A DISSERTATION ON

"THE ANALYSIS ON THE TREND OF SCREENING POSITIVE RATE AND CORELATIVE RISK FACTORS OF RETINOPATHY OF PREMATURITY"

THE TAMIL NADU DR. MGR. MEDICAL UNIVERSITY,

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In partial fulfillment of the regulations

For the award of the degree of

M.D. DEGREE BRANCH-VII

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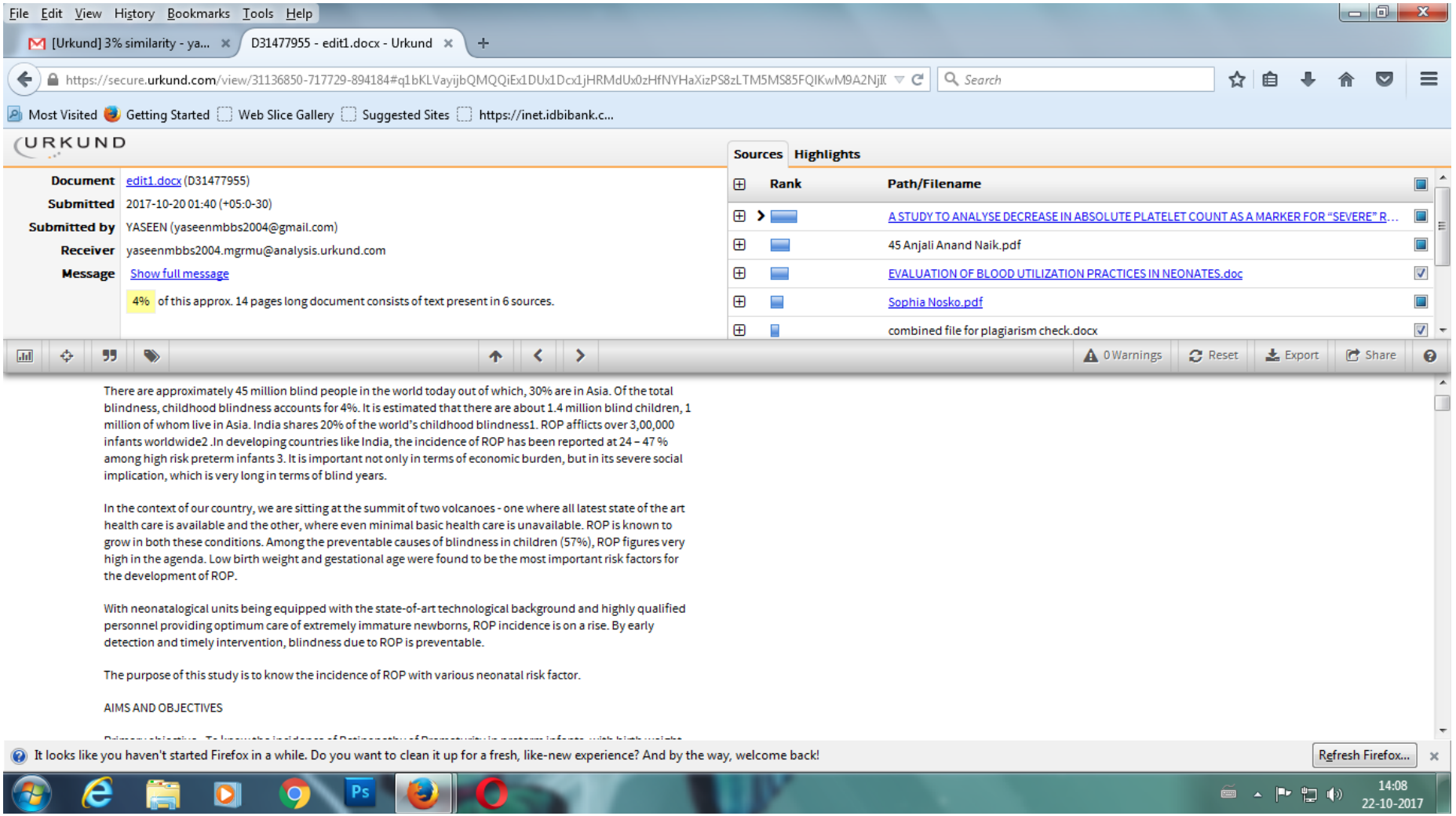
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There are approximately 45 million blind people in the world today out of which, 30% are in Asia. Of the total blindness, childhood blindness accounts for 4%. It is estimated that there are about 1.4 million blind children, 1 million of whom live in Asia. India shares 20% of the world's childhood blindness1. ROP afflicts over 3,00,000 infants worldwide2 .In developing countries like India, the incidence of ROP has been reported at 24 – 47 % among high risk preterm infants 3. It is important not only in terms of economic burden, but in its severe social implication, which is very long in terms of blind years.
In the context of our country, we are sitting at the summit of two volcanoes - one where all latest state of the art health care is available and the other, where even minimal basic health care is unavailable. ROP is known to grow in both these conditions. Among the preventable causes of blindness in children (57%), ROP figures very high in the agenda. Low birth weight and gestational age were found to be the most important risk factors for the development of ROP.
With neonatalogical units being equipped with the state-of-art technological background and highly qualified personnel providing optimum care of extremely immature newborns, ROP incidence is on a rise. By early detection and timely intervention, blindness due to ROP is preventable.
The purpose of this study is to know the incidence of ROP with various neonatal risk factor.
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Ethical Committee Meeting held on 23.12.2015 at 11.00 A.M in the Seminar Hall, IInd Floor, Medicine Block, Govt. Mohan Kumaramangalam Medical College Hospital, Salem 01.

Name of the Presenter with Address	Title	Name of the Guide and Address	Whether it is Approved or not.
Dr. M. Yaseen, I Year, Post Graduate Student of MD (Paediatrics), GMKMC, Salem-30.	"The Analysis on the trend of screening positive rate and Corelative risk factors of Retinopathy of Prematurity in GMKMCH".	Dr. T.S. Sundararajan, MD., HOD of Paediatrics, GMKMC, Salem.	Approved

The Ethical Committee examined the studies in detail and is pleased to accord Ethical Committee approval for the above Post Graduate student of this College to carry out the studies with the following conditions.

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To
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF PHOTOGRAPH

LIST OF FIGURES

LIST OF ABBREVIATIONS

AOP	:	Apnoea of prematurity
APROP	:	Aggressive posteriorretinopathy of prematurity
BT.WT.	:	Birth weight
CRYOROP	:	Cryotherapy for retinopathy of prematurity study 2, 3
DPG	:	2, 3- Diphosphoglycerate
ELBW	:	Extremely Low Birth Weight (<1000 gms)
ETROP	:	Early treatment for ROP trial
FIO2	:	Fraction of inspired concentration of oxygen
gms	:	grams
Hb	:	Haemoglobin
IGF-1	:	Insulin-like growth factor-1
IVH	:	Intraventricular haemorrhage
ICROP	:	International Classification of ROP
Light-ROP	:	Light reduction on ROP study
NICU	:	Neonatal Intensive Care Unit
O2	:	Oxygen
PHPV	:	Persistent Hyperplastic Primary Vitreous
PDA	:	Patent Ductus Arteriosus
PIH	:	Pregnancy Induced Hypertension
ROP	:	Retinopathy of Prematurity
RLF	:	Retrolental Fibroplasia
RDS	:	Respiratory Distress Syndrome
VEGF	:	Vascular Endothelial Growth Factor
wks	:	weeks

ABSTRACT

Background: Retinopathy of prematurity (ROP) is a common blinding disease in children in the developed world despite current treatment, and is becoming increasingly prevalent in the developing world. Improved survival of preterm neonates has increased the incidence of retinopathy of prematurity (ROP) in India.

Objective: To know the incidence of ROP in preterm infants with birth weight ≤ 1500 grams to 2000gms with risk factor and/or gestational age ≤32 to 35 weeks with risk factors and to correlate between development of ROP and the risk factors.

Methods: A longitudinal study of 100 infants weighing ≤1,500 grams to 2000grams and/or GA ≤32 to 35 weeks at birth was conducted. The main clinical outcomes were the incidence of any stage of ROP and severe ROP. The variables considered for the study were: birth weight, gestational age, oxygen, occurrence of sepsis, transfusion, apnoea,.

Results: The incidence of ROP in this study was found to be 27%. 22.22% babies were in stage 1, 59.26% were in stage 2 and 3.70% was in stage3 ROP,and 14.82% developed APROP.

The mean birth weight of the ROP babies was 1280gm, Lower birth weight was significantly associated with increased incidence with

<1500gms (p = <0.001) of ROP. The incidence of ROP was 48.15% in babies weighing ≤ 1500gm at birth.

The mean gestational age of the ROP babies was32 weeks, The incidence of ROP was 36.36% in babies born ≤ 32 weeks of gestational age. Gestational age was found to be a significant risk factor for the development of ROP (p=0.011).

CONCLUSION:

The present study reflects the problem of ROP in a tertiary care centre. Early examination was significantly associated with chances of early detection of ROP and hence all babies should have their first screening within the first four weeks after birth. In our opinion, the effective management of ROP requires a team effort of the neonatologist, ophthalmologist and the NICU staff. Regular screening programme with a criteria of birth weight <1500 gms and gestational age <32 weeks or both and babies more than 1500 gms and >32 weeks with other risk factors should be screened at the discretion of the neonatologist and ophthalmologist. Along with regular screening, an effective control of oxygen delivery, reduction of apneic spells and their early recognition and effective management.

Key Words: Retinopathy of prematurity, Birth weight, Gestational age, Risk factors.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting premature infants. It is one of the most common causes of visual loss in children and can lead to lifelong vision impairment and blindness.

There are approximately 45 million blind people in the world today out of which, 30% are in Asia. Of the total blindness, childhood blindness accounts for 4%. It is estimated that there are about 1.4 million blind children, 1 million of whom live in Asia. India shares 20% of the world's childhood blindness[1]. ROP afflicts over 3,00,000 infants worldwide[2] .In developing countries like India, the incidence of ROP has been reported at 24 – 47 % among high risk preterm infants [3]. It is important not only in terms of economic burden, but in its severe social implication, which is very long in terms of blind years.

In the context of our country, we are sitting at the summit of two volcanoes - one where all latest state of the art health care is available and the other, where even minimal basic health care is unavailable. ROP is known to grow in both these conditions. Among the preventable causes of blindness in children (57%), ROP figures very high in the agenda. Low birth weight and gestational age were found to be the most important risk factors for the development of ROP.

With neonatalogical units being equipped with the state-of-art technological background and highly qualified personnel providing optimum care of extremely immature newborns, ROP incidence is on a rise. By early detection and timely intervention, blindness due to ROP is preventable.

The purpose of this study is to know the incidence of ROP with various neonatal risk factor.

AIMS AND OBJECTIVES

Primary objective - To know the incidence of Retinopathy of Prematurity in preterm infants, with birth weight upto 2000 grams and/or gestational age 35 weeks with risk factor.

Secondary objective – To know the relationship between development of ROP and risk factors.

INCLUSION CRITERIA

- Selecting neonates for screening depends on incidence of ROP at different gestation ages. Gestation age and birth weight cut-off for screening shifts lower as smaller and sicker neonates start surviving.
- Based on current incidence and risk factors reported in Indian literature following group of neonates should be screened.
- Babies with birth weight <=1500 g to upto 2000gms with risk factor
- Babies born with ≤32 to 35 weeks of gestation with risk factor
- Selected preterm infants with a birth weight between 1500 and 2000 g or gestational age of more than 32 weeks with sickness like need of cardiorespiratory support, prolonged oxygen therapy, apnea of prematurity, anemia needing blood transfusion and neonatal sepsis

EXCLUSION CRITERIA

- Term babies with exclusive breast feeding
- Late preterm with risk factors
- Large for gestational age babies
- Term babies with IUGR & LBW
- Term babies with ventilator support

REVIEW OF LITERATURE

HISTORY

RETINOPATHY OF PREMATURITY (ROP) was originally designated Retrolental Fibroplasia (RLF) by Dr. Theodore L. Terry who first connected the condition with premature birth. He proposed that the primary change was the proliferation of the embryonic hyaloid system which incorporated the retina. He stated the unilateral pathological specimens and provided details which that may be identical with bilateral retrolental fibroplasia.

Heath coined the term ROP in 1951. In 1951, Dr Kate Campbell observed that, in a smaller hospital each infant's family was charged for each tank of oxygen that was used and thus much less oxygen was administered, and there was a lower incidence of RLF. She concluded that, "normal oxygen environment required for full-term infant is abnormal for the premature infant".

INCIDENCE

The survival of ELBW-infants increased from 5-65% in the last 40 years, while in VLBW-infants, it increased from 35-90%. This increase in survival rates has lead to increasing the number of diagnosed ROP cases.

In the CRYO-ROP study, the incidence of the disease in a group of premature newborns, with a birth weight <1251gms was 65.8% and it was 81.6% for infants of less than 1000 g birth weight[16]. The overall incidence of more-severe ROP (prethreshold) was 36.9% among infants with ROP in the ETROP Study, whereas the incidence was 27.1% for patients in the CRYO-ROP Study who developed ROP[17].

Some study states that, the incidence and severity of ROP increases with decreasing gestational age and birth weight. The incidence of ROP in different studies done outside India was found to be 9.4%-38.9%[18-21].A study from the Indian subcontinent reveals the incidence to be 17.5%-46%[22-26]

The incidence of severe form of the disease known as Threshold disease is decreasing. There is an overall decrease in incidence of disease whenever there is an ongoing surveillance programme. Aggarwal and co-workers found a drop from 46 to 21% in their study over a period of 7 years[11].

There was a significant decrease in incidence of ROP in infants weighing more than 1250gm[20]. Similar observations were made in multicentre study in UK[27]. Nair[22] and colleagues, Gupta[28] and co-workers found no cases of ROP in babies weighing more than 1250gm.

PATHOGENESIS

NORMAL RETINAL VASCULAR DEVELOPMENT:

Ocular blood supply consists of development of angiogenesis, arteriogenesis, and vascularization. Angiogenesis is the formation of endothelial lined blood vessels. Arteriogenesis is the addition of smooth muscle cells to endothelial cells, forming intact arterioles. Vascularisation is the new arterialization of retina. The combination of these for forming the embryonic vascular tree is termed vasculogenesis.

The posterior segment of the eye has dual blood supply:choroidal and retinal. The choroidal nourishes the outer retina while the inner retina is supplied by the retinal circulation. Up to 16 weeks of gestation, both outer and inner retina is nourished by choridal blod supply, practically inner retina remains avascular. After 16 weeks of gestational age, the first blood supply to inner retina appears in the form of mesenchymal "spindle cells". These spindle cells arises from the adventitia of the hyaloid artery.The origins of the retinal circulation reside at the optic nerve head. The vasculogenic elements begin to spread out over the and vascularisation starts in a relatively concentric fashion out to the ora serrata [34]. Vessels reach the nasal ora first, because the fovea is the eye's center, thus optic nerve is nasal to the retinal center and uninterrupted vascularisation must reach the closer point first i.e.,nasal ora.

PATHOGENESIS OF ROP

At birth, fetal circulation involvesswitch from placental oxygenation to lung oxygenation. Oxygen saturation rises from mixed venous levels to arterial levels. Since the fetal lungs are immature,they are not capable of fully mature oxygen transfer. Medical intervention provides inhaled supplemental oxygen, enhancing the oxygen transfer. Several factors lead to a potential initially hyperoxic state: mixed venous oxygenation to arterial oxygenation; supplemental oxygen; immature but as yet undamaged lungs; and a low retinal metabolic rate of oxygen consumption. After birth, this relative hyperoxia begins to change. The lungs get damaged, alveolar – blood oxygen exchange is compromised, and retinal metabolic demand for oxygen rises according to embryologic events. This gives rise to relative hypoxia. This transition is not a smooth, linear one. There are undoubtedly dramatic swings during the gradual change over from hyperoxia to hypoxia.

Retinal vascularisation is modulated by VEGF. This process is acutely sensitive to relative states of hyperoxia and hypoxia. Hypoxia up-regulates VEGF and hyperoxia down-regulates its production. Along with VEGF, there are insulin like growth factor(IGF-1), basic fibroblast growth factor, and transforming growth factors associated with it.[33,36-39].

RISK FACTORS FOR DEVELOPMENT OF ROP[51]

ROP is a multifactorial disease. Based on the clinical and epidemiological studies, numerous risk factors have been proposed for ROP.

Definitive and well accepted factors

- Oxygen supplementation (Mechanical ventilation)
- Prematurity/ Gestational age/ Birth weight

Associated factors

- Apnea with bag/ mask ventilation Sepsis
- Blood transfusions / Exchange transfusions
- Methyl xanthine administration
- Respiratory distress syndrome
- Asphyxia / Hypoxia
- Shock
- Hypercarbia / Hypocarbia
- Acidosis / Alkalosis
- PDA / Indomethacin

- Vitamin E deficiency
- Intraventricular hemorrhage
- Light
- Maternal factors – Anaemia

PREMATURITY AND BIRTH WEIGHT

In the CRYO-ROP study, the incidence of the disease in a group of premature newborns with a birth weight <1251gms was 65.8% and 81.6% for infants of less than 1000 g birth weight[16]. In the ETROP (multi centric) study done 15 years later, the overall incidence of ROP was found to be 68% in babies with birth weight <1251 grams.. The incidence of ROP in different studies done outside India was found to be 9.4%-38.9%[18-21].A study from the Indian subcontinent reveals the incidence to be 17.5%-46%[22-26]. A Danish study found a statistically significant decrease in incidence of ROP in infants weighing more than 1250gm[20]. Gupta[28] and co-workers found no cases of ROP in babies weighing more than 1250gm. A review of literature reveals that, the incidence and severity of ROP increases with decreasing gestational age and birth weight.

Severe ROP is often encountered in babies with birth weight more than 1250 grams in developing countries based on the retrospective study done by Anand Vinekar[52] et al they suggested that, the western screening guidelines may require modifications before application in developing countries.

OXYGEN AND ROP

The excessive use of oxygen has been proved to be one of the main risk factor for the development of ROP. During this short transition period, the retina probably undergoes frequent and potentially wide swings of hyperoxia /hypoxia. The sickest infants have the most volatile transition phase of retinal oxygenation. The ultimate cause of ROP is related to the mismatch of tissue oxygen need and tissue oxygen supply.

ROP occurs also due to Sudden discontinuation of oxygen and duration of oxygen therapy. Gunn analyzed data from their low birth weight survivors and found a significant association between, the more severe grade of cicatricial disease and duration of oxygen therapy[54].Their finding concurred with the co-operative study of 1977, in which Kinsey emphasized that the strongest association with occurrence of ROP, apart from birth weight, was time in oxygen.

He also noted that, infants under 1200gm, concentration of oxygen administered was significantly associated with ROP . When comparing mean Pa02 levels in normal infants and in ROP infants, he found differences only in babies of low birth weight and only Pa02 levels greater than 150mmHg[53].

Hence, appropriate monitoring of actual Pa02 in at risk infants is

essential. A definite safe range for arterial Pa02 is not known. Until such guidelines are established, keeping Pao2

<100 mm Hg is recommended preferably between 50 and 70mm Hg and saturation between 90-95%[55].

VITAMIN E DEFICIENCY:

Vitamin- E is a fat soluble antioxidant and as a result it is able to scavenge free radicals derived from oxygen. Prophylactic vitamin E has been suggested for the management of retinopathy of prematurity (ROP) .this is because the premature infant and the retina are likely to be particularly vulnerable to the deleterious effects of these oxygen derived free radicals, as a result Three clinical trials[57-59] have document. The spindle cells, mesenchymal precursors of the inner retinal capillaries, are the primary inducers of the neovascularisation associated with ROP. Exposure of spindle cells to elevated oxygen tension increases their gap junction area. This stops the normal vasoformative process and eventually triggers the neovascularisation that is observed clinically 8–12 weeks later. Vitamin E supplementation suppresses gap junction formation and reduces the severity.

APNOEA

Apnoea independently increased the incidence of ROP. In a study by Kim et al[61], they found that frequent apnoeic attacks increased the progression of pre-threshold ROP to threshold ROP. In addition, pre-existing ROP also gets worsened by apnoea. A higher incidence of hypoxemia and apnoeic episodes requiring bagging was found among infants with severe ROP, than in a control group[26,54]. The babies with increased frequency of apnoea appeared to have longer duration of high pC02. Similarly in a study by Chen et al[62] they found that apnoea was one of the independent risk factors of ROP.

SEPSIS

Sepsis is an independent risk factor for the development of ROP. It may act through cytokines and endotoxins or by oxidative burst in the neutrophils consequent to infection. Agarwal[26] reported positive blood cultures in 67 percent of infants who later developed ROP, and in only 31 percent of infants with normal eyes. Liu PM et al fund that sepsis is the most significant factor contributing to ROP. Paediatric Research study found that, Candida sepsis is independently associated with increased severity of ROP and the need for laser surgery in ELBW infants.study done by Parupia H, et al[73] als stressed on the same point. Other studies also support these findings[54]. Thus,Its prevention and early control may reduce the incidence of ROP.

BLOOD TRANSFUSIONS

In recent years, the role of blood transfusions and iron intake as risk factors for ROP has been strongly emphasized[77,78]. Some studies suggest that anaemia per-se is a risk factor for ROP, while others show that a high haematocrit ratio and frequent blood transfusions are important independent risk factors[79-81].

The usual explanation is that, tissue (including retinal) oxygen levels are increased by transfusion, owing to the reduced affinity of adult haemoglobin to oxygen, as compared to fetal haemoglobin. An alternative hypothesis is that, damaging effects of blood transfusion on the retina are mediated by, an increase

in free iron load which may react with various intermediates of oxygen generating highly reactive oxygen radical. Otherwise, protection against free iron is provided by ceruloplasmin and transferrin, but in preterm infants with gestational age lower than 34 weeks, the levels of these binding proteins are very low, and rapid saturation of transferrin occurs[77,78].

A study done by Akter S et al[82] showed that, blood transfusion in first week of life and repeated blood transfusion resulting in large cumulative volume are very significantly associated with occurrence of ROP.

OTHER RISK FACTORS ASSOCIATED WITH ROP

In recent years, additional factors have been implicated in the evolution of ROP. The task of defining any of these factors in the setting of other major factors, such as low birth weight and early gestational age, is again formidable. Because oxidative injury contributes to the development of ROP, bilirubin has been suggested as a physiologically important antioxidant. However, a recent study found no definite association between bilirubin levels and severe ROP.

The use of dopamine in the management of hypotension in high risk prematurely born infants (birth weight < 1,000 gm) has been associated with increased risk for the development of threshold ROP. Thus more vigilant screening of high-risk infants requiring dopamine therapy, for systemic hypotension may be warranted[87].

It is hypothesized that replacement of fetal blood by adult blood, would reduce the overall oxygen affinity of haemoglobin and consequently promote the unloading of oxygen, to the tissues at relatively lower arterial oxygen levels. Several studies have shown that, transfusion of adult blood either by exchange transfusion or top-up transfusion is associated with ROP[22, 88]. In an effort to elucidate further the oxidative influence in the development of ROP, Papp and co- workers examined

the glutathione status of red blood cells in patients with ROP both in vivo and after an in vitro oxidative challenge. After an in vitro oxidative challenge, Infants with active ROP have the lowest levels of reduced glutathione (GSH), the highest levels of the oxidized form (GSSG), the highest GSSG/GSH ratios and the greatest fall in GSH. After an in vitro oxidative stress, defective glutathione recycling was found in patients with preceding ROP (not active ROP) It was suggested as a factor predisposing to oxidative haemolysis. The glutathione redox ratio was warranted as a biochemical screen for active ROP in premature infants[89].

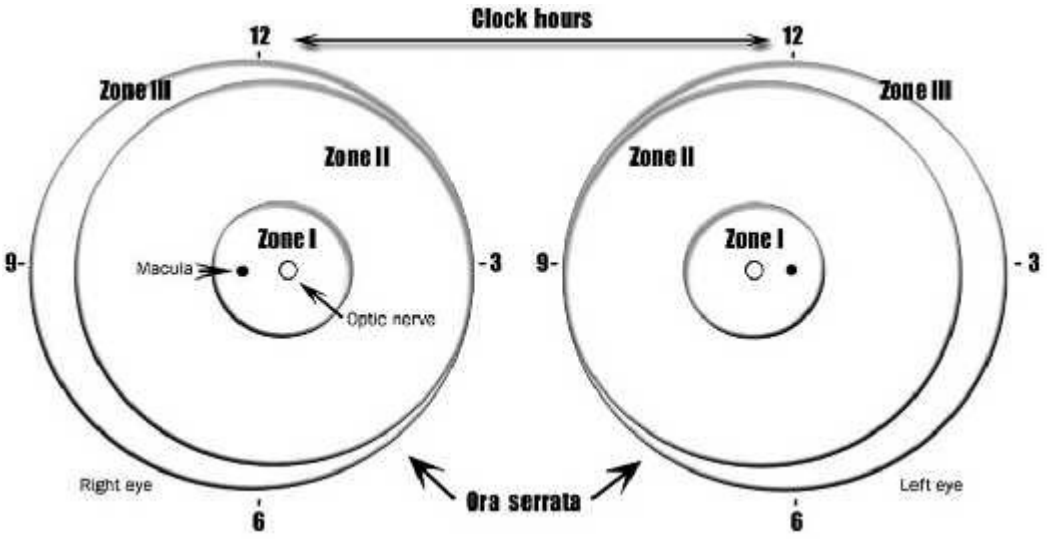
CLASSIFICATION OF ROP

INTERNATIONAL CLASSIFICATION OF ROP (ICROP)[15]:

A. Classification - Consists of five components.

1.Location refers to, how far the developing retinal blood vessels have progressed. The retina is divided into three concentric circles or zones.

Figure 1: International Classification of Retinopathy of Prematurity (ICROP) zones



ZONES

- Zone 1 consists of an imaginary circle with the optic nerve at the center and a radius of twice the distance from the optic nerve to the macula.

- Zone 2 extends from the edge of zone 1 to the equator on the nasal side of the eye and about half the distance to the ora-serrata on the temporal side.

- Zone 3 consists of the outer crescent - shaped area extending from zone 2 out to the ora serrata temporally.

STAGES OF ROP

Stage 1- A demarcation line appears as a thin white line that separates the normal retina from the undeveloped avascular retina .

Stage 2- A ridge of scar tissue with height and width replaces the line of stage 1. It extends inward from the plane of the retina.

Stage 3- The ridge has extra retinal fibro-vascular proliferation. Abnormal blood vessels and fibrous tissue develop on the edge of the ridge and extend into the vitreous.

Stage 4- Partial retinal detachment may result when scar tissue pulls on the retina.

- *Stage 4A* is partial detachment outside the macula, so that the chance for vision is good if the retina reattaches.
- *Stage 4B* is partial detachment that involves the macula, thus limiting the likelihood of usable vision in that eye.

Stage 5- Complete retinal detachment occurs. The retina assumes a funnel shaped appearance and is described as open or narrow in the anterior and posterior regions.

1. **Plus disease:** It is an additional designation, which refers to the presence of vascular dilatation and tortuosity of the posterior retinal vessels. This indicates a more severe degree of ROP and may be associated with iris vascular engorgement, pupillary rigidity, and vitreous haze. Plus disease, that is associated with zone 1 ROP is termed rush disease; this type of ROP tends to progress extremely rapidly.
2. **Extent -** refers to the circumferential location of the disease and is reported as clock hours in the appropriate zone.
3. **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.

B. **Definition of threshold and prethreshold ROP**:

- **Threshold ROP** is present if five or more contiguous or eight cumulative clock hours (30-degree sectors) of stage 3 with plus disease in either zone 1 or 2 are present. This is the level of severity at which the risk of blindness is predicted to approach 50% and thus treatment is recommended.

- **Prethreshold ROP** is any of the following : zone 1 ROP of any stage less than threshold ; zone 2 ROP with stage 2 and plus disease;

zone 2 ROP with stage 3 without plus disease; or zone 2 ROP at stage 3 with plus disease with fewer than the threshold number of sectors of stage 3. Infants with prethreshold ROP have a 1 in 3 chance of needing surgical treatment and a 1 in 6 chance of extreme loss of vision if treatment is not done promptly when threshold is reached. With therapy, they have a 1 in 12 chance of extreme visual loss[35].

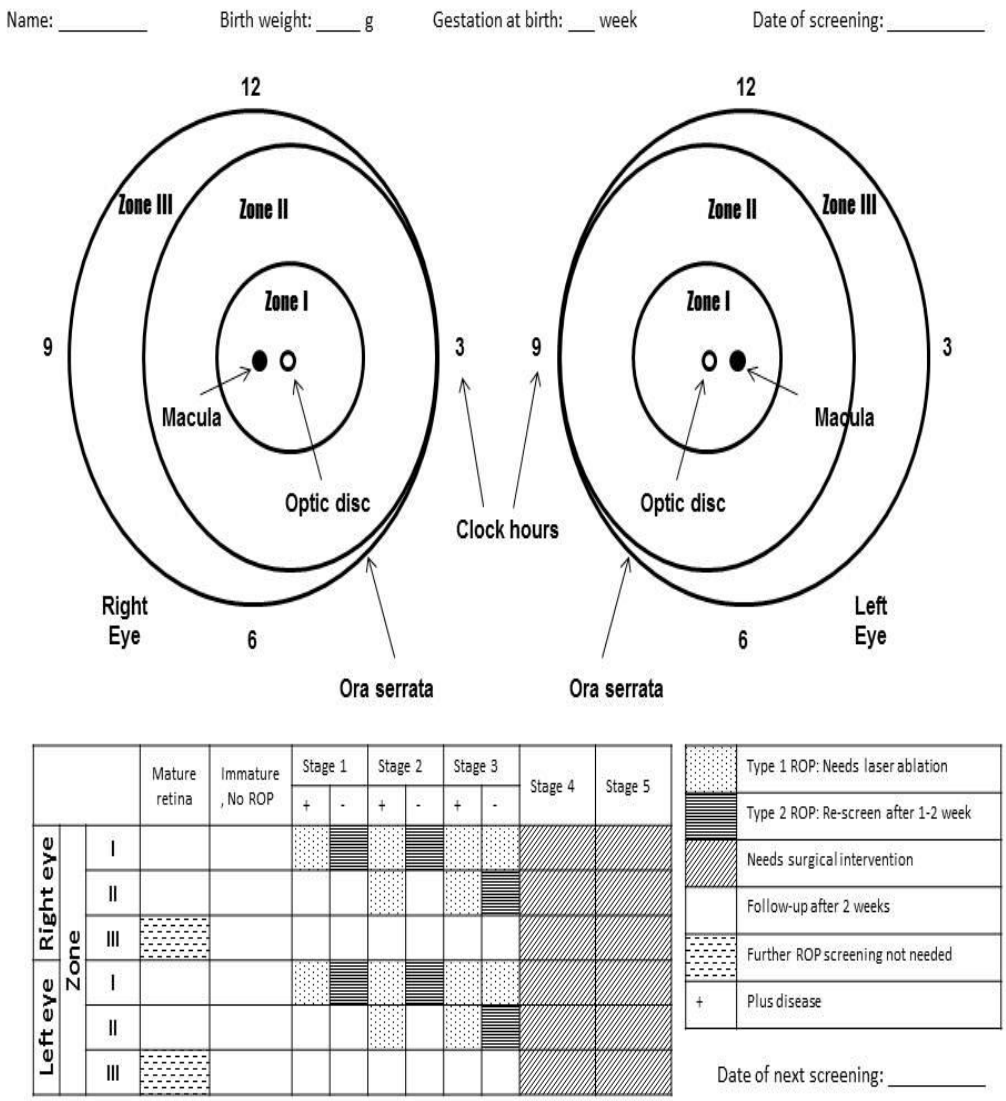
Aggressive posterior ROP (AP-ROP):

It is a rapidly progressing, severe form of ROP. If untreated, it usually progresses to stage 5 ROP. The characteristic features of this type of ROP are its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy. This may not have classical ridge or extraretinal fibrovascular proliferation. This rapidly progressing retinopathy has been referred previously as "type II ROP" and "Rush disease". Observed most commonly in Zone I, but may also occur in posterior Zone II.

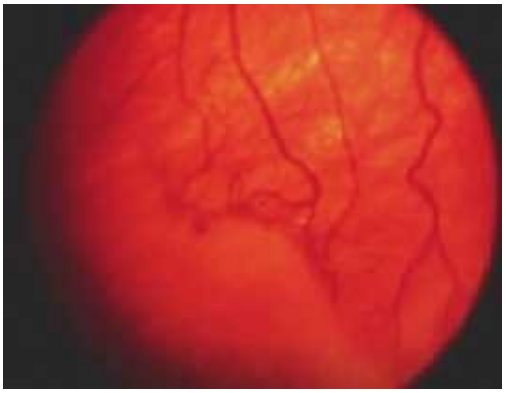
Table :1 Classification of Retinopathy of Prematurity

1. Location	Zone I	Circle with optic nerve at centre and a radius of twice the distance from optic nerve to macula
	Zone II	From edge of Zone I to the nasal ora serrata nasally and equator temporally
	Zone III	Lateral most crescent shaped area from Zone II to ora-serrata temporally
2. 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)
	Stage 5	Complete retinal detachment
3. Plus disease		Presence of dilatation and tortuosity of posterior retinal vessels. Associated with vitreous haze, pupillary rigidity
4. Extent		Extent of involvement of the retina as expressed as clock hours (30 degree sectors)
5.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

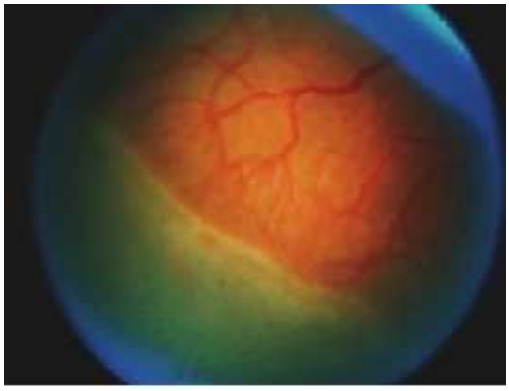
Figure 2: Classification of retinopathy of prematurity



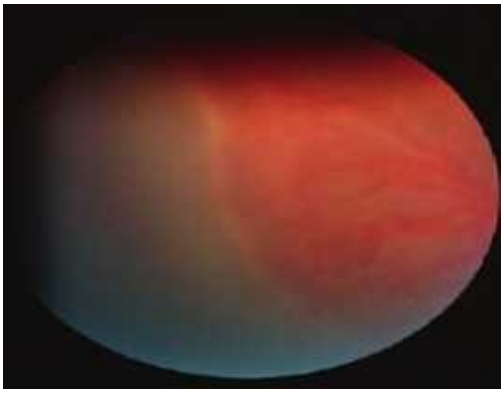
Stages of ROP:



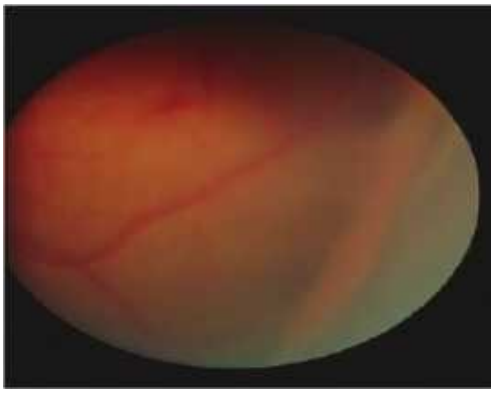
Photograph 1: Stage 1- Demarcation line



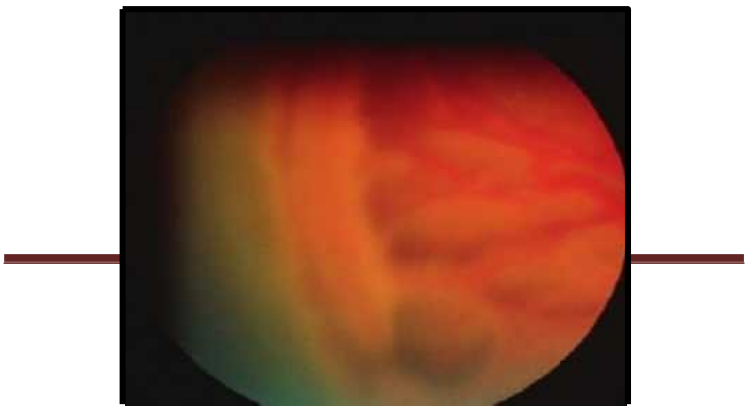
Photograph 2: Stage 2- Ridge



Photograph 3: Stage 3 ROP - Mild

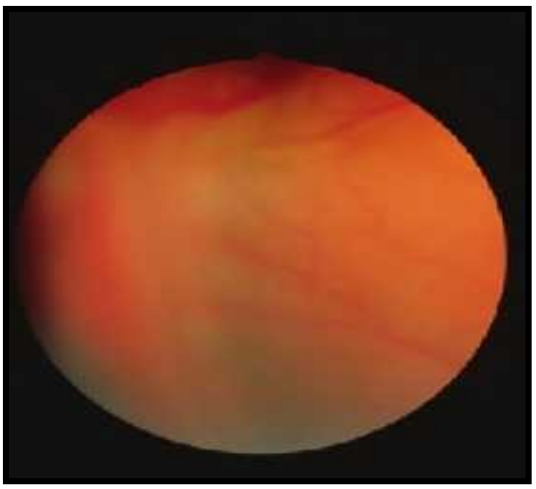


Photograph 4: Stage 3 ROP - moderate

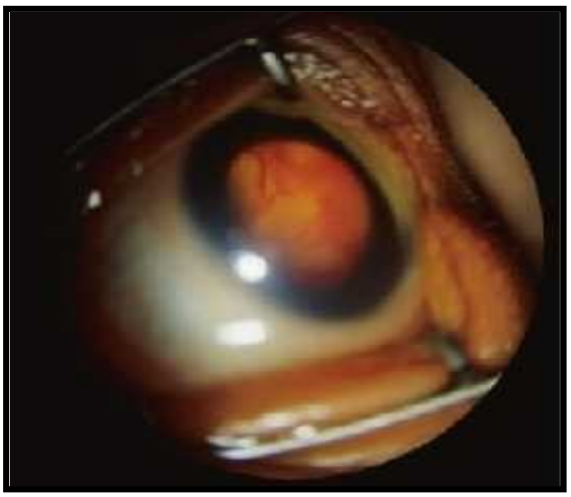


Photograph 3: Stage 3 ROP – Severe

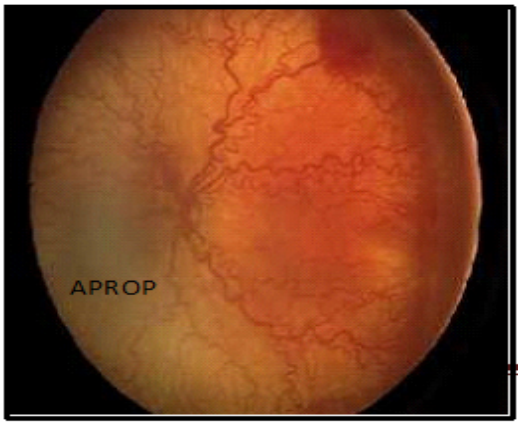
Stages of ROP: (Continue…)



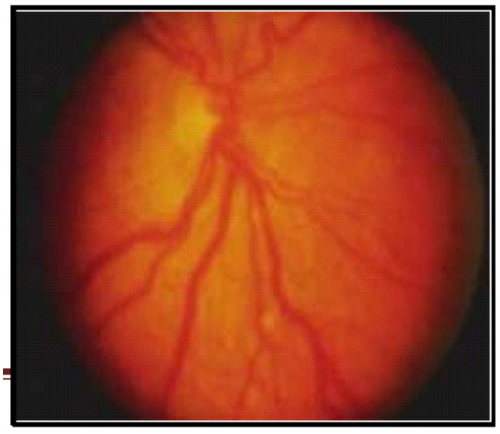
Photograph 6: Stage 4 ROP – Partial RD- Exudative and Tractional



Photograph 7: Stage 5 ROP – Open Funnel RD



Photograph 8: ROP – APROP



Photograph 9: Plus disease

DIAGNOSIS

Screening Window:

Progression of ROP follows a distinct time-table according to the post- menstrual age of the baby. Hardly any ROP is detected before 32 weeks of gestation. The median age for detection of stage 1 ROP is 34 weeks. Pre-threshold ROP appears at 36 weeks of post-menstrual age and threshold disease at 37 weeks. Vascularisation is complete by 40 weeks of gestation. Thus the crucial period for detection of ROP is from 32 weeks to 40 weeks of post-menstrual period. The critical phase is from; 34-35 weeks to 37-38 weeks age during which, the progression of the disease takes place and treatment may have to be instituted It may also be noted that, ROP usually does not develop before 2 weeks of postnatal age.

Babies to screen:

Selecting neonates for screening depends on incidence of ROP at different gestation ages. Based on current incidence and risk factors reported in Indian literature, following group of neonates should be screened.

- Babies with birth weight <1500 g

- Babies born at ≤32 weeks of gestation Selected preterm infants with a birth weight between, 1500 and 2000 g or gestational age of more than 32 weeks, with sickness requiring cardiorespiratory support, prolonged oxygen therapy, apnoea of prematurity , anaemia needing blood transfusion and neonatal sepsis or believed by their attending paediatrician or neonatologist to be at high risk. This 'third criterion' is important as it brings in many larger babies into the screening guidelines, without raising the screening parameters[90].

Follow up:

Follow-up examinations are done based on the retinal findings.

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

- 1to 2-week follow-up
    - Immature vascularisation: 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 vascularisation: Zone II—no ROP
    - Stage 1 or 2 ROP: Zone III
    - Regressing ROP: Zone III

Findings that suggest further examinations are not needed include:

- Zone III retinal vascularisation attained without previous Zone I or II ROP
- Full retinal vascularisation
- Postmenstrual age of 45 weeks and no Prethreshold disease (defined as stage 3 ROP in Zone II, any ROP in Zone I) or worse ROP is present
- Regression of ROP

SCREENING[91]:

Pupils are dilated with Phenylephrine 2.5% and Tropicamide 0.5%. One drop of Tropicamide is instilled every 10-15 minutes, for 4 times starting 1 hour before the scheduled time for examination. This is followed by Phenylephrine, one drop just before examination. Phenylephrine is available in 10% concentration; it should be diluted 4 times before use in neonates. Repeated instillation of phenylephrine is avoided for the fear of hypertension.

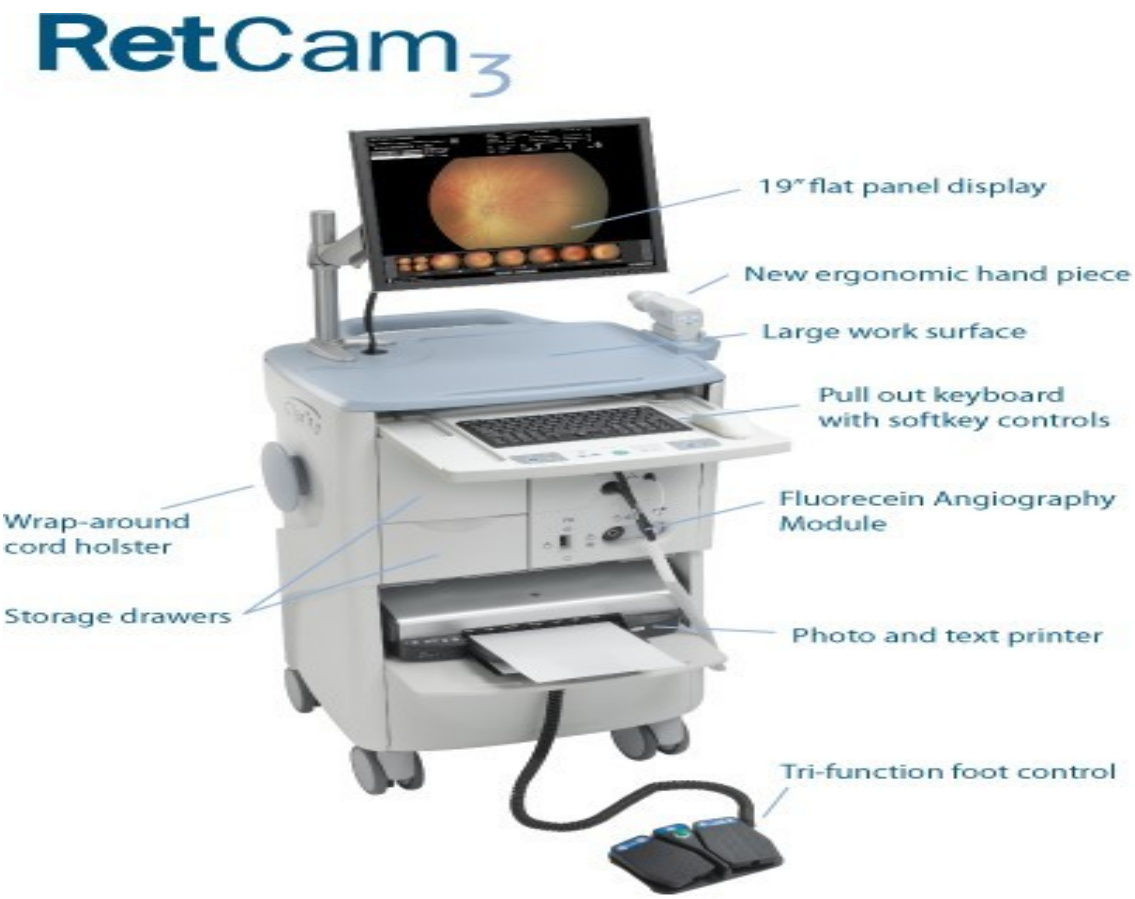
Screening of ROP involves, indirect ophthalmoscopy using 20 D or 28/30 D lens by an experienced ophthalmologist. After instilling a topical anesthetic drop like proparacaine, a wire speculum is inserted to keep the eye-lids apart. First, the anterior segment of the eye is examined to look for tunica vasculosa-lentis, pupillary dilation, and lens / media clarity; followed by the posterior pole, to look for plus disease; followed by, sequential examination of all clock hours of the peripheral retina. A scleral depressor is often used to indent the eye externally, to examine areas of interest, rotate and stabilize the eye.

Ophthalmological notes should be made after each ROP examination, detailing zone, stage and extent in terms of clock hours, of any ROP and the presence of any pre-plus or plus disease. These notes should include a recommendation for the timing of the next examination

(if any) and be kept with the baby's medical record.

ROP screening examinations can have short-term effects on blood pressure, heart rate and respiratory function in the premature baby[92].The examinations should be kept as short as possible and precautions should be taken.

RETCAM



Photograph 10: RETICAM

A wide-field digital camera (RetCam) capable of retinal imaging in preterm infants, has been evaluated as an alternative to indirect ophthalmoscopy for screening. Retinal images taken by camera can be stored, transmitted to expert, reviewed, analyzed and sequentially compared over time and are useful for telemedicine purposes. Studies comparing RetCam with the indirect ophthalmoscope, have reported variable sensitivity and good specificity[93].

However, due to high cost and due to limitations in diagnostic

sensitivity, specificity, and accuracy when image quality is poor, it is not recommended to replace bedside ophthalmoscopic examination. Digital fundus images can be used as a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy.

Place of screening:

All eligible babies were screened at Neonatal Intensive Care Unit.

Preparation of the child:

The pupils were dilated with a mixture of Phenylephrine 2.5% and Tropicamide 0.5% instilled 3 times at 10mins interval about 1 hour before the scheduled examination. Resistance to dilation was noted. Care was taken to wipe off any eye drops with sterile cotton that come out of eyes to cheeks and not to feed the baby immediately before examination as the child might vomit or aspirate.

Instruments used:

- Cordless Indirect ophthalmoscope with 20D lens.
- Pediatric wire speculum.
- Scleral indentor.

Procedure:

All preterm babies who satisfied any one of the inclusion criteria were taken up for the study.

The babies were enrolled into the study at birth. Parents were

explained the nature of the examination and informed consent was taken. Demographic history and risk factors like respiratory distress syndrome, sepsis, multiple blood transfusions, multiple births, apneic episodes and oxygen given was documented using a data collection instrument.

First examination was done at 4 weeks post natal age (age in weeks after birth) by taking all aseptic precautions in a temperature controlled room in the presence of a neonatologist.

Indirect ophthalmoscopic examination was done .One drop of topical paracaine eyedrops was used to anaesthetise the cornea. A pediatric wire speculum was used to keep the eyelids apart .After decreasing the room illumination the anterior segment was first visualized to look for tunica vasculosa lentis, pupillary dilatation and lens and media clarity. Then the posterior pole was examined for any Plus disease. A scleral indenter was used to visualize the periphery. The periphery was examined in all clock hours to look for the extent of changes from nasal to temporal retina. Care was taken not to put too much pressure on the globe. During examination, untoward neonatal complications were looked for and managed appropriately.

The changes in the retina were graded according to the International Committee for the Classification of Retinopathy of Prematurity (ICROP) guidelines-2005[15].

Follow up protocol:

If no ROP was detected at initial examination, the infants were re-evaluated once every two weeks until vascularisation was complete. If ROP was detected, the examinations were performed weekly for stage 1-2 disease and more frequently for stage 3 disease, till the disease started resolving or progressed to threshold stage. Babies showing evidence of regression were followed up till vascularisation was complete. Babies progressing to threshold stage were referred.

Treatment

Early Treatment of Retinopathy of Prematurity (ETROP) trial recruited neonates at 26 centres in the US and compared early treatment of high-risk prethreshold disease with conventional threshold treatment[94]. Four hundred and one babies meeting the criteria for 'high-risk' of an unfavourable outcome with prethreshold in at least one eye were randomized to receive either early or conventional treatment. The level of risk was determined by a risk analysis programme which used, among other factors, degree of ROP (stage, zone and presence of plus), rate of ROP progression, birth weight, gestational age and ethnicity to classify eyes as, either 'high-risk' (i.e. 15% chance) or ≥ 'low-risk' (<15% chance) of an unfavourable outcome without treatment. The results showed, an overall significant benefit for the early treatment of eyes with high-risk prethreshold disease. Based on results of ETROP, two new terminologies have been suggested:

Type 1 ROP:

- 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

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.

Treatment modalities :

Peripheral retinal ablation of avascular retina anterior to the ridge can be done by either cryotherapy or diode laser. Diode laser ablation has replaced cryotherapy, due to lower rate of postoperative ocular and systemic complications and less damage to the adjacent tissues compared to cryotherapy. Other advantages are that, the laser spots are visible during treatment, minimizing the risk of missing areas requiring treatment and that, laser equipment is portable allowing use outside of the operating theatre. The procedure can be carried out under general anesthesia or under sedation, depending on the feasibility and expertise. Treatment for ROP should include, the entire avascular retina anterior to the ridge, with burn spacing between 0.5 to 1 burn-widths apart.

CRYOTHERAPY:

Cryotherapy is an ablative procedure used in severe active ROP. It is aimed at, destroying avascular peripheral retina in order to stop the

rapidly growing vessels that are presumably being driven to grow by an angiogenic factor released by the peripheral avascular retina. The cryotherapy for Retinopathy of Prematurity (Cryo-ROP) is a major landmark study in the battle against ROP. The Cryo-ROP study[53] recommended cryotherapy for threshold ROP, defined as 5 contiguous or 8 cumulative clock-hours of stage 3 plus ROP in zone I and zone II. The technique of cryotherapy involves using the cryo probe to create contiguous cryo marks on the avascular retina. Treatments are performed under continuous monitoring of heart rate, respiratory rate, blood pressure and oxygen saturation. General endotracheal tube anaesthesia is preferred. Cryotherapy is administered with a cryotherapy probe, such as a hammer head-shaped pediatric probe. Continuous cryotherapy is performed under direct observation of the fundus, avoiding over treatment and re treatment. After the cryo treatment, patients can be discharged home on a topical steroid, cycloplegic and antibiotic on the same day, if not anaesthetized[95].

Laser Photocoagulation:

The use of indirect laser via an ophthalmoscope, for retinal photocoagulation in the treatment of ROP has been established. McNamara and coworkers[95] conducted a prospective clinical trial, that randomly assigned infants with threshold ROP to cryotherapy versus

argon laser photocoagulation and showed that infants treated with laser had less ocular inflammation, fewer systemic complications, and no significant difference in effectiveness as compared with those treated with cryotherapy. In addition, general anesthesia typically was not required for infants treated with laser (27% of infants in the Cryo-ROP study underwent general anesthesia). Some experts in ROP have also advocated earlier intervention with laser therapy in eyes with ROP, especially when there is plus disease in any zone (particularly in zone I) and vitreous haze.

Trans-scleral diode laser photocoagulation has been evaluated for the treatment of threshold ROP and results suggested that, it is as effective in the treatment of threshold ROP as is transpupillary diode laser photocoagulation. Trans - scleral diode laser photocoagulation seems to be an advantageous treatment method, if trans-pupillary treatment bears an increased risk of cataract formation[57].

Pre-anesthetic medication:

Oral feeds should be discontinued 3 hours prior to the procedure. Baby should be started on intravenous fluids, and put on cardio-respiratory monitor. Dilatation of pupil is done by using 0.5% Tropicamide and 2.5% Phenylephrine as described in the section on protocol for screening.

Anesthesia/ Sedation:

Topical anaesthesia alone provides insufficient analgesia for ROP treatment and should not be used. Babies may be treated under adequate sedation and analgesia in an operation theatre, if this can be arranged in a timely way. If shifting to operation theatre is not possible or is causing delay in treatment, babies may be treated more rapidly in the neonatal unit under adequate sedation and analgesia.

Procedure:

Both the eyes can be treated at the same sitting time, unless contraindicated by instability of the baby. If baby is not tolerating the procedure, consider abandoning the procedure for the time being. Vital signs and oxygen saturation should be monitored very closely.

Monitoring after laser therapy:

After laser therapy, first examination should take place 5-7 days after treatment and should be continued at least weekly for signs of decreasing activity and regression. Re-treatment should be performed usually 10-14 days after initial treatment, when there has been a failure of the ROP to regress.

Post-operative care:

The baby should be closely monitored. If condition permits, oral

feeds can be started shortly after the procedure. Premature babies, especially those with chronic lung disease may have an increase or re-appearance of apneic episodes, or an increase in oxygen requirement. Therefore they should be carefully monitored for 48-72 hours after the procedure. Antibiotic drops (such as chloramphenicol) should be instilled 6-8 hourly for 2-3 days.

Future therapeutic targets[96]:

The discovery of the importance of VEGF and IGF-1 in the development of ROP is a step forward in our understanding of the pathogenesis of this disease. These studies suggest a number of ways to intervene medically in the disease process. The use of anti-VEGF therapy is the first medical treatment for neovascularisation in age-related macular degeneration and is likely to be useful for proliferative retinopathy. However, prevention of vessel loss will be even more important in the treatment of ROP, since the extent of the second destructive phase of ROP is determined by the amount of vessel loss in the first phase. The finding that, late development of ROP is associated with low levels of IGF-1 after premature birth suggests that, physiological replacement of IGF-1 to levels found in-utero, might prevent the disease by allowing normal vascular development. In addition, the use of a specific agonist to VEGFR-1, PIGF-1, might be used early in the disease process to prevent vessel loss without promoting proliferative disease. The current understanding of ROP pathogenesis also makes clear that, timing is critical in any medical intervention, since

the two phases of ROP require very different approaches. Inhibition of either VEGF or IGF-1 early after birth can prevent normal blood vessel growth while, at the second phase, might prevent pathological neovascularisation. Similarly, providing VEGF or IGF-1 early on, might promote vessel growth, whereas late supplementation in the neovascular phase could exacerbate the disease. In the fragile neonate, any intervention must be made very carefully to promote normal physiological development of both blood vessels and other tissues.

PREVENTION

Prevention can be subdivided into the prevention of premature birth, eliminating ROP at the source; optimizing neonatal care, eliminating ROP by facilitating normal physiologic maturation; and preventing or minimizing ROP itself. The statistics on premature birth are not encouraging. Public health success would provide the greatest social, economic, and medical benefit but unfortunately is often not well funded. Maximizing neonatal care means mimicking the in-utero environment as much as possible.

Prenatal steroids

Use of prenatal steroids is a well-known approach to prevent respiratory distress and intraventricular hemorrhage, two important risk reduced occurrence of ROP, perhaps because it saves smaller babies who are at higher risk of developing ROP, but, as it reduces sickness level in preterm infants, prenatal steroids are likely to reduce severe ROP.

Judicious oxygen therapy

Oxygen is a drug and it should be used judiciously. Each neonatal unit should have a written policy regarding when and how to use oxygen and target saturations.

If a preterm neonate <32 weeks gestation needs resuscitation at birth, inhaled oxygen concentration.

(FiO2) should be titrated to prevent hyperoxia and achieve gradual increase in oxygen saturation.

(70% at 3 minute and 80% at 5 minute after birth).21 During acute care of a sick preterm neonate, ROP is more likely to develop if partial pressure of oxygen in arterial blood is more than 80 mm Hg.

Oxygen level in blood should be continuously monitored using pulse oximetry keeping a saturation target of 90% to 93%, with limits set at 88% and 95%.

It has been observed that if oxygen saturation in a baby on oxygen therapy is kept between 85% and 93%, in about 90% samples partial pressure of oxygen is in desirable range (40 to 80 mm Hg).It is important that a work culture is inculcated wherein physicians and nurses respond to monitor alarms.

Judicious use of blood transfusions

Transfusion of packed RBCs is another risk factor of ROP. Adult RBCs are rich in 2,3 DPG and adult

What is evidence?

A large scale RCT (SUPPORT trial) indicated that maintaining low saturations (85% to 89%) compared to high saturations (91% to 95%) in preterm infants<28 week did not reduce composite outcome of death or severe ROP but it resulted in lower severe ROP and higher death rates. Therefore it is recommended that saturations in preterm neonates be maintained between 90% and 95%. Saturations should be monitored in preterm infants receiving oxygen therapy to prevent hyperoxia or hypoxia.

Hb binds less firmly to oxygen, thus releasing more oxygen to the retinal tissue. Packed cell transfusions should be given when hematocrit falls below following ranges:

- Ventilated infants: 40%
- Infants with cardio-pulmonary disease but not on ventilators: 35%.
- Sick infants but no cardiopulmonary instability: 30%,
- Symptomatic anemia (tachycardia >180/minute or respiratory rate > 60 for ≥ 24hour, doubling of the oxygen requirement in last 48 hours, lactate > 2.5 mEq/L or acute metabolic acidosis with pH

<7.20 or weight gain less than 10 grams/kg/day over 4 days while receiving al/kg/day): 25%

- Asymptomatic anemia:20%.

Bevacizumab

Intravitreal injection of bevacizumab, a neutralizing anti-VEGF molecule has been demonstrated to diminish the neovascular response significantly in animal models[105]. However, due to uncertainties with respect to the dosing, frequency, timing, and adjunct therapies to be used and potential to cause serious systemic adverse effects, use of bevacizumab is not recommended outside the scope of clinical trial.

Other interventions

Supplementation of high doses of Vitamin E or reduced ambient light exposure is not associated with reduced incidence of ROP. In neonates with early stages of ROP administration of supplementation oxygen to achieve oxygen saturation in supra-physiological range and to reduce retinal hypoxia is not associated with halt in progression of ROP.

AUDITING

Following outcomes should be regularly audited in units with ROP screening and treatment programme.

- **Completeness of screening program:** Percentage of eligible babies who receive at least one ROP eye examination.
- **Timing of first screen:** Percentage of eligible babies receiving first ROP screening exam by 4 weeks of postnatal age.
- **Timing of treatment:** Percentage of babies needing ROP treatment for their ROP who are treated within 48 hours of the decision to treat being made.

METHODOLOGY

Source of Data: All preterm infants born with a birth weight of ≤1500 to 2000grams with risk factor at Government Mohan Kumaramangalam Medical College Hospital, Salem.

Method of collection of Data:

A data collection instrument was used in which data was collected

1. Hospital records
2. Examination of the infant

STUDY DESIGN:

Longitudinal study

Study period:

One year -1st March 2016 to 31st March2017.

Sample size: Sample size for incidence with specified confidence level and specified relative precision

Method of Statistical Analysis:

The following methods of statistical analysis have been used in this study.

1. The results for each parameter (numbers and percentages) for discrete data and average (mean + standard deviation) for

continuous data are presented in Tables and Figures. The proportions were compared using Chi-square test of significance.

Chi-Square ($\chi 2$) test for (2 x 2 tables)

GROUP	**Attribute Characteristic finding**		
	ABSENT	**PRESENT**	**TOTAL**
Group 1	A	B	a+b
Group 2	C	D	c+d
Total	a+c	b+d	N

a,b,c,d are the observed numbers.

N is the Grand Total

χ^2 with 1 DF $\quad \frac{N(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)}$

DF=(r-1)*(c-1), where r=rows and c=columns

DF= Degrees of Freedom (Number of observation that are free to vary after certain restriction have been placed on the data)

2. **Student "t' test.**

The student't' test was used to determine whether there was a statistical

difference between male and female subjects in the parameters measured. Student's t test is as follows:

$$t = \frac{\bar{x}_1 - \bar{x}_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \quad \text{---} \quad t_{n1+n2-2} \quad \text{Where } s^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{(n_1 + n_2 - 2)}$$

3. The association between potential related risk factors with ROP and without ROP were studied initially through an Univariate analysis. The categorical variables were assessed using Pearson chi-square and Yates correction applied where needed. Odds Ratio (OR) and 95% Confidence Interval (CI) was calculated. To estimate the independent effect of the factors that were significantly associated with ROP and without ROP the confounding effect they may have on each other, logistic regression analysis was done. The variables were included if their respective univariate analysis yielded P <0.10. A backward stepwise elimination procedure based on the likelihood statistics (using removal probability of 0.10 and considering the change in classification accuracy) was also performed to identify the best subset of variables. In the entire test, the "*p*" value of less than 0.05 was accepted as indicating statistical significance.

RESULTS

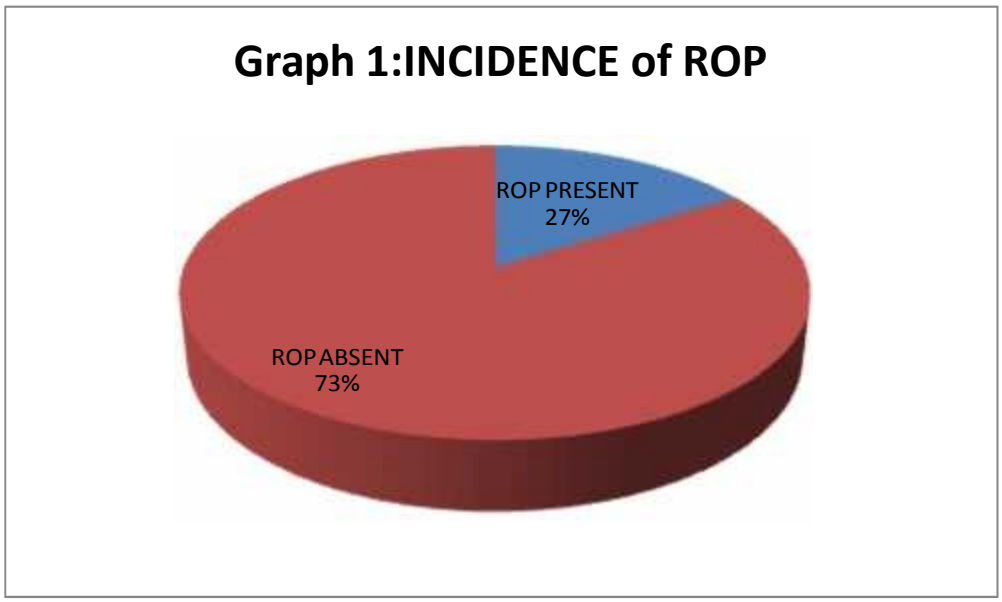
INCIDENCE

100 babies who fulfilled the inclusion criteria were screened and 27 babies were *found* to have ROP. The incidence of ROP in this study is 27%.

Table 2: Incidence of ROP

ROP	No.	%
PRESENT	27	27%
ABSENT	73	73%
TOTAL	100	100

Graph 1:INCIDENCE of ROP



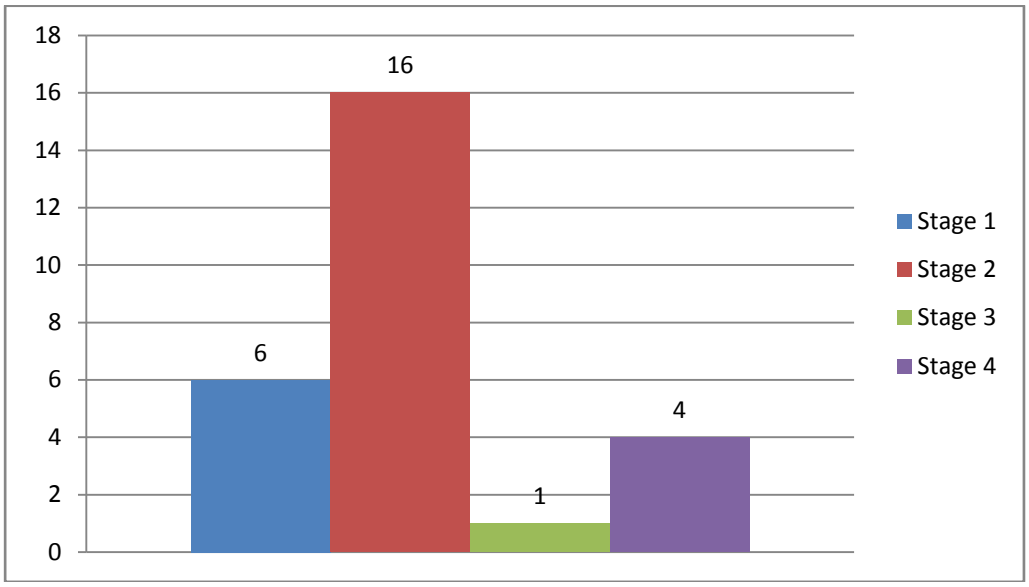
STAGES OF ROP:

Out of 27 babies with ROP, only 6 babies(22.22%) were in stage 1, 16 babies(59.26%) were in stage 2, 1 baby(3.70%) was in stage3 and 4 babies (14.82%) developed APROP (stage4).

Table 3: Stages of ROP

	RETINOPATHY OF PREMATURITY STAGES				
	1	2	3	APROP	TOTAL
ROP PRESENT	6	16	1	4	27
%	22.22%	59.26%	3.70%	14.82%	100%

Graph 2: Stages of ROP



SEX DISTRIBUTION:

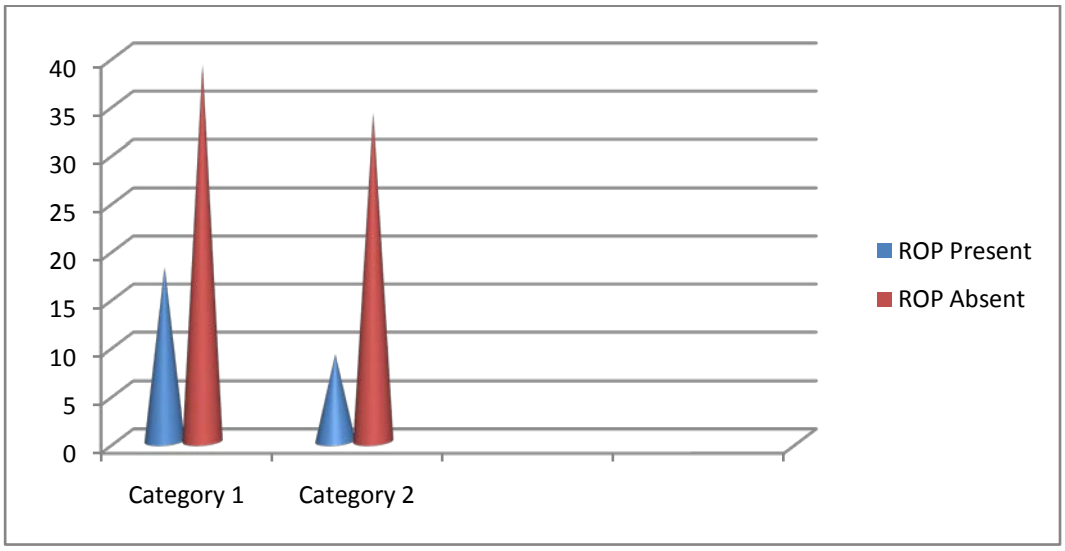
Out of 100 babies screened, 57 were male and 43 were female. Among 57 male babies 18 (31.58%) developed ROP and out of 43 female babies 9 (20.90%) had ROP. In this study gender *did not* significantly influence the incidence (p=0.82) of ROP.

Table 4: Sex distribution of ROP babies

	SEX and ROP			
		ROP		
		PRESENT	ABSENT	TOTAL
SEX	MALE	18(31.58%)	39(68.42%)	57
	FEMALE	9(20.90%)	34(79.10%)	43
	TOTAL	27	73	100

P value =0.82

Graph 3: Sex distribution of ROP babies



BIRTH WEIGHT AND ROP

The birth weight of the ROP babies ranged from 800gm-1500 gm (mean 1280 gm).

Lower birth weight was *significantly associated* with birth weight < 1500gm.

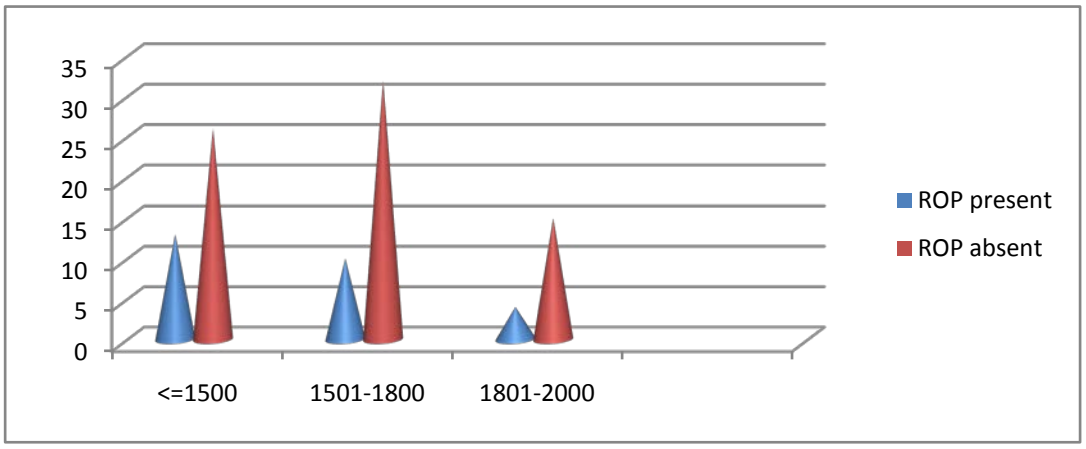
This study included the birth weight upto 2000gm, p value is 0.48 which is insignificant

The incidence of ROP was 48.15% in babies weighing ≤ 1500gm at birth, And more than 1500gm -2000gm the incidence was 51.85%.

Table 4: Distribution as per birth weight

	DISTRIBUTION AS PER BIRTH WEIGHT			
		ROP		
		PRESENT	ABSENT	TOTAL
BIRTH WEIGHT	<=1500	13	26	39
	1501-1800	10	32	42
	1801-2000	4	15	19
	TOTAL	27	73	100

Graph 4: Distribution as per birth weight



GESTATIONAL AGE AND ROP:

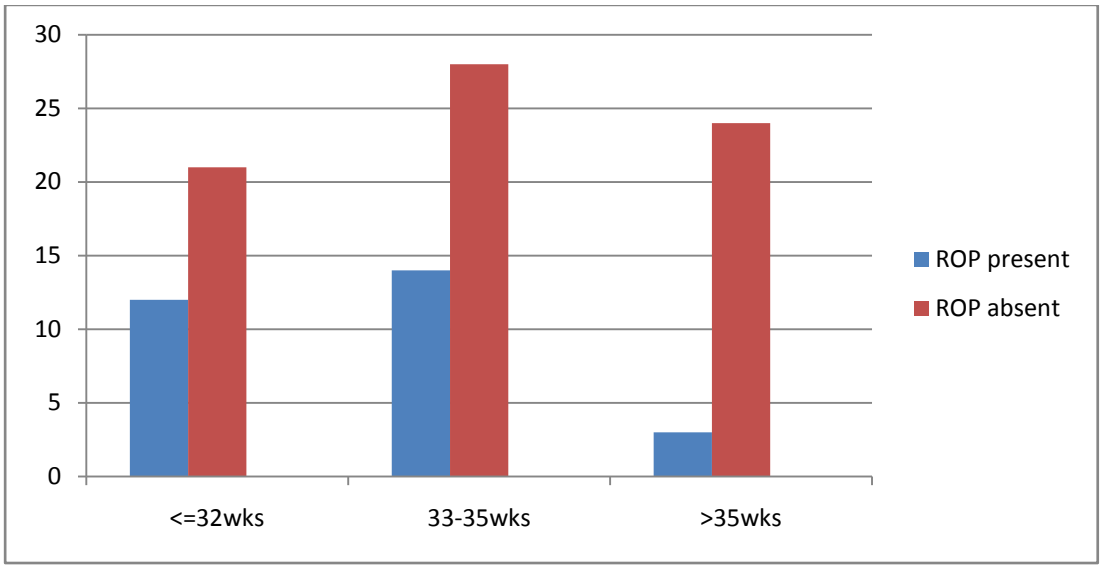
The incidence of ROP was 36.36% in babies born ≤ 32 weeks of gestational age. Gestational age was *found to be a significant* risk factor for the development of ROP (*p*=0.011).

Table 5: Distribution of gestational age and ROP

	DISTRIBUTION OF GESTATIONAL AGE			
		ROP		
		PRESENT	ABSENT	TOTAL
GESTATIONAL AGE	<=32	12(36.36%)	21(63.64%)	33
	33-35	14(33.33%)	28(66.67%)	42
	>35	1(4.00%)	24(96.00%)	25
	TOTAL	27	73	100

p value=0.011

Graph 5: Distribution of gestational age and ROP



OXYGEN AND ROP:

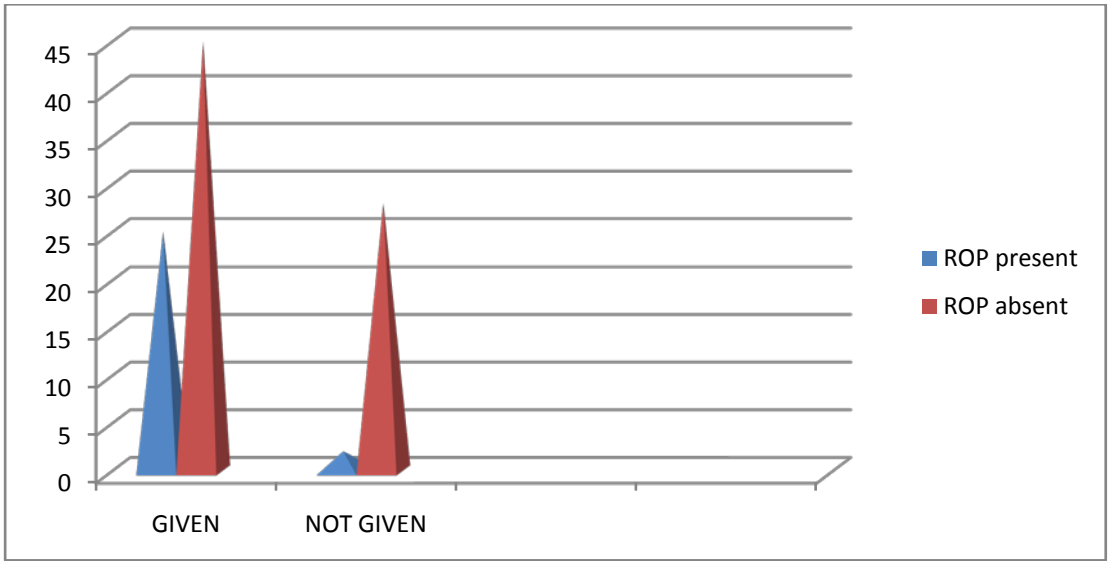
Out of 100 babies screened 70 were given O2 and 25 (35.71%) babies developed ROP. Oxygen administration *was a significant risk factor* for the development of ROP (p = 0.001).

Table 6: OXYGEN AND ROP

	OXYGEN AND ROP		
		ROP	
OXYGEN		Present	Absent	Total
	Given	25(35.71%)	45(64.29%)	70
	Not Given	2(6.67%)	28(93.33%)	30
	Total	27	73	100

p value = 0.001

Graph 6: OXYGEN AND ROP



SEPSIS AND ROP:

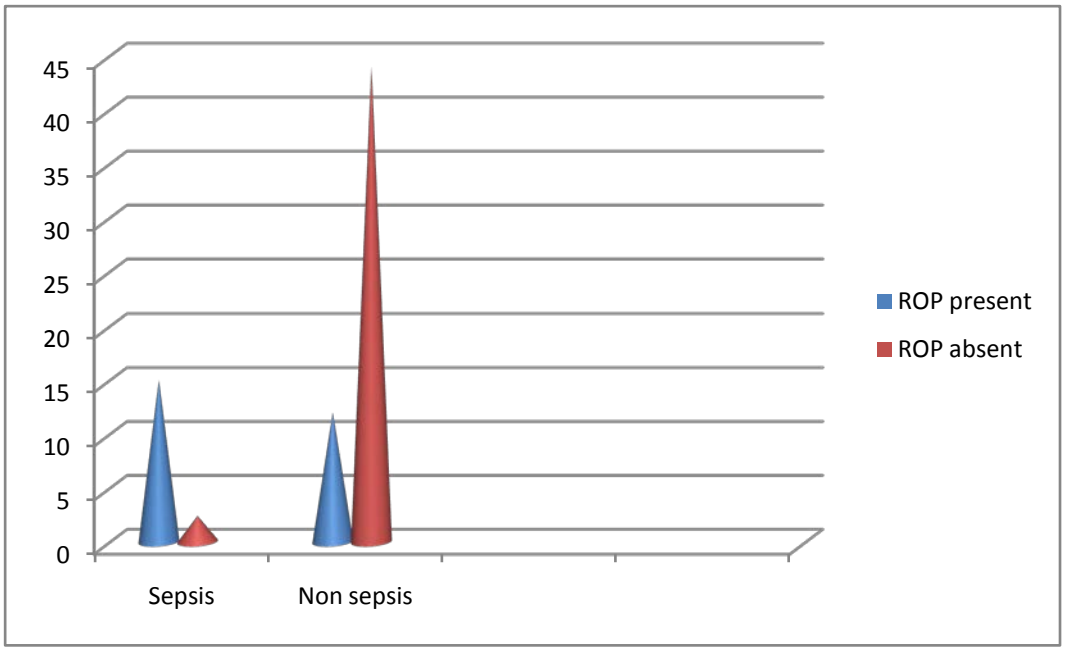
Out of 100 babies screened, 44 had sepsis and 15 babies (34.1%) developed ROP. Sepsis was *not a significant risk factor* for the development of ROP in this study (p=0.16).

Table 7: SEPSIS AND ROP

	SEPSIS AND ROP			
		ROP		
		Present	Absent	Total
SEPSIS	Present	15(34.1%)	29(65.9%)	44
	Absent	12(21.4%)	44(78.6%)	75
	Total	27	73	100

p value = 0.16

Graph 7: SEPSIS AND ROP



TRANSFUSION

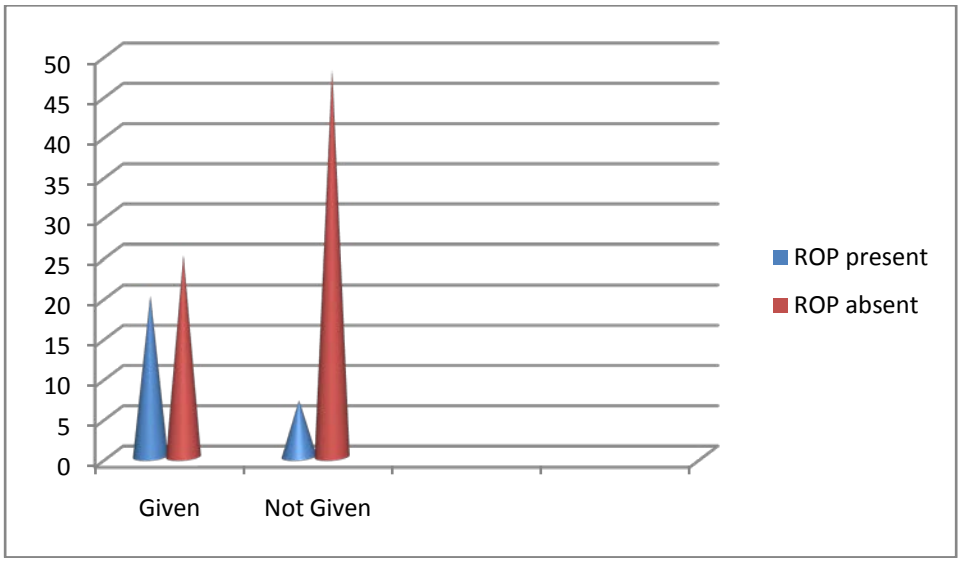
Out of 100 babies screened, 45 were given transfusion and 20(44.44%) developed ROP. Transfusion *was found* to be a significant risk factor for the development of ROP in this study (p=0.004)

Table 8: TRANSFUSION AND ROP

	TRANSFUSION AND ROP			
		ROP		
		PRESENT	ABSENT	TOTAL
TRANSFUSION	GIVEN	20(44.44%)	25(55.56%)	45
	NOT GIVEN	7(12.73%)	48(87.27%)	55
	TOTAL	27	73	100

p value = 0.004

Graph 8: TRANSFUSION AND ROP



APNOEA OF PREMATURITY AND ROP:

Out of 100 babies screened, 39 babies had AOP and 11(28.21%) developed ROP. AOP *was found* to be a insignificant factor for the development of ROP in this study (p=0.8).

Table 9: APNOEA OF PREMATURITY AND ROP

	APNOEA OF PREMATURITY AND ROP			
		ROP		
		PRESENT	ABSENT	TOTAL
AOP	PRESENT	11(28.21%)	28(71.79%)	39
	ABSENT	16(26.23%)	45 (73.77%)	61
	TOTAL	27	73	100

p = 0.8

Graph 9: APNOEA OF PREMATURITY AND ROP

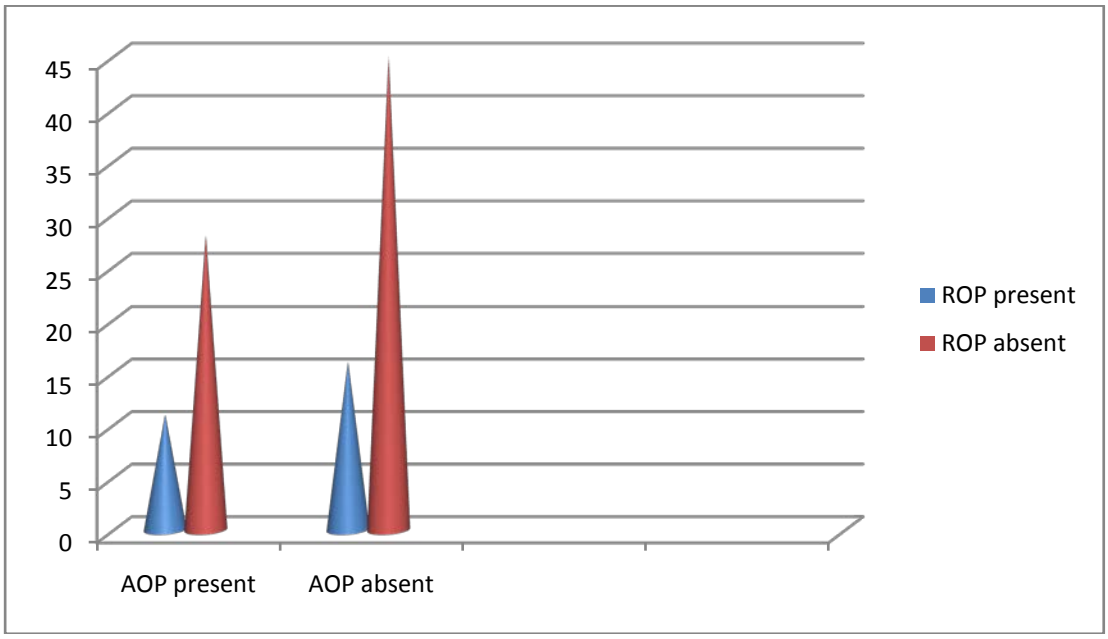


Table 10: Analysis of risk factors

Gestational age	*p*= 0.011
Birth weight	*p* = 0.48
Oxygen	*p* = 0.001
Sepsis	*p* = 0.16
Transfusion	*p* = 0.04
Apnoea	*p=0.8*

DISCUSSION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting premature infants. It is one of the most common causes of visual loss in children. It can lead to lifelong vision impairment and blindness.

Out of 45 million blind people in the world today, there are about 1.4 million blind children. ROP afflicts over 3,00,000 infants worldwide[2] .In developing countries like India, the incidence of ROP has been reported at 24 – 47 % among high risk preterm infants[3]. Among the preventable causes of blindness in children (57%), ROP figures very high in the agenda. Low birth weight and gestational age were found to be the most important risk factors for the development of ROP.

We screened babies admitted to our NICU with birth weight ≤ 1500g and gestation ≤ 32 weeks. Infants with birth weight >1500g and gestation more than 32 weeks were screened only if they had additional risk factors. In an article, Chawla et al[91], have suggested the same screening.

INCIDENCE:

With neonatalogical units equipped with the state of art technological background and highly qualified personnel providing optimum care of extremely immature newborns, ROP incidence is on a rise.

The overall incidence in the present study was found to be 27%, with only one case of severe ROP (APROP). It is of current knowledge that, aggressive posterior ROP seems to occur especially among smaller and more immature neonates .In our study the baby which developed APROP, the birth weight was 1500 grams and gestational age was 33 weeks. In the CRYO-ROP study, the incidence of the disease in a group of premature newborns with a birth weight <1251gms was 65.8% and 81.6% for infants of less than 1000 g birth weight[16]..

A review of literature reveals that, the incidence and severity of ROP increases with decreasing gestational age and birth weight. The incidence of ROP in different studies done outside India was found to be 9.4%-38.9%[18-21].A study from the Indian subcontinent reveals the incidence to be 17.5% - 46%[22-26] comparable to the present study. Patil et al[25] in 1997 reported overall incidence as 17.5% and no severe ROP. They studied 40 babies with <32wk or < 1250gms.

Maheshwari et al[24] in 1996 reported overall incidence as 20% and severe ROP as 7%. They studied 66 babies with <35wk or < 1500gms. Gupta et al[28] in 2003 reported overall incidence as 21.7% and severe ROP as 5%. They studied 60 babies with ≤ 35wk or ≤1500gms. Dutta et al[88] screened 108 babies of ≤32 wk or ≤1700gms and reported overall incidence as 21%.

The incidence of severe form of the disease (Threshold disease) is decreasing A Danish study[20] found a statistically significant decrease in incidence of ROP in infants weighing more than 1250gm. Agarwal and co-workers[11] found a drop from 46 to 21% in their study over a period of 7 years.. Similar observations were also made in a multicentre study in UK[27]. Nair[22] and colleagues, Gupta[28] and co-workers found no cases of ROP in babies weighing more than 1250gm.

TABLE 11: Comparison of incidence of present study with other national and international studies

INDIAN STUDIES			
	G AGE	BT WT	INCIDENCE
1.Rekha[23],1996	≤ 34	<1500	46%
2.Maheshwari[24],1996	<35	<1500	20%
3.Patil[25],1997	<32	<1250	17.5%
4.Agarwal[26],2002	<35	<1500	20%
5.Gupta[28], 2003	≤35	≤1500	21.7%
6.Nair[22],2003	≤32	<1500	25.4%
7.Present study	≤32-35	≤1500-2000	27%
INTERNATIONAL STUDIES			
1.Hussain[29],1999	<32	<1500	21.3%
2.Fledelius[20],2000	<32	<1500	9.4%
3.Blair[21], 2001	<30	<1250	38%
4.Conarth[30],2004	≤32	<1750	10%
5.Shah[18] ,2005		<1500	29.2%
6.Fortes[31],2007		≤1000	48.9%

RISK FACTORS:

In our study birth weight, gestational age, oxygen, transfusion and apnoea of prematurity were found to be significant risk factors on Chi Square analysis. On univariate analysis, risk factors associated with ROP were oxygen, and transfusion. Using the forward method oxygen and transfusion were also found to be significant.

Birth Weight and Gestational age:

In our study both low birth weight (p=<0.48) and prematurity (p= 0.011) were found to be significant risk factors for the development of ROP.

The birth weight of the ROP babies ranged from 800-1500 gm (mean 1280gm) Lower birth weight was insignificantly associated with this study because birth weight included upto 2000gms,whereas significant upto 1500gms. The incidence of ROP was 48.15% in babies weighing ≤ 1500gm at birth.

The incidence of ROP was 26.32% in babies born ≤ 32 weeks of gestational age. Gestational age was found to be a significant risk factor for the development of ROP (p=0.011) in this study.

Oxygen:

In our study oxygen was found to be significant risk factor for the development of ROP on Chi square analysis (p=0.005), on univariate analysis and also on multivariate analysis. Out of 100 babies screened 59 were given O2 and 15 (25.42%) babies developed ROP. The causal link between ROP and supplemental oxygen has been confirmed by controlled trials and clinical studies. Gunn analyzed data from their low birth weight survivors and found a significant association between, the more severe grade of cicatrical disease and duration of oxygen therapy[54].Kinsey noted that, concentration of oxygen administered was significantly associated with ROP in infants under 1200gm. When comparing mean Pa02 levels in normal infants and in ROP infants, he found differences only in babies of low birth weight and only Pa02 levels greater than 150mmHg. However, a safe level of oxygen usage has not been defined, keeping Pao2 <100 mm Hg is recommended, preferably between 50 and 70mm Hg and saturation between 90-95%. Preliminary work has suggested that, continuous oxygen monitoring may reduce the incidence of ROP.

Table 12: Comparison of oxygen as a risk factor of ROP in different studies

Study	p-value
Gupta[28] et al	0.002
Rekha23et al	0.005
Present study	0.001

CONCLUSION

1. The present study reflects the problem of ROP with various risk factors in a tertiary care centre.

2. The incidence of ROP in the present study is 27%.

3. Out of 27 babies with ROP, only 6 babies(18.75%) were in stage 1, 16 babies(68.75%) were in stage 2,1 baby(6.25%) was in stage3 and 4 baby(6.25%) developed APROP.

4. The birth weight of the ROP babies ranged from 800-1500 gm (mean 1.32 gm) lower birth weight was significantly associated with increased incidence (p = 0.48) of ROP. The incidence of ROP was 48 % in babies weighing ≤ 1500gm at birth.

5. The incidence of ROP was 36.36 % in babies born ≤ 32 weeks of gestational age. Gestational age was found to be a significant risk factor for the development of ROP (p=0.011).

6. Oxygen, Sepsis, Transfusion and Apnoea of Prematurity were found to be significant risk factors on Chi Square analysis.

7. The risk factors associated with ROP were Oxygen, Sepsis and Transfusion .

8. In our opinion, the effective management of ROP requires a team

effort of the neonatologist, ophthalmologist and the NICU staff.

9. Regular screening programme with a criteria of Gestational age <32 weeks and birth weight <1500 gms and or both Gestational age>32 weeks and babies more than 1500 gms with other risk factors should be screened at the discretion of the neonatologist and ophthalmologist.
10. Along with regular screening, an effective control of oxygen delivery, reduction of apnoeic spells and their early recognition are required.

SUMMARY

A one year duration of longitudinal study done to know the incidence of ROP and to correlate with the risk factors.

100 babies satisfied the inclusion criteria and were enrolled in the study. The incidence of ROP in the study was 27%. Out of 27 babies with ROP, only 6 babies(22.22%) were in stage 1, 16 babies(59.26%) were in stage 2,1 baby(3.70%) was in stage3 and 4 babies(14.82%) developed APROP.

The mean birth weight of the ROP babies was 1280 gm, Lower birth weight was significantly associated with increased incidence ($p = <0.001$) of ROP. The incidence of ROP was 48.15% in babies weighing $\leq$ 1500gm at birth. The mean gestational age of the ROP babies was 32 weeks. The incidence of ROP was 48.15% in babies born $\leq$ 32 weeks of gestational age. Gestational age was found to be a significant risk factor for the development of ROP ($p=0.011$).

By using the forward method oxygen and transfusion were also identified to be important.

Our study concluded that early examination was significantly associated with chances of early detection of ROP and hence all babies should have their first screening within the first four weeks after birth.

In our opinion, the effective management of ROP requires a team effort

of the neonatologist, ophthalmologist and the NICU staff. Regular screening programme with a criteria of birth weight <1500 grams and gestational age <32 weeks or both and babies more than 1500 grams and >32 weeks with other risk factors should be screened. Screening should be intensified in the presence of risk factors like administration of oxygen, sepsis, transfusion and apnoea.

Along with regular screening, an effective control of oxygen delivery, reduction of apnoea and their early recognition and effective management of sepsis are required.

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KEY TO MASTER CHART

A	Anaemia
AOP	Apnoea of Prematurity
BO	Birth Order
BW	Birth Weight
CBW	Code for Birth Weight
CGA	Code for Gestational Age
FD	Fetal Distress
GA	Gestational Age
Hypt	Hypertension
Hyt	Hypotension
MA	Metabolic Acidosis
N	Name
O	Oxygen
PCAFE	Post Conception Age at First Examination
P	Phototherapy
PIH	Pregnancy Induced Hypertension
ROP	Retinopathy of Prematurity
RDS	Respiratory Distress Syndrome
S	Sepsis
St	Stage of ROP
Sex	Gender of the baby
T	Transfusion
Z	Zone of ROP

KEY TO MASTER CHART

CGA : 1 :≤32
2: 33-35
3:>35

CBW: 1:≤1500
2:1501-1800
3:1801-2000

O: 1: Given
2: Not given

S: 1: Present
2: Absent

ROP: 1: Present
2: Absent

Z: 1: Zone 1
2: Zone 2
3: Zone 3
4: Mature retina

St: 1: Stage 1 ROP
2: Stage 2ROP
3: Stage 3ROP
4: APROP

S: 1: Male
2: Female

T: 1: Given
2: Not given

AOP: 1: Present
2: Absent

"THE ANALYSIS ON THE TREND OF SCREENING POSITIVE RATE AND CORELATIVE RISK FACTORS OF RETINOPATHY OF PREMATURITY"

PATIENT OPD NO- [ ] PATIENT ID NO- [ ]

NAME:_____

BIRTH WEIGHT(gms): [ ] INFORMED CONSENT: [ ]

GESTATIONAL AGE(wks): [ ] DATE OF BIRTH: [ ]

ADDRESS:_____

___

_____

Ph no:_____

SEX: [ ] (1-MALE,2-FEMALE)

CATEGORY: [ ] (1-AFD/2-SFD/3-LFD)

BIRTH ORDER: [ ] (1-SINGLE/2-TWIN/3-TRIPLET)

DELIVERY: [ ] (1-SVD/2-FORCEPS/3-VACUUM/4-LSCS)

MATERNAL RISK FACTORS: [ ] (1-YES/2-NO)

a) PIH: [ ] f)IDDM: [ ]

b) Placenta previa: [ ] g)GDM: [ ]

c)Abruptio placenta: [ ] h)Fetal bradycardia: [ ]

d)Fetal distress: [ ] i)Fetal tachycardia: [ ]

e) Meconium stained liquor: [ ] J)Antenatal steroids: [ ]

Neonatal Risk factors 0=no/1=yes

a.1 minute APGAR	☐	b.5 minute APGAR	☐
c.Respiratory Distress	☐	d.Apnoea of prematurity	☐
e.PDA	☐	f.CCF	☐
g.Sepsis(proved/suspected)	☐	h.NEC	☐
i.Pneumonia	☐	j.Meningitis	☐
k.Intracranial Haemorrhage	☐	l.Hypotension	☐
m.HIE	☐	n.Anaemia	☐
o.Respiratory acidosis	☐	p.Metabolic acidosis	☐
q.Hyperoxia(paO_2>100mmHg)	☐	r.Hypoxia(paO_2<50mmHg)	☐
s.Hypercapnia($paCO_2$>50mmHg)	☐		

Treatment 0=no/1=yes

a.Oxygen supplementation	☐	b.Surfactant	☐
c.Aminophylline	☐	d.Dexamethsone	☐
e.Phototherapy	☐	f.Transfusion (FFP/Platelet/Packed cell)	☐

ROP SCREENING PROFORMA

NAME: _____

DATE OF SCREENING: ☐

CHRONOLOGICAL AGE(wks): ☐

POST CONCEPTIONAL AGE(wks): ☐

ANTERIOR SEGMENT EXAMINATION OF THE EYE:

	RE	LE
TUNICA VASCULOSA LENTIS		
PUPILLARY DILATATION		
LENS		
MEDIA CLARITY		

FUNDUS EXAMINATION:

RIGHT EYE

IMMATURE ☐

ZONE ☐☐☐

STAGE OF ROP

☐☐☐☐☐☐☐

CLOCK HOURS INVOLVED (1-12)
INVOLVED(1-12)

PLUS DISEASE ☐

AP-ROP ☐

LEFT EYE

IMMATURE ☐

ZONE ☐☐☐

STAGE OF ROP

☐☐☐☐☐☐☐

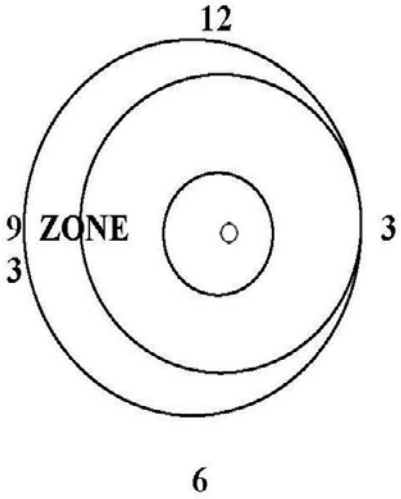
CLOCK HOURS

PLUS DISEASE ☐

AP-ROP ☐

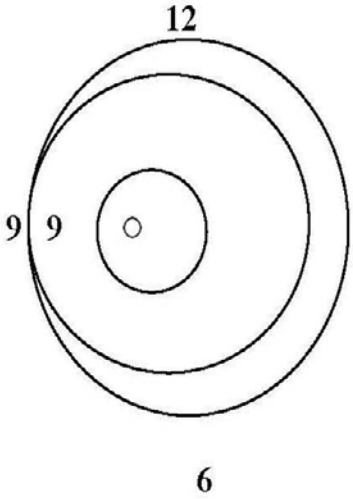
RIGHT EYE

MATURE ☐



LEFT EYE

MATURE ☐



IMPRESSION:_____

_____

FOLLOW UP EXAMINATION:

Follow up	Gestational age	Post natal age	Stage of ROP	Next follow – up date
1				
2				
3				

MASTER CHART

S.NO	IP.NO	NAME	GA	CGA	BW	CBW	Sx	O	S	AOP	T	ROP	St	Z
1	3909	TAMILARASI	32	1	1.8	2	1	1	2	2	1	2	5	2
2	3799	MANIMEGALAI	35	3	2	3	2	2	2	2	2	2	5	3
3	3888	RUKKUPRIYA	34	2	1.9	3	1	1	1	2	1	2	5	3
4	3602	PRIYANGA	33	2	1.7	2	1	2	2	2	2	2	5	2
5	3946	RATHINAM	33	2	1.6	2	2	1	1	2	2	2	5	3
6	3803	KAVIPRIYA	33	2	1.8	2	1	1	1	2	1	2	5	4
7	3887	KANDHARUBINI	33	2	1.8	2	1	1	1	2	2	2	5	3
8	3541	VAITHIGHA	35	3	2	3	1	2	2	2	1	2	5	4
9	3994	DEVAGHI	35	3	1.5	1	2	2	2	1	2	2	5	4
10	3948	VINOTHINI	35	2	1.5	1	1	1	2	2	1	2	5	4
11	3993	THENMOZHI	32	1	1.5	1	2	1	2	2	2	2	5	3
12	3988	REVATHI	32	1	2	3	2	2	2	2	2	2	5	4
13	3986	VEERAMMAL	35	2	1.7	2	2	1	2	2	1	2	5	3
14	3710	SATHIYA	35	3	1.6	2	2	2	2	1	2	2	5	4
15	4029	SEETHA	35	3	1.9	3	2	2	2	2	1	2	5	4
16	3942	NOORJAHAN	33	2	1.5	1	1	1	2	1	2	2	5	3
17	4032	LAVANYA	32	1	1.6	2	1	2	2	1	2	2	5	3
18	4030	HAMSAVENI	35	3	1.7	2	2	2	2	2	1	2	5	4
19	4028	MAHESH	35	3	1.8	2	1	2	2	2	2	2	5	4
20	4076	PUSPHA	33	2	1.7	2	1	1	1	2	1	1	4	2
21	4033	BANUPRIYA	32	1	1.6	2	1	1	2	2	2	2	5	2
22	4063	VINOTHINI	35	3	2	3	2	1	2	2	1	2	5	4
23	3987	KALAISELVI	35	3	2	3	2	2	2	2	2	2	5	4
24	4105	AMAIKKA	33	2	2	3	1	2	2	2	2	2	5	3
25	4108	SURIYA	30	1	1.4	1	2	1	2	1	2	2	5	2
26	4151	JEYABHARATHI	28	1	1.1	1	1	1	2	1	1	1	4	2
27	4152	KARTHIKA	34	2	1.7	2	1	1	2	2	1	2	5	4
28	4158	SATHIYA	32	1	1.6	2	2	1	1	2	2	2	5	2
29	4156	GAYATHRI	34	2	1.4	1	1	1	1	1	1	2	5	2
30	4153	SIVASANKARI	35	3	1.4	1	2	1	2	1	2	2	5	4
31	4196	SHRUTHI	34	2	2	3	1	2	1	2	1	1	1	1
32	4199	SUDHA	33	2	1.5	1	2	1	2	1	1	1	2	2
33	4200	MAHALAKSHMI	35	3	1.7	2	1	2	1	2	2	2	5	4
34	4197	MANIMEGALAI	32	1	1.4	1	2	1	1	2	1	2	5	4
35	4198	GOMATHI	33	2	1.2	1	2	1	2	1	2	2	5	3
36	4157	DEVI	32	1	1.6	2	1	1	1	1	1	1	4	2
37	4110	PRIYADHARSHINI	32	1	1.7	2	1	1	2	2	1	2	5	3
38	4236	KALPANA	31	1	1.5	1	1	1	2	1	1	1	2	2
39	4233	MYTHILI	33	2	2	3	1	2	2	2	2	2	5	3
40	4237	PARIMALADEVI	33	2	1.1	1	1	1	1	2	1	1	2	2
41	4235	SANGEETHA	31	1	1.1	1	1	1	2	1	2	2	5	2
42	4276	KAALIGA DEVI	35	3	1.7	2	1	1	1	2	1	2	5	4
43	4274	PARAMESHWARI	35	3	2	3	1	1	2	2	1	1	2	2
44	4159	SRIDEVI	32	1	1.8	2	1	1	1	2	1	1	2	2
45	4154	GOMATHI	30	1	1.2	1	2	1	2	1	2	2	5	2
46	4195	SATHYAPRIYA	35	3	1.6	2	2	2	1	2	1	2	5	3
47	4193	SUDHAMANI	33	2	1.5	1	2	1	1	1	1	1	3	2
48	4144	PRIYADHARSHINI	32	1	1.6	2	2	1	1	2	1	1	2	2
49	4100	GOKILA	34	2	1.7	2	1	2	2	2	2	2	5	2
50	4110	SANGEETHA	32	1	1.2	1	2	1	1	1	1	2	5	3
51	4236	SOUNDHARYA	32	1	1.5	1	1	1	1	1	2	2	5	2
52	4490	MAHESWARI	32	1	1.3	1	1	1	1	1	1	2	5	2
53	4314	PAANJALAI	34	2	1.6	2	2	1	1	1	1	1	2	2
54	4368	VELLIMANI	33	2	1.1	1	2	1	1	1	2	2	5	4
55	4233	CHITHRA	34	2	1.1	1	2	1	2	1	2	1	1	2
56	4319	MONIKA	35	3	2	3	1	1	1	2	1	2	5	4
57	4467	KAVITHA	32	1	1.3	1	1	1	1	1	2	2	5	2
58	4237	PRABHA	31	1	0.8	1	1	1	1	1	1	1	2	2

S.NO	IP.NO	NAME	GA	CGA	BW	CBW	Sx	O	S	AOP	T	ROP	St	Z
59	4480	REVATHI	32	1	1.6	2	1	1	2	2	1	1	1	2
60	4276	SANGEETHA	33	2	1.7	2	2	1	1	2	1	1	4	1
61	4415	VALLIYAMMAL	33	2	1.3	1	1	1	2	1	2	2	5	3
62	4488	RAMBA	33	2	1.6	2	1	1	1	2	2	2	5	4
63	4237	PUSPHA	33	2	1.3	1	2	1	2	1	2	1	2	2
64	4366	PRIYA	35	3	2	3	2	2	1	2	2	2	5	3
65	4488	SATHYAPRIYAA	35	3	1.6	2	2	1	2	2	1	2	5	3
66	4344	RADHA	32	1	1.6	2	2	1	1	2	2	2	5	3
67	4423	GOWTHAMI	33	2	1.2	1	2	1	2	1	1	2	5	2
68	4377	SUDHAMANI	33	2	1.5	1	2	1	1	1	2	2	5	2
69	4449	MYTHILI	33	2	2	3	1	2	1	2	1	1	2	2
70	4343	RANJITHA	35	3	1.4	1	1	1	2	1	1	2	5	4
71	4438	PAANJALI	34	2	1.8	2	1	1	1	2	2	2	5	3
72	4350	HASHINI	35	3	1.8	2	2	2	1	2	1	2	5	3
73	4475	KOKILA	33	2	1.5	1	2	1	2	1	1	2	5	4
74	4461	GEETHA	30	1	1	1	1	1	1	2	2	1	1	2
75	4494	KEERTHIKA	35	3	1.8	2	1	1	2	1	1	2	5	4
76	4523	PARAMESWARI	35	3	2	3	1	2	2	2	1	2	5	3
77	4545	PRIYADHARSHINI	32	1	1.8	2	1	1	1	2	2	1	1	2
78	4578	JERIN	33	2	1.7	2	1	1	1	1	2	2	5	4
79	4625	SHRUTHI	34	2	2	3	1	2	2	2	1	1	1	2
80	4536	MAHALAXMI	35	3	1.7	2	1	1	1	2	2	2	5	3
81	4573	RETTIKANTHAM	32	1	1.3	1	2	1	1	2	1	2	5	4
82	4618	MANIMEGALAI	32	1	1.4	1	2	1	2	2	2	2	5	3
83	4697	PUSPA	33	2	1.3	1	2	1	2	1	1	1	2	2
84	4519	DEVI	32	1	1.7	2	2	1	2	2	2	2	5	3
85	4555	MOULIKA	32	1	1.7	2	1	1	2	2	1	2	5	4
86	4641	MYTHILI	33	2	2	3	1	2	2	1	2	2	5	2
87	4690	KALPANA	31	1	1.5	1	1	1	2	1	1	1	2	2
88	4538	KALPANA2	30	1	1.2	1	1	1	2	2	2	1	2	2
89	4560	MARIYAMMAL	35	3	1.6	2	2	1	1	1	1	2	5	4
90	4584	VENNILA	33	2	2	3	1	2	2	2	2	2	5	4
91	4638	KUSPOO	34	2	1.3	1	1	2	1	2	2	2	5	4
92	4556	THANGAMANI	35	3	1.7	2	2	1	1	2	1	2	5	3
93	4597	SINDHU	33	2	1.7	2	1	1	2	2	2	1	2	2
94	4685	MAHALAXMI	34	2	1.4	1	1	1	2	1	2	2	5	3
95	4713	VEDATHAL	35	3	1.2	1	2	1	1	1	1	2	5	3
96	4569	MOHANAPRIYA	34	2	2	3	1	2	2	2	2	2	5	3
97	4581	SATHIYA	32	1	1.7	2	1	1	2	1	2	2	5	2
98	4670	NANTHINI	31	1	1.4	1	2	1	1	2	1	1	2	2
99	4728	SATYA	32	1	1.6	2	2	1	2	1	2	2	5	4
100	4593	SINDHUJA	33	2	1.8	2	1	1	1	2	1	1	2	3