidence.**

| Sex | Total neonates Screened | Neonates with retinopathy of prematurity (n=116) | Incidence |
|---|---|---|---|
| Male | 322 | 64 | 19.87% |
| Female | 308 | 52 | 16.86% |

Male: female ratio = 1.23:1

**Table 6: Gestational age and incidence of ROP.**

| Gestational age | Total screened patients | Patients of ROP (Percentage) |
|---|---|---|
| <28 weeks | 88 | 31 (26.72%) |
| 28-32 weeks | 218 | 67 (57.75%) |
| >32weeks | 324 | 18 (15.51%) |

The mean gestational age was 33.02±1.72 weeks; 88 were ≤32 weeks, 218 were between 28 to 32 weeks and 324 were >32 weeks. P value is 0 which suggest there is significant correlation between gestational age and ROP.

**Table 7: Different stages of ROP.**

| Stages of ROP | Number of patients |
|---|---|
| Stage 1 | 88 (75.86%) |
| Stage 2 | 23 (19.82%) |
| Stage 3 | 5 (4.3%) |
| Stage 4 | 0 |
| Stage 5 | 0 |

**Table 8: Gestational age and ROP staging.**

| Stages of ROP | Number of patients with positive ROP | | |
|---|---|---|---|
| | <28 weeks (n=31) | 28-32 weeks (n=67) | >32 weeks (n=18) |
| Stage-1 | 15 | 58 | 15 |
| Stage-2 | 12 | 8 | 3 |
| Stage-3 | 4 | 1 | 0 |
| Stage-4 | 0 | 0 | 0 |
| Stage-5 | 0 | 0 | 0 |

**Table 9: Birth weight and ROP.**

| Birth weight | Total patients | ROP positive | Percentage |
|---|---|---|---|
| <1.25kg | 38 | 19 | 50% |
| 1.25-1.5kg | 52 | 16 | 30.76% |
| 1.5k-1.75kg | 258 | 43 | 16.67% |
| 1.75-2.0kg | 163 | 27 | 16.56% |
| >2.0kg | 119 | 11 | 9.2% |

The birth weight ranged from 880 to 2010 g with a mean of 1330±245 g. P value is 1.1 which suggests there is no significant correlation between birth weight and ROP.

**Table 10: O2 supplementation and ROP.**

| | Patients developed ROP | Patients not developed ROP | Total |
|---|---|---|---|
| O2 given | 95 | 328 | 423 |
| O2 not given | 21 | 186 | 207 |
| Total | 116 | 514 | 630 |

P value-0.0001; So there is significant correlation between $O_2$ therapy and development of ROP. Relative risk=2.21 attributable risk=12.31. a=95; b=328; c=21; d=186.

Relative risk= $\frac{a/(a+b)}{c/(c+d)}$

***Relative risk or risk ratio (RR)***

It is the ratio of the probability of an event occurring (for example, developing a disease, being injured) in an exposed group to the probability of the event occurring in a comparison, non-exposed group.

Attributable risk= $a/(a+b) - c/(c+d) \times 100$

**Table 11: Neonatal risk factors and ROP.**

| Neonatal risk factors | Frequency (n=630) | Neonates having ROP |
|---|---|---|
| Prematurity | 630 (100%) | 87 (15.9%) |
| Apnea | 82 (13%) | 19 (23.02%) |
| Oxygen supplementation | 409 (64%) | 89 (21.7%) |
| Respiratory distress syndrome | 208 (33%) | 46 (22.1%) |
| Intraventricular hemorrhage | 44 (7%) | 05 (11.4%) |
| Septicemia | 168 (26%) | 65 (38.69%) |
| Anemia needing blood transfusion | 53 (8.41%) | 19 (3%) |

P value=0 so significant corelation between above risk factors and development of ROP.

**Table 12: Treatment.**

| Medical treatment | Surgical (laser) treatment |
|---|---|
| 3 | 20 |

Treatment in cases of ROP positive neonate had been given according to stage and involved zone. The following are conditions in which treatment had been given:

- Zone I, any stage ROP with plus disease
- Zone I, stage 3 ROP with or without plus disease
- Zone II, stage 2 or 3 ROP with plus disease

So total 20 patients were given laser treatment and 3 patients were given injection bevacizumab.

**Table 13: Outcome.**

| ROP stage | Number of patients | Outcome |
|---|---|---|
| Stage-1 | 88 (75.86%) | All patients showed spontaneous regression |
| Stage-2 | 23 (19.82%) | 12 patients need treatment and other patients show spontaneous regression on follow up |
| Stage-3 | 5 (4.3%) | All 5 patients needed treatment and improved |

All neonates having stage 3 ROP required treatment, out of 23 patients having stage 2 ROP, only 12 neonates needed treatment and all the neonates with stage-1 had spontaneous regression.

## DISCUSSION

Retinopathy of prematurity is a disorder of retinal vascular development in preterm infants. It continues to be a significant complication in preterm neonates despite advances in neonatal care and remains a major cause of childhood blindness worldwide.[5]

***Incidence***

In present study, incidence of retinopathy of prematurity in preterm neonate is 18.4% which was lower than previously reported by other studies; 24% in India, 29.2% in Singapore, and 32.4% in Pakistan.[6-8] However, it is higher than the study done in Beijing which involved infants with higher gestational age and birth weight (up to 2 kg and /or 34 weeks gestational age) and reported an incidence of 10.8%.[9]

***Risk factor***

The most significant risk factors for development of ROP were low gestational age and low birth weight, as shown in many studies.[10-12] In present study, low gestational age, prematurity, apnea, respiratory distress syndrome, sepsis, oxygen therapy, intraventricular hemorrhage and frequency of blood transfusions were found to be risk factors for development of ROP independently.

As regard the effect of low gestational age occurrence of ROP, we found it the most important risk factor in ROP. This was in agreement with the results of studies done by Shah et al, Karna et al, and Fortes et al.[13-15] As regard the effect of birth weight on the occurrence of ROP, in study of Arroe and Peitersen, we found that birth weight was

non-significant factor for development of ROP.[16] This was contradictory to with many studies, which reported that lower birth weight was significantly associated with development of ROP, and explained that by more susceptibility for oxygen therapy, prolonged ventilation, sepsis, and blood transfusion in very low birth weight infants.[7,15,16]

In this study, we found that sepsis was significantly associated with the development of ROP. This was in agreement with Shah et al, and Vinekar et al, which may be due to the effect of endotoxins on retinal blood vessels.[7,17] In present study, we found that the frequency of blood transfusions is a significant risk factor for development of ROP, and this agreed with Chawla et al.[18] This can be explained by the fact that, adult RBCs are rich in 2,3 DPG and adult hemoglobin which binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue.

Other risk factors including patent ductus arteriosus, hypotension, and phototherapy showed no significant relationship with the occurrence of ROP. Similarly Taqui et al, reported no significant relation between ROP and patent ductusarteriosus and intraventricular hemorrhage, but we observed a significant relation between respiratory distress syndrome and the development of ROP and related this to the fact that systemic hypoxia results in retinal hypoxia and more need for oxygen therapy.[8] On the other hand, Shah et al, reported a significant relation between ROP development and patent ductus arteriosus, intraventricular hemorrhage and hypotension.[13] Chaudhari et al observed no significant effect of phototherapy on ROP.[1]

***Treatment***

In agreement with Coats et al we found that the twenty cases that required laser intervention improved and ROP regressed with regular follow-up.[1,21]

***Outcome***

Most patients of positive ROP have stage-1 disease (76%). Stage 2 and stage 3 more common in neonates with gestational age <28 weeks as compared to neonates with gestational age 28-32 weeks and >32 weeks. Earlier detection by screening done according to above schedule leads to treatment and prevention of blindness.

## CONCLUSION

The incidence of ROP in this study was 18.4%, the data of this study suggest that low gestational age, sepsis, oxygen therapy and frequency of blood transfusions are independent risk factors in the development of ROP. Clinicians should be aware of the presence of the additional risk factors when monitoring preterm infants. The analysis of risk factors for ROP development will help to understand and predict it in preterm infants. The timely retinal screening of high-risk preterm infants is important to prevent the development of advanced ROP. Since ROP may produce serious squeal up to complete blindness, all efforts must be made to prevent the development of advanced ROP through elimination of preterm births, changes in the neonatal care and improvement in detection of threatening ROP markers.

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