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Retinopathy of Prematurity

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Abstract: ***Background: Retinopathy of Prematurity is a leading cause of blindness among premature infants. It is a disorder of retinal blood vessels due to abnormal response of premature infants' retinal vasculature to prematurity and therapy for its management. Present study was undertaken to develop effective screening program in order to screen such premature infants especially those with risk factors for this disease and to study the characteristics and grading of this disease in them. Objectives: 1. To identify neonates who are at risk of developing Retinopathy of Prematurity and screen them for the same, 2. To study the risk factors associated with Retinopathy of Prematurity., 3. To study the morphological characteristics and grading of this disease. Methods: A total of 90 neonates of birth weight less than 2000gms and gestational age less than 36 weeks were screened and these neonates were followed up for the presence or retinopathy of prematurity .Risk factors in these infants were noted and if present morphological characteristics of this disease were recorded and graded. Eye examination was done using an indirect ophthalmoscope and a +20 dioptre lens after dilating the pupils with tropicamide 0.5% and phenlyephrine 2.5% which was instilled twice at 5 minute intervals, in both eyes. Results: Overall Incidence of this disease was calculated in addition to incidence in neonates of various categories of birth weights and gestational ages and stage specific incidence. Chi square test and P value was calculated to check the statistical correlation between various risk factors and the presence of this disease in the infants screened. A table of comparison was drawn up to compare results of this study with the Palmer et al (Cryo-ROP study). In our study 17 of the 90 infants screened were found to have the disease thus the incidence was found to be 18.88% for any stage of the disease. Of the 17 infants 11 (64.7%) were in stage 1, 2 (23.5%) were in stage 2, l (5.88%) were in stage 3 and 1 (5.88%) were in stage 4. The incidences of ROP in various gestational age groups were as follows 28-30 weeks (33%), 30-32 weeks (37.5%), 32-34 wks (12.5%) and 34-36wks (6.2%). The incidence of ROP with respect to various birth weights was as follows <1000 grams (33%) 1000-1250 grams (42.82%) 1251-1500 grams (7.14%) 1500-2000gms (15.2%). A statistically significant correlation was found between birth weight and ROP and Gestational age and ROP. Interpretation and Conclusion: The lower incidence of ROP in our study as compared to Palmer et al (Cryo ROP study) scan be attributed to the fact that most neonates in our study had a birth weight of >1000 grams. As inferred from previous studies this study also showed that lower gestational age and lesser birth weight make independent contributions to the overall incidence of ROP. Anemia, blood transfusion, hyperbillirubinaemia and phototherapy were not found to be significantly associated with ROP in our study. Other factors like septicaemia, apnoea, RDS, and maternal factors like infection, diabetes and hypertension were not significantly associated with ROP in this study.***

Keywords: ROP - Retinopathy of Prematurity, RLF - Retrolental Fibroplasia, PCA - Postconceptional Age, PMA - Postmenapausal age, LP - Light Perception, NLP - No Light Perception

1. Introduction

Retinopathy of Prematurity is a leading cause of blindness among premature infants. It is a disorder of retinal blood vessels due to abnormal response of premature infants retinal vasculature to prematurity and therapy for its management. Present study was undertaken to develop effective screening program in order to screen such premature infants especially those with risk factors for this disease and to study the characteristics and grading of this disease in them.

2. Objectives of the Study

a) To identify neonates who are at risk of developing Retinopathy of Prematurity and screen them for the same.
b) To study the risk factors associated with Retinopathy of Prematurity.
c) To study the morphological characteristics and grading of this disease

3. Materials and Methods

This study was conducted at Santhiram Medical College and General Hospital, Nandyal during the period August 2018 to July 2019. A total of 90 neonates were screened and followed up for the presence of retinopathy of prematurity.

All neonates of less than 36 weeks gestational age or birth weight less than 2000gms were selected for screening and the risk factors were noted.

The following history was recorded:

1) History of the mother
a) Obstetric history
b) Presence of any antenatal complications e.g. diabetes, hypertension, infections, pih, multiple pregnancy, prom, infertility treatment, abruptio placenta, placenta previa, chorioamniotis, oligo/polyhydramnios.

2) Details of delivery
a) Type of delivery: Vaginal delivery or caesarian section
b) Complications eg Cord around the neck, breech, apgar score
c) Birth weight and gestational age
d) Antenatal steroid administration

3) Postnatal complications were noted eg
a) Anemia
b) Blood transfusion
c) Hyperbilirubinaemia
d) Phototherapy and duration
e) Sepsis and use of antibiotics
f) Apnoeac episodes
g) Oxygen given and no of days
h) Rds and use of surfactant

i) Seizures and medication
j) Congenital abnormalities eg. atrial septal defect, ventricular septal defect, patent ductus arteriosis and any other malformations
k) Hyaline membrane disease
l) Administration of vit E

4) ROP
a) Presence of immature retina and zone
b) Zone and worst stage of rop
c) Presence or absence of plus, prethreshold or threshold disease
d) The gestational age at which examination is done is recorded
e) anterior segment complications eg rubeosis iridis, corneal abnormalities, secondary glaucoma and catractous lens were looked for.

Method of examination
Anterior segment examination was first done with torch light and pupillary reactions were noted. Eye examination in the neonate, was performed by dilating the pupils with tropicamide) 0.5% and phenylephrine 2.5%.instilled twice at 5 –minute intervals, in both eyes. The excess drops were wiped away each time.An infant eye speculum was used which was disinfected each time with spirit and sterilized in the boiler prior to use. The examination was performed 25 to 30 mins later with an indirect ophthalmoscope and a +20 dioptre lens. The peripheral vascular changes were documented, the risk factors noted and the neonates were followed up as and when required.

The Development of the Retinal Vasculature System
The earliest retinal vasculature is provided by the hyaloid artery, which is part of the primary vitreous and is present at 6 weeks gestation. The retina is an avascular structure till 16 wks gestation. At 16 weeks intraretinal vessels can be recognized as buds coming of the hyaloid artery. Retinal vasculature reaches the ora serrata on the nasal side by 36 weeks and the temporal ora by full term.

Pathogenesis of ROP

Concepts of Retinopathy of Prematurity has dramatically changed ever since Terry first described it in 1942.Supplemental oxygen administration was for a long time considered as the most important causative factor is now considered as only a risk factor. Low birth weight and decreased gestational age are now considered primary causative factors.

The important hypotheses described are:

(1) The Classical theory
(2) Spindle cell theory

(1) The Classical Theory
Ashton and Patz proposed the classical pathogenesis of ROP11.According to this theory which was once widely accepted, supplemental oxygen administration was considered as the main causative factor. Elevated arterial PO2 causes retinal vasoconstriction, leading to vascular closure and if vasoconstriction is sustained, subsequent permanent vascular occlusion occurs. Endothelial cell proliferation adjacent to closed capillaries followed when neonate returns to room air thus leading to neovascularisation. Subsequent extension of this neovascularisation may reach the vitreous, producing haemorrhage leading to fibrosis and causing vitreous traction and Retinal Detachment.

(2) Spindle Cell Theory
This theory which was proposed by Kretzer et al3, postulates the induction of retinal and vitreal neovascularisation by spindle cell insult. In premature new born, the peripheral retina is avascular and thin. After birth the spindle cells are exposed to hyperoxic environment because of increased oxygen diffusion through this retina from choroidal vasculature. Oxygen free radicals behave as cytotoxic agents. They attack compromised spindle cells, which has deficient anti-oxidative defense mechanism. These “activated spindle cells” probably secrete an angiogenic factor that promotes vasoproliferation at the border between vascular and avascular retina. **Growth Factors in ROP** Vasoformative factors play a vital role in the normal development of Retinal Vasculature.4.Many vasoformative factors have been described but vascular endothelial growth factor (VEGF) was among first to be identified and cloned. VEGF is produced anterior to the vascular area. Adequate amount of VEGF is required for retinal growth.If the avascular zone is larger and when this is exposed to the hyperoxic state, VEGF expression is decreased leading to vasobliteration. This causes hypoxia and ischaemia in nonperfused area if insult is sustained.This again stimulates VEGF production and neovascularisation. Over the time if VEGF production decreases, ROP will regress. If VEGF production increases or persists ROP will progress. The manipulation of these factors could be beneficial therapeutically.

Incidence of ROP
Incidence and severity of ROP increases with decreasing birth weight and gestational age. Thus 9 out of 10 infants with birth weight less than 750 grams or less will develop ROP while only 4.7 out of ten in a birth weight group of 1000-1250 grams will develop ROP. Similarly, the incidence of ROP reported in gestational age groups of 24-27, 28-31, 32-35 and above 36 weeks is 89%, 63%, 26%, and 19% respectively.

Risk Factors

1) Birth weight less than 2000 gm
2) Gestational age less than 34 weeks
3) Gestational age between 34 to 36 weeks but with risk factors such as:
   a) Cardio-respiratory support,
   b) Prolonged oxygen therapy,
   c) Respiratory distress syndrome,
   d) Chronic lung disease,
   e) Fetal hemorrhage,
   f) Blood transfusion,
   g) Neontal sepsis,
   h) Exchange transfusion,
   i) Intraventricular haemorrhage,
   j) Apneas,

k) Poor postnantal weight gain.

Zones and Stages and Clock Hours for Recording ROP

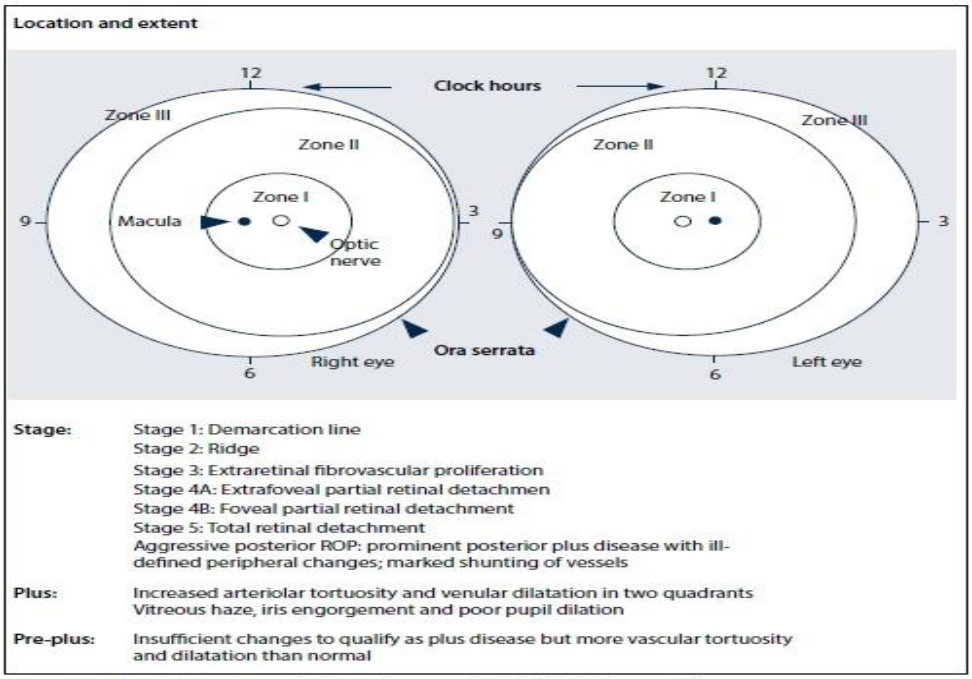
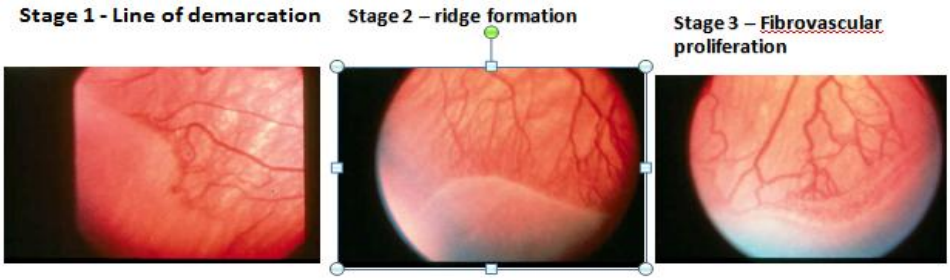
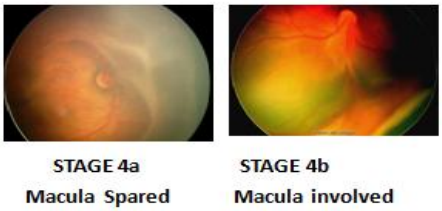
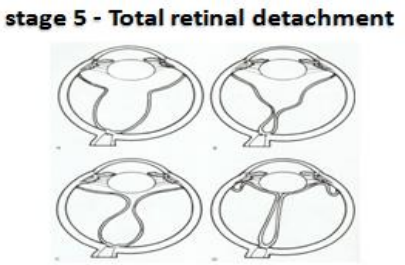


Fig. 1. The Revised International Classification of ROP (ICROP) system.[6]

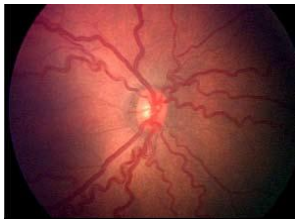
Stages of ROP







Plus Disease



Screening Criteria for ROP

Which babies to screen1

1) Birth weight of less than 1500 gms (though in India this is reported up to 1700 gms1.
2) Gestational age at birth (length of pregnancy) of less than 34-35 weeks
3) Exposed to oxygen for more than 30 days.
4) Infants weighing less than 1200 gms at birth and those born at 24-30 weeks gestational age are at particular high risk not only developing ROP but also developing it earlier, in more aggressive forms (Rush disease) Hence the definite need to screen these smaller babies at the earliest.
5) Other factors that can increase risk of ROP and where screening should be considered are other premature babies (<37 weeks and/or <2000 gms) with
   a) Respiratory distress syndrome
   b) Sepsis
   c) Multiple blood transfusions

d) Multiple births (twins, triplets, etc)
e) Apnoeic episodes
f) Intraventricular haemorrhage
g) Paediatrician has index of concerns for ROP

Time for Screening the Neonates at Risk

When to screen- Screen all eligible babies at

1) 31 weeks PCA (post conceptional age) or 3-4 weeks after birth (whichever is earlier).
2) Infants weighing less than 1200grams at birth and those born at 24-30 weeks gestational age are screened early, usually not later than 2-3 weeks after birth.
3) No examination is necessary in first 2-3 weeks of life.
4) Next date of examination is to be decided by the ophthalmologist based on initial findings.
5) Complete one screening session definitely before day 30 of the infants life.

Follow –Up Schedule for ROP Screening/Treatment

How frequently to examine

1) Mature retina Follow up 3 months to 1 year
2) Threshold ROP/AP-ROP - Early treatment within 72 hours
3) Retinal Detachment in ROP Early surgical treatment

Table 1. Follow up examination schedule based on retinal findings

Zone of retinal findings	*Stage of retinal findings*	*Follow up interval*
Zone 1	Immature vascularization	1-2 weeks
	Stage 1 or 2	1 week or less
	Regressing ROP	1-2 weeks
Zone 2	Immature vascularization	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 or 2	2-3 weeks
	Regressing ROP	2-3 weeks

Aggressive Posterior ROP

Earlier known as **'RUSH Disease'**

- posterior location
- Rapidly evolving with plus disease and neovascularization.
- Progress to stage IV & V in 2-3 weeks without passing through characteristic stages II and III
- Requires Intravitreal Anti VEGF injection and laser treatment more than once

TREATMENT ALGORITHM BASED ON RESULTS OF ET-ROP STUDY

ZONE 1	PLUS DISEASE	ANY STAGE ROP	CONSIDER TREATMENT
	NO PLUS DISEASE	STAGE 1 or 2	OBSERVE VERY CLOSELY FOR PROGRESSION OR PRESENCEOF PLUS DISEASE
		STAGE 3	CONSIDER TREATMENT
ZONE 2	PLUS DISEASE	STAGE 1	OBSERVE FOR PROGRESSION
		STAGE 2 or 3	CONSIDER TREATMENT
	NO PLUS DISEASE	STAGE 1 or 2 or 3	OBSERVE FOR PROGRESSION OF PRESENCE OF PLUS DISEASE
ZONE 3			
	PLUS DISEASE	ANY STAGE ROP	OBSERVE CLOSELY FOR PROGRESSION
	NO PLUS DISEASE		OBSERVE FOR PROGRESSION OR PRESENCE OF PLUS

4. Treatment

Cryoapplication

Since Cryotherapy is a painful procedure it should be performed under general or local anaesthesia. After dilation of the pupil, cryotherapy is performed under direct visualization through the indirect ophthalmoscope.

Laser Photocoagulation

The new diode laser has been used for ablation of avascular retina. Laser can be very accurately placed and is simpler to deliver in posterior disease. This Treatment is better tolerated than cryotherapy, with fewer ocular and systemic side effects[4, 13]. Diode laser is more preferred compared to argon laser as it requires less power and causes less tissue destruction the instrument is transportable and an ordinary electrical outlet can be used as a source of power.

Indication for peripheral retinal ablation

The treatment involves ablation of peripheral normal avascular retina and thereby abolishing hypoxic drive of retina (mediated by over-expression of vascular endothelial growth factor; VEGF). This results in regression of established ROP. Care is taken not to touch the retina with ROP as it would result in severe bleeding.

Treatment of ROP is based on differentiation of following two types of ROP:

Type 1 ROP

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

Type 2 ROP

• Zone I, stage 1 or 2 ROP without plus disease
• Zone II, stage 3 ROP without plus disease

Peripheral retinal ablation should be carried out for all cases with type 1 ROP and continued serial examinations are advised for type 2 ROP.

Bevacizumab

Intravitreal injection of bevacizumab, a neutralizing anti-VEGF molecule has been demonstrated to diminish the

neovascular response significantly in animal models and human studies. As VEGF is an important mediator of lung growth and brain development, and there is significant systemic absorption of anti VEGF medication after intravitreal injection, there are concerns regarding toxicity of such therapy. Due to lack of data on potentially serious systemic adverse effects, administration of intravitreal bevacizumab (anti-VEGF monoclonal antibody) is not routinely recommended in neonates with ROP. It may be used only when laser photocoagulation fails and after taking informed consent from the parents.

Surgical Therapy [4]

The surgical options for treatment of eyes that develop partial retinal detachment (stage 4), and total retinal detachment (stage 5) include scleral buckle, combined vitrectomy, vitrectomy with lens conservation and observation.

Surgical Management of Stage 4 ROP

Stage 4A: Focal traction with no RD=follow up
Stage 4A: Generalised traction with no RD=Follow up with or without buckling
Stage 4A: Generalised traction with RD=Bucking/lens sparing vitrectomy
Stage 4B: Lens sparing vitrectomy

Surgical Approach for Stage 5 ROP

The surgical techniques in stage 5 ROP are confined to closed lensectomy, pars plana vitrectomy (with membrane peeling accompanied occasionally by drainage of subretinal fluid), and rarely scleral buckling.Open sky vitrectomy with intracapsular lensectomy and membrane peeling has also been used.

Long term vision concerns of Regressed ROP

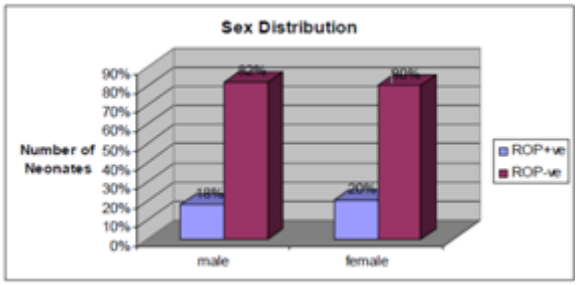
- Refractive errors
- Myopic astigmatism
- Strabismus
- Cataract
- glaucoma
- Retinal detachment

5. Results

Table 1: Sex Distribution

	Male	Female
ROP+ve	9 (18%)	8 (20%)
ROP-ve	41 (82%)	32 (80%)

$X^2 = 0.058$, p=0.810 NS

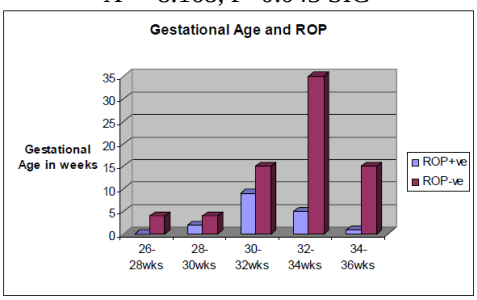


Of the 90 neonates screened, 40 (44.44%) were females and 50 (55.66%) were males. 9 (18%) among the males and 8 (20%) among the females developed retinopathy of prematurity. In this study no significant statistical correlation was seen.

Table 2: Gestational age and ROP

	26-28 weeks	28-30 weeks	30-32 weeks	32-34 weeks	34-36 weeks
ROP+ve	0	2	9	5	1
ROP-ve	4	4	15	35	15
Total infants	4	6	24	40	16

$X^2 = 8.168$, P=0.043 SIG

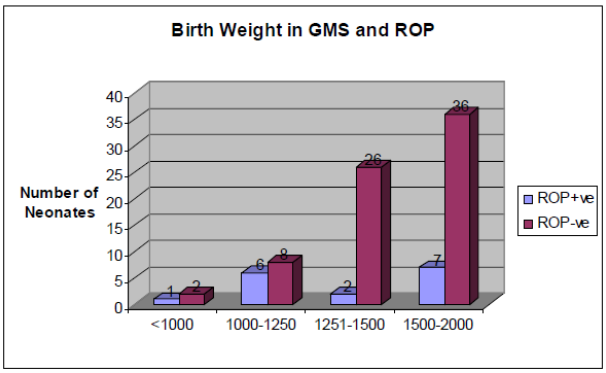


Of the 6 infants who fell in the gestational age group 28-30 wks 4 (33%) developed Retinopathy of prematurity. Of the 24 infants in the 28-30 wks gestational age group 15 (37.5%) developed Retinopathy of prematurity. Of the 40 infants who fell in the gestational age group 32-34wks 5 (12.5%) developed Retinopathy of prematurity. Of the 16 infants who fell in the gestational age 34-36wks 1 (6.2%) developed Retinopathy of prematurity. A statistical significant correlation was seen between gestational age and ROP.

Table 3: Birth Weight in grams and ROP

	<1000	1000-1250	1251-1500	1500-2000
ROP+ve	2	6	2	7
ROP-ve	3	8	26	36
Total	5	14	28	43

$X^2 = 8.441$, P=0.015 SIG

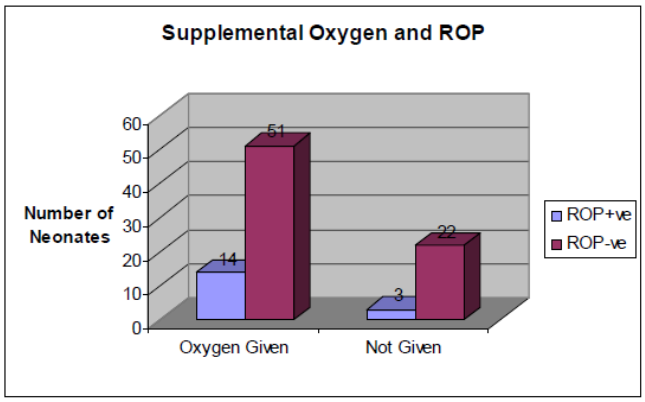


With respect to birth weight, the incidence of retinopathy was as follows;1 (33%) of the neonates weighing less than 1000, 6 (42.85%) of the 14 neonates weighing between 1000-1250gms, 2 (7.14%) out of 28 infants weighing between 1251-1500 gms and 7 (15.2%) of infants weighing between 1500 and 2000 gms developed retinopathy of prematurity. Incidence was found to be greater with lesser birth weight. A statistically significant correlation was found between birth weight and ROP.

Table 4: Supplemental Oxygen and ROP

	Oxygen Given	Not Given	Total
ROP+ve	14	3	17
ROP-ve	51	22	73

$X^2 = 1.072$, P=0.300 NS

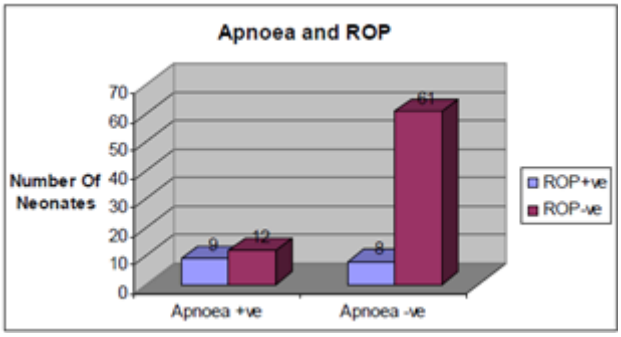


A Total of 14 (27.4%) of 51 (56.6%) infants who received oxygen developed ROP. No statistically significant correlation was seen.

Table 5: Apnoea and ROP

	Apnoea Present	Apnoea Absent	Total
ROP+ve	9	8	17
ROP-ve	12	61	73

$X^2 = 10.271$, P=0.001 NS

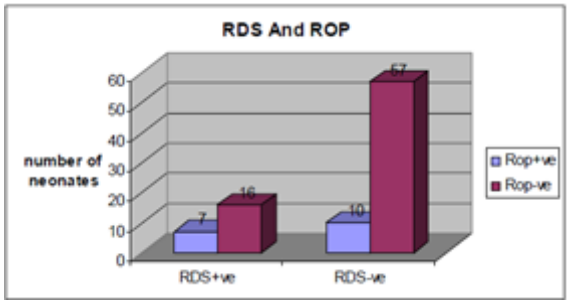


Of the 21 (23%) infants who had apnoea attacks 9 (42.85%) developed ROP and of the total 69 (76.66%) infants who had no apnoea attacks 8 (11.6%) developed ROP. No significant statistical correlation was seen.

Table 6: RDS and ROP

	RDS Present	RDS Absent	Total
ROP+ve	7	10	17
ROP-ve	16	57	73

$X^2 = 2.688$, P=0.101 NS

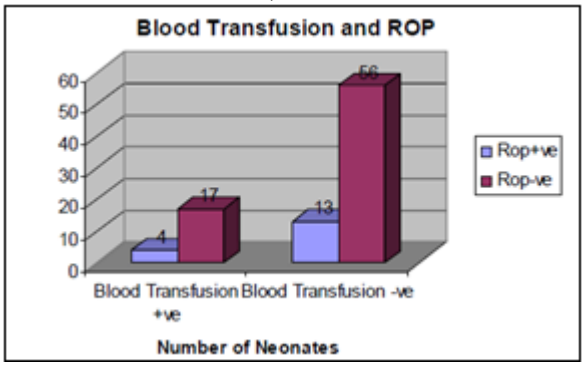


Of the total 23 (25.5%) neonates who developed RDS 7 (30.43%) developed ROP while of the 67 (74.4%) neonates without RDS 10 (14.9%) developed ROP. No statistically significant correlation was seen.

Table 7: Blood Transfusion and Rop

	Given	Not Given	Total
ROP+ve	4	13	17
ROP-ve	51	22	73

$X^2 = 0.002$, P=0.983 NS



Of the total 21 (23.33%) of infants who received blood transfusion 4 (19%) developed ROP while of the total 69 (76.6%) who did not receive blood transfusion 13 (18.6%) developed ROP. No significant statistical correlation was seen.

6. Discussion

A total of 90 neonates weighing less than 2000 grams at birth with gestational age less than 36 weeks were screened during the study period.Of these 90 infants, 50 (55.66%) were male and 40 (44.44%) were female.9 (18%) among the males and 8 (20%) among the females developed retinopathy of prematurity.

The incidence of ROP was independent of whether the infant was male or female. A similar observation was also noted in the study by Palmer et al1 which was a part of the Multicentre Trial of Cryotherapy in which the incidence among males was 66.4% and among females 65.3%.

17 of the 90 infants developed ROP and the incidence of ROP was 18.88% for any stage.Of the 17 infants 11 (64.7%) were in stage 1, 2 (23.5%) were in stage 2, 1 (5.88%) was in stage 3 and 1 (5.88%) was in stage 4.

In the study by Palmer et al1 as part of the Cryo-ROP study, the overall incidence of ROP was found to be 65.8%.Of this 25.2% had stage 1 disease, 21.7% had stage 2 disease and 18.3% had stage 3 disease.

Of the total 6 infants who fell into the gestational age group of 28-30 weeks 2 (33%) developed retinopathy of prematurity. Of the 24 infants who fell into the gestational age group of 30-32wks 9 (37.5%) developed retinopathy of prematurity. Of the 40 infants who fell into the gestational age group of 32-34wks 5 (12.5%) developed retinopathy of prematurity while of the 16 infants who fell into the gestational age group of 34-36 wks 1 (6.2%) developed retinopathy of prematurity. The incidence was found to be higher in the lower gestational age group.A statistically significant correlation was found to exist between gestational age and retinopathy of prematurity.
The incidence of ROP among neonates of 28-31 weeks gestational age was 55.3%and among infants of 32-34weeks

gestational age group was 22.9%in the study by Palmer et al1.

The incidence of ROP with respect to various birth weights was as follows < 1000 grams 33%, 1000-1250 grams, 42.82%, 1251-1500grams, 7.14%and 1500-2000gms, 15.2%.

In the Multicentre trial of cryotherapy, the incidence of ROP was highest (90%) in infants with birth weight <750 grams, 78%among neonates weighing between 750 to 999 grams and 47% among infants weighing 1000-1250 grams. It was found that the incidence of threshold ROP was 15.5%in the lowest birth weight category.

The lesser incidence of ROP on our study could be attributed to the fact that all the neonates in our study had a birth weight of >1000 grams, A total of 14 (27.4%) of 51 infants who received supplemetal oxygen developed ROP. Supplemental oxygen was given to these neonates for varying periods ranging from 3 hours to 10 days. No significant association was found between supplemental oxygen therapy and ROP.

The STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold retinopathy of prematurity) study found that the use of supplemental oxygen did not cause additional progression of prethreshold disease but did not reduce the number of infants requiring peripheral retinal ablative therapy.

In a prospective study at a tertiary care newborn unit in Delhi15 the incidence of ROP among at risk neonates (birth weight <1500grams, gestational age <35weeks and those requiring supplemental oxygen for more than 24 hours) as 20% for any stage. The incidence of threshold ROP was 7%.

In a study done in North India, the incidence of ROP was found to be 47.2% (78 out of 165 babies weighing <1700 grams at birth, and between 26 weeks to 40 weeks gestational age.)

In another prospective study conducted at a nursing home in Bombay on 35 neonates, with birth weight <=1250grams and <32weeks gestational age, 17.1% had stage 1 disease, 25.7% had stage 2 disease, 5.7% stage 3 and 25.8% stage 4.

Of the total 21 (23.33%) of infants who received blood transfusion 4 (19%) developed ROP. Thus no statistically significant correlation was found between blood transfusion and ROP.

The other factors like septicemia, phototherapy, neonatal jaundice, respiratory distress syndrome, antenatal dexamethasone administration to the mother and maternal hypertension were not found to be significantly associated with ROP.

7. Summary

The overall incidence of ROP in this study was 18.88% of which 64.7% had stage 1, 23.5% had stage 2 5.88% had stage 3 and 5.88% had stage 4 disease. The incidence was 33% in neonates of 26-28 weeks, 37.5% in neonates of 28-30 weeks, 32-34%in neonates of 30-32 weeks and 6.2% in neonates of 34-36 weeks.

The incidence of ROP in neonates weighing less than 1000gms was 33%, 42.85% in infants weighing between 1000-1250 gms, 7.14% in infants weighing 1251-1500gms and 15.2% in infants weighing between 1500-2000 gms.

As inferred from previous studies, this study also showed that lower gestational age and lesser birth weight make independent contributions to the overall incidence of ROP.

Supplemental oxygen therapy was not significantly associated with development of ROP in this study.

Anemia, blood transfusion, hyperbilirubinaemia and phototherapy were not significantly associated with development of ROP.
Factors like septicemia, apnoea, maternal infections, maternal diabetes, maternal hypertension and respiratory distress syndrome were not significantly associated with ROP in this study.

8. Conclusion

.
As inferred from previous studies, this study also showed that lower gestational age and lesser birth weight make important independent contributions to the overall incidence of ROP.

Technological advances in neonatal care have enabled salvaging extremely small and low birth infants. This has led to an increased risk of development of ROP among susceptible neonates. It is thereby essential to impress upon all those involved in the care of neonates, about the necessity and effectiveness of a screening programme. An effective screening programme helps to identify those neonates who have the potential to reach threshold ROP or have already reached threshold ROP. Early diagnosis and prompt treatment of threshold disease with laser or cryotherapy promotes a better visual outcome and prevents irreversible blindness in children.

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