RETINOPATHY OF PREMATURITY AMONG PREMATURE BABIES

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LIST OF ABBREVIATIONS USED

APROP	:	Aggressive posterior retinopathy 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
FFP	:	Fresh Frozen Plasma
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 Cardiac 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
Transfusion	:	Fresh Frozen Plasma / Packedcell transfusion/Platelet
VLBW	:	Very Low Birth Weight (< 1500 gms)
VEGF	:	Vascular Endothelial Growth Factor
Wks	:	Weeks
YC	:	Yates Correction

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INTRODUCTION

Retino pathy of prematurity (ROP), or retrolental fibroplasia as it was originally named, has had a most curious life span as a twentieth century disease. Theen igmatic findings of the disease, with scar tissue behind the neonate lens associated with retinal detachment, have been responsible for the two largest “epidemics” of blindness in neonates in modern times.

These outbreaks of the disease occurred approximately 25 years apart in the mid1950s and late 1970s[1]. Over the last 59 years since this disease was first correlated with prematurity by Terry in 1942, a plethora of literature has emerged on retrolental fibroplasia (RLF)and retinopathy of prematurity (ROP[1]).

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, million of whom live in Asia. India shares 20% of the world's childhood blindness[2].

ROP afflicts over 3,00,000 infants worldwide3.In developing countries like India, the incidence of ROP has been reported at 24 – 47 % among high risk preterm infants[1]. 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.

There appears to have been an “oxygen epidemic” from the late 1940s throughthemid1950s. During this period ROP, was the leading cause of blindness in neonates. Although the percentage of arterial oxygen delivered per se could not be incriminated, the duration of oxygen administration was found to be of significance[1].

Over the next 25 years a number of factors, including phototoxicity, ischemia, elevated oxygen levels, low oxygen levels, adrenocortical deficiency, elevated and low carbon dioxide levels, vitamin E or A deficiency, iron deficiency, maternal factors, multiple gestation, poor

nutrition, cyanotic congenital heart disease,anencephaly, exchange and replacement transfusion, complications of pregnancy,congenital anomalies, intraventricularhemorrhage, septicemia and prematurity itself,were advanced as possible causes of the diseases.

Despite meticulous attention tooxygen use, however, the disease is increasingly prevalent. In fact, it has occurred interm infants who have never been given supplemental oxygen as well as in thehypoxic infant. Therefore, this disease of fibrovascular proliferation in the neonatalretina, largely, remains an enigma[4].

The purpose of this study is to know the incidence of ROP and to correlate it with maternal and neonatal risk factor.

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HISTORY OF ROP

In Boston in February of 1941, two premature infants, each approximately 1Kg in weight, were born with nystagmus, almost flat anterior chambers, greyish red reflexes, and grey membranes with blood vessels on the back surface of both lenses.

These infants were at the forefront of a blindness epidemic that extended over the next15 years. This became known as the retrolental fibroplasia (RLF) epidemic, in reference to the scar tissue that developed behind the lens[4].

RETINOPATHY OF PREMATURITY (ROP)

Was originally designated Retrolental Fibroplasia (RLF) by Dr. Theodore L. Terry1, who in 1942 first connected the condition with premature birth. It was based on his impression that the primary change involved a proliferation of the embryonic hyaloid system which incorporated the retina.

He studied the unilateral pathological specimens (most likely to be PHPV) and provided details which he thought, may be identical with bilateral cases of retrolental fibroplasia. He postulated that "some new factor has arisen in extreme prematurity to producesuch a condition" and he argued that this new factor was 'excess light'.

The term ROP was coined by Heath in 1951. In 1951, Dr Kate Campbell5observed that, in a smaller hospital where each infants' family was charged for each tank of oxygen that was used, much less oxygen was administered, and there was a lower incidence - of RLF.

She concluded that, "normal oxygen environment of the newborn full term infant is abnormal for the premature infant". More convincing evidence came within a year from Crosse and Evans[6] in England, and from a randomised trial by Patzet al[7] in the USA, followed by a cooperative trial by Kinsey et al[8] in 1956.

Two ROP epidemics occurred in industrial developed countries during the past 60 years. The first epidemic was diagnosed in 1940-1950. In spite ofcareful oxygen supply monitoring, in the course of 1970-80, a second ROP wasregistered while it was noted that, a greater percentage of ELBW- infantssurvivedin industrial developed countries[9-11].

In 1981, Phelps[12]estimated the incidence of ROP associated with increase in survival rates of infants with birth weight less than 1000gms.

In 1982Kalina and Karr[13] reported 2 decades of experience at the Universityof Washington with RLF in infants weighing less than 2 kg. The incidence of ROP or RLF in surviving neonates from 1960 through 1967 was 14%. From 1968 through 1980, 20% of 140 infants developed cicatricial disease.

Most of these neonates retained useful vision, however in most of these eyes cicatricial RLF was mild and regression occurred spontaneously. Careful oxygen monitoring was thought to be a major factor in the favourable visual outcomes. Oxygen levels and durations were not specified.

Garg R in 2003 found that glucose levels in the first month of life had an association with the development of ROP. They found an increased ROP risk for each 10 mg/dl increase of mean glucose. It was also concluded that each IU/kg/day of vitamin E supplementation reduced the risk of ROP.[14]

Gupta VP in 2004 concluded that the incidence of retinopathy was 21.7% in the cohort, 33.3% in babies of less than or equal to 32 weeks of GA and 36.4% in babies weighing less than or equal to 1250 gm.

Oxygen administration, sepsis and apnoea were found to be independent risk factors of ROP. ROP was significantly more severe in babies with hyaline membrane disease and lower birth weight. Severe disease was never seen before 6.5 weeks of age[15].

Wright KW in 2006 at Los Angeles, did a prospective observational study on the incidence of threshold ROP in very low birth weight premature infants from three neonatal intensive care units (NICUs) before and after implementation of a physiologic reduced oxygen protocol (PROP). The hypothesis was that maintaining SpO2 values between 83% and 93% in the immediate post gestation life, with strict control of oxygen fluctuations, prevents the early vaso-obliterative phase and subsequent development of severe ROP[16].

Combined Anand Vinekar in his study in 2007 found risk factors for threshold ROP or worse disease were mainly, 'out born babies', respiratory distress syndrome and exchange transfusion[17].

In 2008, Chawla D in his study on the risk factors of ROP found prematurity as the most important risk factor. Other factors like, problems with oxygenation, frequent blood transfusions, sepsis and apnea have also been implicated in the causation of ROP[18].

In 2009, Austeng D in Sweden did a study on the incidence of ROP in extremely preterm infants less than 27 weeks during a 3years period at Sweden. They concluded that ROP had an incidence of 72.7%[19].

Chen ML in 2010 in his study, concluded that in preterm infants with a GA of less than or equal to32 weeks, early low and late high oxygen saturation were associated with a reduced risk for severe ROP[20].

Sabzehei MK in 2013, among 414 neonates the incidence of ROP was 17.14%. In their study, low birth weight, multiple gestation, resuscitation at birth, blood transfusion > 45 ml/kg, oxygen therapy, were the major risk factors for development of ROP in newborns[21].

The International Classification of ROP was devised in 1983 under the leadership of John Flynn[22].

With the advent of tele medicine to aid in the screening and diagnosis of ROP and laser photo coagulation replacing cry otherapy as the standard mode of treatment, more and more babies are being diagnosed earlier and treated.

EXPERIMENTAL FINDINGS:

In the early 1950s, the kitten model was used extensively because it demonstrated selective response to oxygen by the Immature retinal vessels[23-26]. Lesions closely resembling the early stages of human ROP were produced. In the term new born kitten, the immature retinal vascularization is comparable to that of 6½ months gestational human fetus, thus providing the unique opportunity to study the response to oxygen of the immature retina, albeit in a term, healthy subject.

The hyperoxia animal models demonstrated that only incompletely vascularized retina was susceptible to oxygen, and that the more immature the vascularization, the greater the response to oxygen. These findings supported the clinical observations that the infant with a more immature retina has greater susceptibility to ROP[26].

CURRENT INCIDENCE :

The incidence and severity of ROP both rise with the level of immaturity; <1000g, 53%[27] and 89%[27]; <1250g. 43%[28] and 66%[29] ;<1300g, 56%[28] and 74%[27];<1500g, 48%[30] and 60%[27].

Stage 1 and 2 ROP resolve completely and the term severe disease is confined to stage 3 or above which may lead to visual impairment. The incidence of stage 3ROP is as follows: <750g, 37-54%; 750 — 1000g, 19-30%; 1000-1250g, 3-9%[27-29]. For neonates <27 weeks GA, 25-29% will develop severe ROP where as for those at 28-31 weeks GA this is around 2-11%.

In a report on the current incidence of retinopathy of prematurity in neonates(22-36 weeks GA), it was found that the incidence of ROP was 21.3% for any stageand 4.6% for stage 3 ROP or greater. No ROP was noted in infants born at >32 weeks GA.

Using birth weight (BW) criteria, stage 3 ROP was not noted in infants with birth weight>1500g. Hence, despite increased survival of extremely low birth weight infants, considerable reduction in incidence and severity of ROP compared with reports from an earlier chronological period was found which was attributed to the present era of surfactant the rapy[31].

In a prospective study in a tertiary care newborn unit in New Delhi, the incidence of ROP among at – risk neonates (BW <1500g; GA <35 weeks and preterm neonates who required supplemental oxygen for >24 hours) was 20% for any stage. The incidence of threshold ROP was 7%[32].

RETINOPATHY OF PREMATURITY :

Retinopathy of prematurity is a vaso-proliferative retinopathy that occurs principally, but not exclusively, in premature infants. It occurs in two somewhatoverlapping phases.

(1) an acute phase in which normal vasculogenesis is interrupted and a response to the injury is observable in the retina and

(2) a chronic or late proliferation of membranes into the vitreous during which tractional detachment of the retina, ectopia, and scarring of the macula and significant visual loss occur. More than 90% of cases of acute ROP go on to spontaneous regression, healing with minimal scarring and little or no visual loss. Fewer than 10% of the involved eyes go on to significant cicatrization.

NORMAL RETINAL VASCULAR DEVELOPMENT:

Ocular blood supply involves the development of angiogenesis, arteriogenesis, and vascularization. Angiogenesis is the formation of endothelial lined blood vessels. Arteriogenesis is the addition of smooth muscle cells to end othelial cells, forming intact arterioles[33]. Vascularisation is the newart erialization of a tissue i.e., the retina. The combination of these three elements in forming the embryonic vascular tree is termed vasculo genesis.

The posterior segment of the eye has a dual system of blood supply:choroidal and retinal. The choroidal blood supply nourishes the outer retina while the inner retina is supplied by the retinal circulation.

Up to 16 weeks of gestation, choroidal vessels alone nourish both outer and inner retina, practically inner retina remains avascular. At about 16 weeks of gestational age, the first blood supply to inner retina appears in the form of mesenchymal "spindle cells". It arises from the adventitia of the hyaloids artery.

The origins of the retinal circulation reside at the optic nerve head. The vasculogenic elements begin to spread out over the retina from there and vascularization proceeds 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, the optic nerve is therefore nasal to the retinal center and uninterrupted vascularization must reach the closer point first i.e. nasal ora. The rate of growth of the advancing spindle cells is 0.1nm/day andreaches nasal ora by 36 weeks and then temporal ora-serrata by 40 weeks of gestational age[35].

3

PATHOGENESIS OF ROP

At birth, fetal circulation is transformed by the switch from placental oxygenation to lung oxygenation. Oxygen saturation rises from mixed venous levels to arterial levels. However, these fetal lungs are immature and are not capable of fully mature oxygen transfer. Medical intervention provides inhaled supplemental oxygen, enhancing the oxygen transfer. So several factors lead to a potential initially hyperoxic state: mixed venous oxygenation to arterial oxygenation; supplemental inspired oxygen; immature but as yet undamaged lungs; and a low retinal metabolic rate of oxygen consumption.

At some point after birth, this relative hyperoxia begins to change. The lungs become damaged, alveolar – blood oxygen exchange is compromised, and retinal metabolic demand for oxygen rises precipitously according to rigidly timed embryologic events. This gives rise to relative hypoxia. And 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 transforminggrowth factors associated with it.[33,36-39].

Typical ROP appears to occur in two phases, a vaso-cessation phase and a vaso-proliferative stage. Phase I, the vaso-cessation phase, begins with the initial hyperoxia that occurs in the immediate neonatal period. Arterial oxygen, increased FIO2 (fraction of inspired oxygen) and low retinal oxygen utilization secondary to a low metabolic rate, all combine to produce this relative hyperoxia.

The relative nature of the hyperoxia is important. The tissue saturation may not be higher than the normotoxic levels of a mature retina, but retinal vascularization should be normally occurring under the in utero hypoxic conditions characteristic of mixed venous blood supply.

So, the tissue oxygen tension is high, VEGF production is diminished, and normal vascularization ceases.

Phase II is the vaso-proliferative stage. As one would expect, this phase is driven by hypoxia and increasing VEGF levels. The relative hypoxia is fuelled by decreasing alveolar oxygen exchange and increasing retinal oxygen utilization. It is important to recognize that transition between these two phases is not abrupt. It is undoubtedly a phased transition, albeit within a probably tight timeframe.

During this possibly short transition period, the retina probably undergoes frequent and potentially wide-swings of hyperoxia /hypoxia. The sickest infants, undoubtedly have the most volatile transition phase of retinal oxygenation with medical intervention chasing the tissue oxygenation needs. It suggests that the ultimate cause of ROP is related to the mismatch of tissue oxygen need and tissue oxygen supply.

Two important hypothesis described are

a) **The Classical Theory:** Ashton and Patz40 proposed the classical pathogenesis of ROP. Elevated arterial PO2 causes retinal vasoconstriction, leading to vascular closureand subsequent permanent vascular occlusion. Endothelialcellproliferationoccurs adjacent to closed capillaries when neonate returns to room air, leading to neo-vascularization. Subsequent extension of this neo-vascularization may reach vitreous, producing haemorrhage which leads to fibrosis and causes vitreous traction and retinal detachment.

b) **Spindle Cell Theory:** This theory proposed by Kretzeret al41, postulates that the induction of retinal and vitrealneo-vascularization occurs by spindle cell insult. After birth, the spindle cells are exposed to hyperoxic environment because of increased oxygen diffusion through the thin and avascular peripheral retina. Free radical formation occurs, which attacks compromised spindle cells, which have deficient anti-oxidative defense mechanism. These abnormal spindle cells stop migration and canalization, with neo-vascularization occurring at the shunt site.

GROWTH FACTORSIN ROP :

Retinal vascularization is modulated by VEGF, which is constructed by highly regulated VEGF mRNA4[2-45]. This process is acutely sensitive to relative states of hyperoxia and hypoxia. Hypoxia up regulates VEGF and hyperoxia down regulates its production. VEGF is not the only vasoactive molecule within the retina There are insulin like growth factor (IGF-1), basic fibroblast growth factor, and transforming growth factors[33 36-39].

These cytokines create a complex milieu in which relative oxygen concentrations drive vascularization and this vessel formation and tissue invasion create modifiable changes in the extra cellular matrix[46-49].

Astrocyte development and migration parallel this vascularization and may be the source of VEGF. If the avascular zone is larger and when this is exposed to the hyperoxic state, VEGF expression is decreased leading to vaso-obliteration. This causes hypoxia and ischemia in non-perfused area, if insult is sustained. This again stimulates VEGF production and thus neo-vascularization.

Over the time VEGF production decreases, ROP will regress. If VEGF production increases or persists, ROP will progress. Manipulation of these factors could be beneficial therapeutically[50].

4

RISK FACTORSFOR DEVELOPMENT OF ROP

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

DEFINITIVE AND WELL ACCEPTED FACTORS

- Prematurity/ Gestational age/ Birth weight
- Oxygen supplementation

ASSOCIATED FACTORS

- Light
- Vitamin E deficiency
- Apnea with bag/ mask ventilation
- Methyl xanthine administration
- Respiratory distress syndrome
- Asphyxia / Hypoxia
- Shock
- Hypercarbia / Hypocarbia
- Acidosis / Alkalosis
- Sepsis
- PDA / Indomethacin
- Blood transfusions / Exchange transfusions
- Intraventricular hemorrhage
- Chronic in-utero hypoxia
- 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 weight52. 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%[53-56].A study from the Indian subcontinent reveals the incidence to be 17.5%-46%[57-59].

A Danish study found a statistically significant decrease in incidence of ROP in infants weighing more than 1250gm[55]. Gupta[15] 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.

Contrary to these reports, in a retrospective study done by Anand Vinekaret al17 found that, severe ROP is often encountered in babies with birth weight more than 1250 grams in developing countries and suggested that, the western screening guidelines may require modifications before application in developing countries.

OXYGEN AND ROP :

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

Sudden discontinuation of oxygen and duration of oxygen therapy are also incriminated in the pathogenesis of ROP[60]. 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[61].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, 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[60]. Hence, appropriate monitoring of actual Pa02 in infants at risk is essential. A definite safe range for arterial Pa02 is not known, nor do we know the critical duration of oxygen exposure.

Until such guidelines are established, keeping Pao2 <100 mm Hg is recommended preferably between 50 and 70mm Hg and saturation between 90-95%[62].

LIGHT:

The LIGHT-ROP Study[63] was a multicenter, prospective, randomized, controlled, clinical trial designed to determine if a reduction in ambient light exposure to premature infants eyes would reduce the incidence of retinopathy of prematurity (ROP).

Previous clinical reports were contradictory and had one or more methodological flaws. The investigators hypothesized that, reducing the amount of light that reaches the eyes of preterm infants may be effective in preventing ROP. The study showed that the reduction in the ambient-light exposure did not alter the incidence of ROP.

VITAMIN E DEFICIENCY[64-66]:

Vitamin- E is a fat soluble antioxidant and as a result it is able to scavenge free radicals derived from oxygen. 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 prophylactic vitamin E has been suggested for the management of retinopathy of prematurity (ROP).

Three clinical trial shave documented the efficacy of vitamin E supplementation in suppressing the development of severe ROP. The spindle cells, mesenchymal precursors of the inner retinal capillaries, are the primary inducers of the neo-vascularization associated with ROP. Exposure of spindle cells to elevated oxygen tension increases their gap junction area.

This early morphologic event immediately halts the normal vaso formative process and eventually triggers the neo-vascularization that is observed clinically 8–12 weeks later. Vitamin E supplementation above the deficient plasma levels of these infants67 suppresses gap junction formation and clinically reduces the severity, without altering the total incidence of ROP.

APNEA :

In a study by Kim et al[68], they found that apnea independently increased the incidence of ROP. Furthermore, frequent apneic attacks increased the progression of pre-threshold ROP to threshold ROP. In addition, apnea may not only increase the risk of developing ROP, but may also worsen pre-existing ROP.

A higher incidence of hypoxemia and apneic episodes requiring bagging was found among infants with severe ROP, than in a control group. The babies with increased frequency of apneaappeared to have longer duration of high pC02. Similarly, in a study by Chen et al69they found that apnea was one of the independent risk factors of ROP.

HYPOXIA :

Szewczyk[70] the first to suggest that, ROP was produced by too rapid a reduction of the level of oxygen after a child had been habituated to an enriched oxygen atmosphere. He found the condition could actually be treated by returning the infant to the high oxygen level, followed by a slow return to breathing air. He implied that ROP was a result of hypoxia and not due to oxygen toxicity.

An association between ROP and hypoxia was also noted by Cohen and co-workers, who found that 45% of 43 children with ROP had other abnormal neurological signs; 14% had a definite history of anoxia in the immediate postnatal period[71].

In reviewing the neonatal course of 50 infants who developed ROP, Katzman and his colleagues found no significant difference in total duration of oxygen therapy, or exposure to different concentrations of oxygen, when those with more severe (stages III to V) disease were compared with those with less severe (Stages I to II) disease[72].

They did, however, find that the more severe stages were associated with significantly more hours spent with arterial PO2 levels below 35 mmHg. Similar results were reported by Shohat and co-investigators among infants weighing < l,250gm[73].

HYPOCARBIA AND HYPERCARBIA :

Hypercarbia prevents the retinal vasoconstriction that occurs as a normal and perhaps protective response to hyperoxia, as the retina would then

more likely be exposed to the damaging effects of hyperoxic blood as suggested by Bauer andWidmayer[74].

Walbarsht and co-workers postulated that hyperoxia may be responsible for impaired removal of CO2 from the retina. This could result both from, arteriolar constriction with resultant decreased retinal perfusion and from the interference with haemoglobin binding of CO2, when haemoglobin in the retinal venous circulation is nearly 100% saturated with oxygen. For both these reasons, CO2 could accumulate and lead to retinal vasodilatation, which precedes the vaso-proliferationof ROP[75].

It should be noted that the second cooperative study on ROP did not find a clinical association between higher PCO2 and development of ROP, nor did the study of Shohatet al[73].

Similarly a study by BalazsGellenet al[76].showed that, neither variable blood carbon dioxide tension nor duration of hypercarbia or hypocarbia in the first 2 weeks of life was associated with the development or severity of ROP.

A study by Liao SL et al[77] found that hypercarbia or hypocarbia in the first 3 days of mechanically ventilated preterm neonates did not affect the subsequent development of ROP.

Shohatet al[73].study found a highly significant association between hypocarbia and the development of severe ROP i.e., an increased frequency of episodes of hypocarbia (PaC02 <25) and alkalosis (pH>7.55) among infants developing 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. Its prevention and early control may reduce the incidenceof ROP.

Liu PM et al[78] in her study, found sepsis as the most significant factor contributing to ROP. In a study published by Mittal M et al in Paediatric Research79they found that, Candida sepsis is independently

associated with increased severity of ROP and the need for laser surgery in ELBW infants .Similar findings were found in a study done by Parupia H et al[80]where they found that, the risk of threshold ROP requiring laser treatment was higher in infants who developed fungal sepsis.

BLOOD TRANSFUSIONS :

In recent years, the role of blood transfusions and iron intake as risk factors for ROP has been strongly emphasized. Reports have provided conflicting views on the relative role that transfusions may play. Some studies suggest that anemia per-se is a risk factor for ROP, whereas others contend that a high hematocrit ratio and frequent blood transfusions are important independent risk factors[86-88].

The usual explanation is that, tissue (including retinal) oxygen levels are increased by transfusion, owing to the reduced affinity of adult hemoglobin to oxygen, as compared to fetal hemoglobin. An alternative hypothesis is that,damaging effects of blood transfusion on the retina are mediated by, an increasein 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[84,85].

A study done by AkterS et al89showed 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.

INTRAVENTRICULAR HEMORRHAGE :

Intraventricular hemorrhage has been significantly correlated with ROP. Hungerford et al[81] reported IVH in 79% of infants with any stage ROP. In a review of all infants weighing <l,500g, born between 1976 and 1978, and surviving for at least one month, Procianoy[82]and assistants found that IVH was the only condition significantly correlated with ROP. It was proposed that as cerebral and retinal circulations respond similarly to changes in PaO_2, $PaCO_2$ and blood pressure and the two conditions might be caused by a common mechanism.

Watts P et al[83]concluded that, with improvements in neonatal care and a reduction in the prevalence of severe IVH, there appears to be a weakening of the previously reported association between severe IVH and severe ROP. However, the presence of even a minor grade of IVH may be a significant risk factor for threshold ROP once stage 3 disease is encountered.

SURFACTANT :

Repkaet al[90] in his study concluded that, the widespread use of prophylactic surfactant therapy, will not change the incidence of retinopathy of prematurity in extremely low-birth-weight infants. However, the absolute number of affected patients will likely increase because of the decrease in mortality of extremely low-birth-weight patients, the patients most at risk for retinopathy of prematurity. However, surfactant replacement therapy may have a beneficial effect on the development of cicatricial, severe ROP.

Several other studies revealed no significant effect of surfactant on the incidence or severity of ROP. Yet, others have shown that improving survival rates of very premature infants with synthetic surfactant, does not result in increased number of infants with impairments(e.g-neurodevelopmental defects, mental retardation, cerebral palsy and ROP), with detrimental effect on developmental outcome or late morbidity[90].

ROLE OF DEXAMETHASONE :

The effects of early dexamethasone therapy on pulmonary mechanics and chronic lung disease and on the progression of ROP in very low birth weight infants have been investigated. In a prospective randomized controlled trial, Durand and colleagues[91] showed that, early dexamethasone therapy in very low birth weight infants markedly improves respiratory compliance and tidal volume,reduces fractional inspired oxygen concentration and mean airway pressure, facilitatesextubation, and reduces the duration of mechanical ventilation.

It decreases chronic lung disease without causing additional risk for the development of infection, intraventricular hemorrhage and ROP.

In a recent study, Tsukahara and associates[93] showed that, early dexamethasone therapy (at 4-7 days of age) for prevention of chronic lung disease in preterm infants did not influence the incidence 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[94].

It is hypothesized that replacement of fetal blood by adult blood, would reduce the overall oxygen affinity of hemoglobin 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[95].

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. 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 challenge.

After an in vitro oxidative stress, defective glutathione recycling was found in patients with preceding ROP (not active ROP) and was suggested as a factor predisposing to oxidative hemolysis. The glutathione redox ratio was warranted as a biochemical screen for active ROP in premature infants[96].

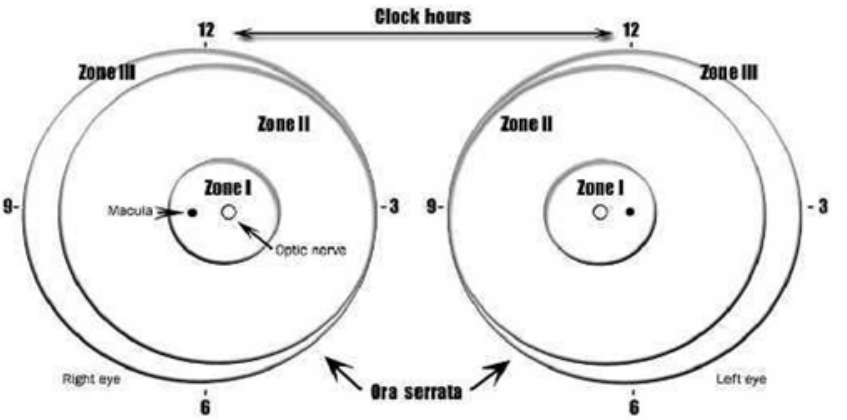
5

CLASSIFICATION OF ROP

International classification of ROP(ICROP)[22]:
Classification - Consists of five components.

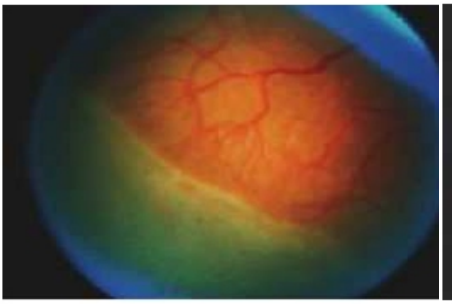
1. Location refers to, how far the developing retinal blood vessels have progressed. The retina is divided into three concentric circles or zones.

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

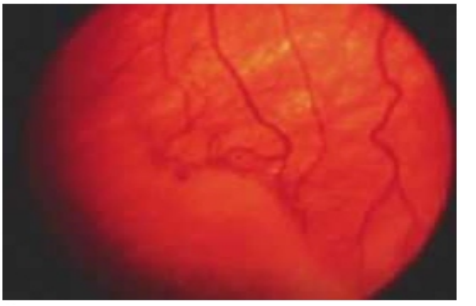


- **Zone 1** consists of an imaginary circle with the optic nerve at the centerand a radius of twice the distance from the optic nerve to the macula.
- **Zone 2** extends from the edge of zon9e 1 to the equator on the nasal side ofthe eye and about half the distance to the ora-serrata on the temporal side.
- **Zone 3** consists of the outer crescent - shaped area extending from zone 2 out to the ora-serrata temporally.

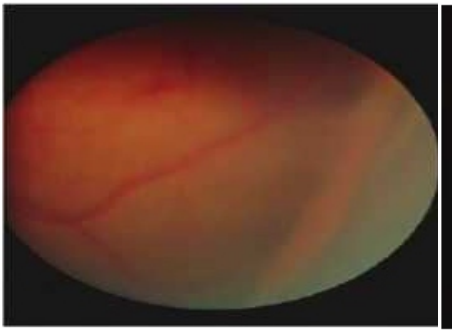
2. Stage of ROP:



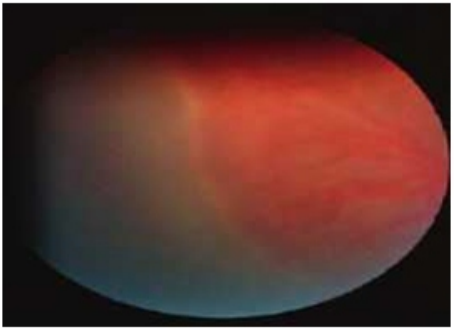
Photograph 1: Stage 1- Demarcationline



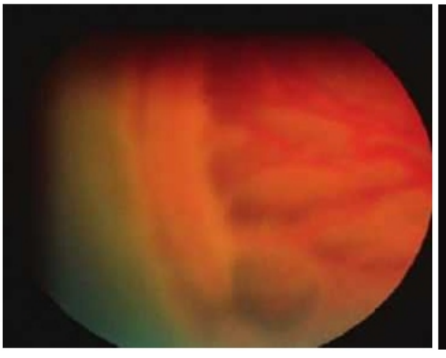
Photograph 2: Stage 2- Ridge



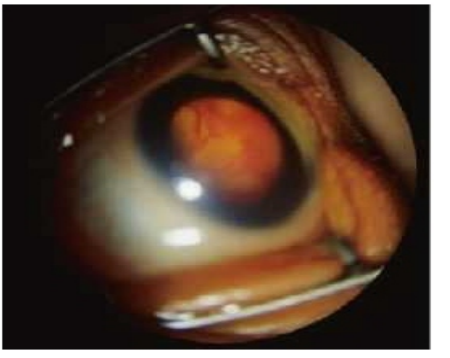
Photograph 3: Stage 3 ROP–Mild



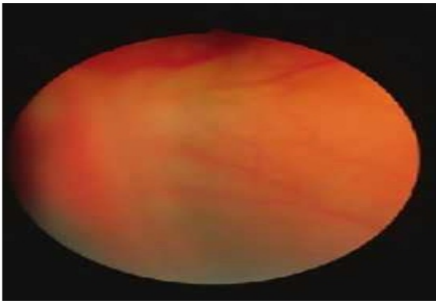
Photograph 4: Stage 3 ROP- moderate



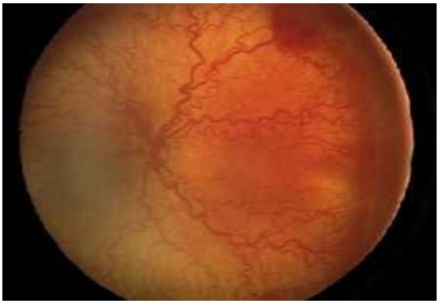
Photograph 5: Stage 3 ROP– severe



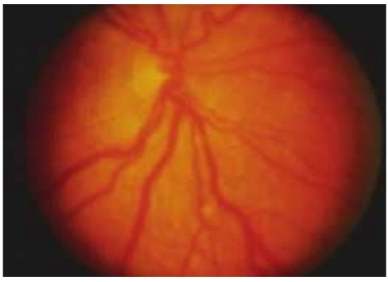
Photograph 6: Stage 4 ROP– PartialRetinal Detachment-



Photograph 7: Stage 5 ROP– Open Funnel Retina



Photograph 8: ROP– APROP



Photograph 9: Plus disease

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.

3. 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.

4.EXTENT :

Refers to the circumferential location of the disease and is reported as clock hours in the appropriate zone.

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.

DEFINITION OF THRESHOLD AND PRETHRESHOLD ROP:

Threshold ROP is present if five or more contiguous or eight cumulative clock hours (30- 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 treatmentand 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 12chance of extreme visual loss[97].

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 extra retinal 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.

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, following group of neonates should be screened.

- Babies with birth weight <2000grams
- Babies born at ≤35weeks of gestation

First screening – babies will be screened between 2-3 weeks after birth.

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

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

- 2-week follow-up
  - Stage 1 ROP: Zone II
  - Regressing ROP: Zone II

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

Findings that suggest further examinations are not needed include:

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

6

PROCEDURE OF EXAMINATION

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.

Instruments used:

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

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 baby99. The examinations should be kept as short as possible and precautions should be taken to ensure that emergency situations can be dealt with promptly and effectively.

Eye examination during screening lasts several minutes and may cause considerable pain to the neonate. A systematic review and meta-analysis comprising four studies have reported that, oral sucrose reduces pain during eye examination.

Of two studies reporting the role of topical proparacaine drops, one has observed significant pain reduction. Discomfort to the baby should be minimized by administering oral sucrose just before examination, pretreatment of the eyes with a topical proparacaine and swaddling the baby. Baby should not have been fed just before examination, to avoid vomiting and aspiration. Hand washing should be done and asepsis maintained.

RETCAM:

Photograph 10: RetCam

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[100].

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.

7

TREATMENT OF ROP

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 treatment101. Four hundred and one babies meeting the criteria for 'high-risk' of an unfavorable outcome with pre-thresholdin 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 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[102].

LASER PHOTOCOAGULATION:

The use of indirect laser via an ophthalmoscope, for retinal photocoagulation in the treatment of ROP has been established. McNamara and Coworkers104 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 vitreoushaze.

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.

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[103]:

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 neovascularization 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. Thefinding that, late development of ROP is associated with low levels of IGF1afterpremature 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, PlGF-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 neo-vascularization. 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.

8

PREVENTION OF ROP

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. Unfortunately that eludes our technology. Neonatal care is still primarily reactive and focused in a piecemeal fashion on organ support.

JUDICIOUS OXYGEN THERAPY

Oxygen is a drug and it should be administered in a quantity that is absolutely necessary. Each neonatal care unit should have a written policy outlining appropriate use of oxygen therapy. If a preterm neonate born at < 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)[104].

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[105].

Oxygen level in blood should be continuously monitored using pulseoximeter. 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 mmHg)[106].

Various observational studies have reported that, incidence and severity of ROP is lowered if oxygen saturation targets are kept in desirable range and if units implement written policies regarding oxygen administration and monitoring[107,108].

During recovery phase of respiratory illness in preterm neonates, targeting higher oxygen saturations has been associated with increased incidence/ severity of bronchopulmonary dysplasia without any benefit in stopping progression of ROP or improving growth and development.

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 Hb binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue. Packed cell transfusions should be given when hematocrit falls below following ranges: ventilated babies 40%, babies with cardio-pulmonary disease but not on ventilators 35%, sick neonates but not having cardiopulmonary manifestations 30%, symptomatic anemia 25% and asymptomatic anemia 20%.

VITAMIN E SUPPLEMENTATION

Very low birth weight neonates should receive 15-25 IU of vitamin E daily as supplement. However, higher doses given by intravenous route have been associated with, increased risk of neonatal sepsis.

PRENATAL STEROIDS

Use of prenatal steroids, is a well-known approach to prevent respiratory distress and intraventricular hemorrhage - the two important risk factors of ROP. Although there are some concerns that, prenatal steroids may induce ROP, this is not borne out by other studies.

We believe prenatal steroids prevent acute illnesses in premature babies and should be administered to all mothers with preterm labor between 24-34 weeks of gestation. The preferred preparation of steroids for prenatal used is betamethasone in two doses of 12 mg each, given intramuscularly, 24 hours apart.

BEVACIZUMAB

Intravitreal injection of bevacizumab, a neutralizing anti-VEGF molecule has been demonstrated to diminish the neovascular response significantly in animal models[112]. However, due to uncertainties

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.

Long Term Follow-Up

The importance education the parents regarding long term follow-up should not be overlooked, irrespective of what stage of ROP the child has had, as these children are likely to have refractive errors, especially high myopia, glaucoma, strabismus and retinal detachments in the future.

First examination: The following time table should be used for screening

Table : Timing of First Screening Eye Examination Based on GestationalAge at Birth

Gestation age at birth(weeks),	Age at initial examination (Postmenstrual age) (weeks)	Chronological age(weeks)
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

First screening examination was carried out at 31 weeks of gestation or 4 weeks of age, whichever was later. For this purpose, gestational age was calculated fromthe last menstrual period.

9

OUR EXPERIENCE OF ROP OVER ONE YEAR

Of the 153preterm neonates screened, 64 were males (53.33%) and 56 were females(46.67%). Among the neonates who developed ROP, 28 were males (32.6%) and 21were females (31.3%),25neonates were in stage 1(51.02%), 19 in stage 2 (38.8%) and 5 in APROP (10.20%) of the disease. Totalincidence of ROP in our centre was found to be 32.02 %.

One of the major ROP risk factors is birth weight. The lesser the birth weight,greater are the chances of developing ROP. Our study showed statistically significant correlation between birth weight and ROP by Ridit analysis.

Out of 19 neonates in stage 2, 17 neonates resolved spontaneously. Two neonates of stage 2 plus disease after being followed they found to progresstowards higher stages (increasing tortuosity and avascular retina). So, they have beentreated with laser photocoagulation. Five neonates of APROP were given laser photocoagulation as they had high risk of going for stage 5.

These laser photocoagulated babies are followed first after 2 weeks then atmonthly intervals later every year to ophthalmologist to look for complications of ROP like refractiveerrors, amblyopia, glaucoma and retinal detachment which may develop later.

10

BIBLIOGRAPHY

1. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens: I, preliminary report. Am J Ophthalmol. 1942; 25:203–204.
2. Seyedeh Khatami et al "ROP among 1000-2000 gram Birth Weight Newborn Infants". Iran J Pediatr. 2008 Jun;18(2) :137-142.
3. Reza Saeida et al "Prevalence and Predisposing Factors of Retinopathy of Prematurity in Very Low – birth - weight Infants Discharged from NICU". Iran J Pediatr. Mar 2009; 19 (1):59-63.
4. Terry TL. Fibroplastic overgrowth of persistent tunica vasculosalentis in infants born prematurely. Studies in development and regression of hyaloid artery and tunicavasculosalentis. Am J. Ophthalmol 1942; 25: 409-423.
5. Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia; a clinical approach. Med. J. Austral. 1951;2(2):48 –50.
6. Crosse V M, Evans P J. Prevention of retrolental fibroplasia. Arch Ophthalmol. 1952; 48:83–87
7. Patz A, Hoeck L E, de la Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. 1. Nursery observations. Am J Ophthalmol .1952; 35:1248–1253
8. 8. Kinsey V E, Jacobus J T, Hemphill F. Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. Arch Ophthalmol. 1956;56:481–543.
9. Gibson DL, Sheps S B, Schechter M T, et al. Retinopathy of prematurity: a new epidemic? .Pediatrics. 1989; 83:486-92.
10. Keith C G, Doyle L W, Kitchen W H, et al. Retinopathy of prematurity in infants of 24-30 weeks gestational age. Med J Aust. 1989;150:213-16.
11. Valentine P H, Jackson J C, Kalina R E, et al. Increased survival of low birth weight infants: Impact on the incidence of retinopathy of prematurity. Pediatrics. 1989;84:442-45.
12. Phelps, DL: Retinopathy of prematurity: an estimate of vision loss in the United States -1979. Pediatrics.1981; 67:924-26.

13. Kalina RE, Korr DJ. Retrolental fibroplasia: Experience over two decades in the institution. Ophthalmology 1982; 89: 291-295.
14. Garg R, Agthe AG, Pamela K, Donohue SCD, Lehman CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. Journal of Perinatology2003;23:186-194.
15. Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of prematurity - risk factors. Indian J Pediatr2004;71:887-892.
16. Wright KW, Sami D, Thompson L, Ramanathan R, Joseph R, Farzavandi S. A physiologic reduced oxygen protocol decreases the incidence of threshold retinopathy of prematurity. Trans Am OphthalmolSoc2006 ;104:78-84.
17. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. Indian J Ophthalmol2007;55:331-336.
18. Chawla D, Agarwal R, Deorari AK, Paul VK. Retinopathy of prematurity. Indian J Pediatr2008 ; 75 :73-76.
19. Austeng D, Källen KB, Ewald UW, Jakobsson PG, Holmström GE. Incidence of retinopathy of prematurity in infants born before 27weeks'gestation in Sweden. Arch Ophthalmol2009 ; 127 :1315-1319.
20. Chen ML, Guo L, Smith LEH, Dammann CEL, Dammann O. High or Low Oxygen Saturation and Severe Retinopathy of Prematurity: A Meta-analysis. Pediatrics 2010 ; 125 : 1483-1492.
21. Sabzehei MK, Afjeh SA, Dastjani FA, Shamshiri AR, Esmaili F. Retinopathy of prematurity: Incidence, risk factors, and outcome. ArchIran Med2013; 16: 507 -512.
22. Committee for the classification of retinopathy of prematurity: An international classification of retinopathy of prematurity. Arch Ophthalmol. 1984;102:1130-34.
23. Ashton, N. Ward, B. and Serpell G. Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Br J.Ophthalmol 1954; 38: 397-432.
24. Ashton, N, Ward, B, and Serpell, G. Role of oxygen in the genesis of retrolental fibroplasia; a preliminary report. Br J Ophthalmol 1953; 37: 573-520.
25. Locke JC, Reese AB. RLF: The negative role of light, mydriatics and the ophthalmoscope exam in its etiology. Arch Ophthalmol 1952; 48: 44-47.

26. Phelps DL. Retinopathy of Prematurity: An estimate of vision loss in the United States - 1979. Pediatrics 1981; 67: 924-926.
27. Acheson JF, Schulenburg WE. Surveillance for retinopathy of prematurity in practice: experience from one neonatal intensive care unit. Eye 1991;5:80-85.
28. Palmer EA, Flynn JT, Hardy RJ. The Cryotherapy for Retinopathy of Prematurity Co-operative group. Incidence and early course of retinopathy of prematurity. Ophthalmology 1991; 98: 1628-40.
29. Schaffer DB, Johnson L, Quinn GE, Weston M, Bowen FW. Vitamin E and retinopathy of prematurity. Ophthalmology 1985; 92: 1005-11.
30. Hussain N, Clive J, Bhandari V. Current incidence of retinopathy of prematurity.1989-1997, Pediatrics 1999 Sep; 104(3) : e 26.
31. Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari HK. Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J India 1996 Sept-Oct; 9(5):211-4.
32. The STOP-ROP Multicenter Study Group: Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP). A randomized controlled trail. I. Primary outcomes, Pediatrics 2000; 105: 295- 310.
33. Carmeliet P. Mechanisms of angiogenesis and arteriogenesis. Nat. Med.2000; 6: 389–95.
34. Casey R, Li WW. Factors controlling ocular angiogenesis. Am. J. Ophthalmol.1997;124: 521–29 .
35. Cloherty JP. Auditory and Ophthalmologic problems. Manual of neonatal care.5th edition: Lippincott; 677-83.
36. Robinson, C.J., Stringer S.E. The splice variants of vascular endothelial growth factor (VEGF) and their receptors.J. Cell Sci. 2001;114: 853–65.
37. Hellstrom A., Engstrom E., Hard A.L., et al . Postnatal serum insulin-like growth factor-I deficiency is associated with retinopathy of prematurity and other complications of premature birth. Pediatrics.2003;112 : 1016–20.
38. Hellstrom, A., Perruzzi, C., Ju, M., et al. Low IGF-I suppresses VEGF-survival signaling in retinal endothelial cells. Direct correlation with clinical retinopathy of prematurity. Proc. Natl Acad. Sci. USA 98.2001; 5804–08.

39. Smith L.E., Shen W., Perruzzi C., Soker S, Kinose F, Xu X, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. Nat. Med.1999;5: 1390–1395.
40. Ashton N, Ward B, SerpellG . Effect of oxygen on developing retinal vessels with particular reference to the problem of retrolental fibroplasia. Br. J. Ophthalmol .1954; 38:397-432.
41. Kretzer, Frank L, et al: vitamin E protects against Retinopathy of prematurity through action on spindle cells. Nature.1984; 309:793-95.
42. Stone J., Itin A., Alon T., Jacob P. et al.: Development of retinal vasculature is mediated by hypoxia - induced vascular endothelial growth factor (VEGF) expression by neuroglia. J. Neurosci.1995; 15: 4738–47.
43. Alon A., Hemo I., Itin A., et al. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat. Med.1995; 1: 1024–28.
44. Pierce E.A., Foley E.D., Smith L.E.H.: Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. Arch. Ophthalmol.1996; 114:1219–28.
45. Aiello, L.P.: Vascular endothelial growth factor. Invest Ophthalmol. Vis. Sci. 1997;38: 1647–52.
46. McGuire P.G., Jones T.R., Talarico N., et al.: The urokinase/urokinasereceptor system in retinal neovascularization: Inhibition by A6 suggests a new therapeutic target. Invest Ophthalmol. Vis. Sci.2003; 44: 2736–42.
47. Majka S., McGuire P.G., Das A.: Regulation of matrix metalloproteinase expression by tumor necrosis factor in a murine model of retinal neovascularization. Invest Ophthalmol. 1Vis. Sci.2002; 43: 260–66.
48. Majka S., McGuire P.G., Colombo S., et al.: The balance between proteinases and inhibitors in a murine model of proliferative retinopathy. Invest Ophthalmol. Vis. Sci.2001; 42:210–15.
49. Das A., McLamore A., Song W., et al.: Retinopathy neovascularization is suppressed with a matrix metalloproteinase inhibitor. Arch. Ophthalmol.1999; 117: 498–503.

50. Eric A, Pieru. Regulation of vascular endothelial growth factor by oxygen in a model of Retinopathy of prematurity. Arch Ophthal. 1996; 114: 1219-28.
51. Azad RV. ROP: Risk Factors In: Azad R. Retinopathy of prematurity: A Text and Atlas, 1st Ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2006.p.28.
52. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. Ophthalmology. 1991;98:1628–40.
53. Shah VA et al "Incidence, risk factors of retinopathy of prematurity among very low birth weight infants in Singapore" Ann Acad Med Singapore. 2005 Mar;34(2):169-78.
54. Vivek B Wani et al " Results of screening for retinopathy of prematurity in a large nursery in Kuwait : Incidence and risk factors" .Indian J Ophthalmol.2010;58:204-08
55. Fledelius H C, Dahl H. Retinopathy of Prematurity, a decrease in frequency and severity. Trends over 16 years in a Danish county. ActaOphthalmolScand. 2000;78: 359-61.
56. Blair B M, Hallmoran H S, Pauly T H, Stevens J L. Decreased incidence of Retinopathy of Prematurity. J AAPOS. 2001;5(2):118-22.
57. Nair P, Ganesh A, Mitra S, Sham S, Ganguly. Retinopathy of Prematurity in VLBW and extreme LBW babies. Indian J Pediatrics. 2003; 70(4): 303-06.
58. Rekha S, Battu R R. Retinopathy of prematurity: incidence and risk factors.Indian Pediatrics. 1996; 33: 999-1003.
59. Patil J, Deodhar J, Wagh S, Pandit AN. High risk factors for development of retinopathy of prematurity. Indian Pediatrics. 1997; 34: 1024 – 27
60. Kinsey VE, Arnold HS, Kalina RE. PaO2 levels and retrolental fibroplasias –A report of co-operative study. Pediatrics. 1997; 60:655-58.
61. Gunn TR, Easdown J, Outerbridge EW. Risk factors in retrolental fibroplasia. Pediatrics. 1980; 65:1096.
62. American Academy of Pediatrics and American College of Obstetrician and Gynecologists: Guidelines for perinatal care of newborn infants. Pediatrics. 2001; 108: 809-11.
63. The design of the multicenter study of light reduction in retinopathy of prematurity (LIGHT-ROP). J PediatrOphthalmol Strabismus. 1999 Sep-Oct;36(5):257-63.

64. Johnson, L., Schaffer D., Boggs T. R. The premature infant, vitamin E deficiency and Retrolental fibroplasia. Am. J. Clin. Nutr.1974; 27, 1158–73.
65. Finer, N .N, Schindler RF, Grant G., Hill GB, Peters KL. Intramuscular effect of vitamin E on frequency and severity of retrolental fibroplasia. Lancet. 1982; i:1087-91
66. Finer, N. N., Schindler, R. F., Peters, K. L. & Grant, G. D. Vitamin E and retrolental fibroplasia. Improved visual outcome with early vitamin E.Ophthalmology .1983;90: 428–35.
67. Farrell P. M. J. Vitamin E deficiency in premature infants. Pediatr.1979; 95: 869–72.
68. Kim TI, Sohn J, Pi SY, Yoon YH. Postnatal risk factors of retinopathy of prematurity. PaediatrPerinatEpidemiol. 2004 Mar; 18(2):130-34.
69. Chen Y, Li XX, Yin H, Gilbert C, Liang JH, Jiang YR, Zhao MW. Risk factors for retinopathy of prematurity in six neonatal intensive care units in Beijing, China.; Beijing ROP Survey Group. Br J Ophthalmol. 2008 Mar; 92(3):326-30.
70. Szewczyk TS. Retrolental fibroplasia: etiology and prophylaxis. Amer J Ophthalmol. 1951;34:1609.
71. Cohen J, Alfans JE, Boshes LD. Clinical evaluation of school age children with retrolental fibroplasia. ActaPediatr Scand. 1964; 57: 41-57.
72. Katzman G, Sathish M, Krishnan V. Comparative analysis of lower and higher stage retrolental fibroplasias, abstracted. Pediatric Res. 1982; 16:294A .
73. Shohat M, Reisner SH, Krikler R. Retinopathy of prematurity. Incidence and risk factors. Pediatrics. 1983; 72: 159-63.
74. Bauer CR, Widmayer SM. A relationship between PaCO2 and retrolental fibroplasias. Pediatrics .1981; 15:649.
75. Walbarsht ML, George GS, Kyalstra J. Does carbon dioxide play a role in retrolental fibroplasia?. Pediatrics. 1982; 70: 500.
76. BalazsGellen, Neil McIntosh, Janet R McColm, et al.Is the partial pressure of carbon dioxide in the blood related to the development of retinopathy of prematurity?. Br JOphthalmol. 2001; 85: 1044-45.
77. Liao SL, Lai SH, Kuo CY .Effect of carbon dioxide tension in the first three days of life on the development of retinopathy of prematurity. Chang Gung Med J. 2000 Dec;23(12):755-60.

78. Liu PM, Fang PC, Huang CB, Kou HK, Chung MY, Yang YH et al. Am J Perinatol. Risk factors of retinopathy of prematurity in premature infants weighing less than 1600 g. 2005 Feb;22(2):115-20.
79. Mittal M, DhanireddyR , Higgins RD .Candida sepsis increases the severity of retinopathy of prematurity in extremely low birth weight (≤1000 grams) infants. Pediatric Research.1997; 41: 165–65.
80. Parupia H, Dhanireddy R. Association of postnatal dexamethasone use and fungal sepsis in the development of severe retinopathy of prematurity and progression to laser therapy in extremely low-birth-weight infants. J Perinatol.2001;;21(4):242-47.
81. Hungerford J, Stewart A, Hope P. Ocular sequelae of preterm birth and their relation to ultrasound evidence of cerebral damage. Br J Ophthalmol. 1986;70:463–68.
82. Procianoy RS, GraciaPrats JA, Hittner HM. An association between retinopathy of prematurity and Intraventricular hemorrhages in very low birth weight infants. ActaPediatr Scand. 1981; 70: 473-77.
83. Watts P, Adams G, Thomas R, Bunce C. Intraventricularhaemorrhage and stage 3 retinopathy of prematurity .Br J Ophthalmol. 2000 June; 84(6): 596–99.
84. Hesse L, Eberl M, Schlaud C, Poets F. Blood transfusion, iron load and retinopathy of prematurity. Eur J Pediatr. 1997; 156: 465-70.
85. Cooke RWI, Clark D, Hickey DM, Weindling AM. The apparent role of blood transfusions in the development of retinopathy of prematurity. Eur J Pediatr. 1993; 152: 833 -36.
86. Sacks LM, Schaffer DB, Anday EK, Peckham GL. Retrolental fibroplasia and blood transfusion in very low-birth-weight infants. Pediatrics. 1981; 68: 770-74.
87. Aranda JV, Clark TE, Maniello R, Outerbridge EW. Blood transfusion (BT): possible potentiating risk factor in retrolental fibroplasia. Pediatr Res. 1975; 9: 362.
88. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet. 1997; 350: 12-14.
89. Akter S, Hossain MM, Shirin M, Khalil I, Anwar K S. Blood Transfusion: A risk factor in retinopathy of prematurity. Bangladesh J child health. 2010; 34(2): 38-43.
90. Repka M, Hardy R, Phelps D, Summers C. Surfactant prophylaxis and retinopathy of prematurity. Arch Ophthalmol. 1993;111: 618-20.

91. Durand M, Sardesai S, McEvoy C. Effects of dexamethasone therapy on pulmonary mechanics and chronic lung disease in very low birth infants. Pediatrics. 1995; 95:584-90.
92. Higgins RD, Mendelsohn A L, DeFeo MJ, Ucsel R, HendricksMunozKD.Antenatal Dexamethasone and Decreased Severity of Retinopathy of Prematurity.ArchOphthalmol. 1998;116(5):601-05.
93. Tsukahara H, Watanable Y, Yasutomi M. Dexamethasone therapy for chronic lung disease in preterm infants. Biol Neonate. 1995; 95:584-90.
94. Mizoguchi M, Chu T, Murphy F. Dopamine as a risk factor for the development of threshold retinopathy of prematurity. Br J Ophthalmol. 1999; 83: 425-28.
95. Narang A, Dutta S, Dogra M, Gupta A. Risk factors of threshold retinopathy of prematurity. Indian Pediatrics. 2004; 41: 665-70.
96. Papp A, Nemeth I, Karg E, Papp E, Glutathione levels in retinopathy of prematurity. Free RadicBiol Med. 1999; 27: 738-43.
97. Azad R, Chandra P, Patwardhan SD, Gupta A. Importance of the 'third criterion' for retinopathy of prematurity screening in developing countries. J PediatrOphthalmolStrabismusn. 2009;46:332-4
98. Chawla D, Agarwal R, Deorari A, Paul VK, Chandra P,AzadRV.Retinopathy of prematurity-AIIMS- NICU protocols 2010. www.newbornwhocc.org accessed on 15th Oct 12.30 pm.
99. Sun X, Lemyre B, Barrowman N, O'Connor M. Pain management during eye examinations for retinopathy of prematurity in preterm infants: a systematic review. ActaPaediatr. 2009.
100. Kemper AR, Wallace DK, Quinn GE. Systematic review of digital imaging screening strategies for retinopathy of prematurity. Pediatrics. 2008;122:825-30.
101. Early Treatment For Retinopathy Of Prematurity Cooperative G. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684-94.
102. McNamara J, Tasman W, Brown G. Argon laser photocoagulation for stage 3+ retinopathy of prematurity. Ophthalmology. 1991;98: 576–80.

103. Chen J, Lois E, Smith H. Retinopathy of prematurity. Angiogenesis . 2007; 10:133–40.
104. Finer N, Leone T. Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. Pediatr Res. 2009;65:375-80.
105. Flynn JT, Bancalari E, Snyder ES, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med. 1992;326:1050-54.
106. Castillo A, Sola A, Baquero H, et al. Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: is 85% to 93% an acceptable range? Pediatrics 2008;121:882-89.
107. Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001;84:F106-10.
108. Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111:339-45.
109. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349:959-67.
110. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOPROP), a randomized, controlled trial. I: primary outcomes. Pediatrics. 2000;105:295-310.
111. Brion LP, Bell EF, Raghuveer TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2003:CD003665.
112. Micieli JA, Surkont M, Smith AF. A systematic analysis of the off-label use of bevacizumab for severe retinopathy of prematurity. Am J Ophthalmol. 2009;148:536-43 e2.
113. Section on Ophthalmology American Academy of Pediatrics ;American Academy of Ophthalmology ; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2006 ; 117:572-76.
114. Akkoyun I, Oto S, Yilmaz G, Gurakan B, Tarcan A, Anuk D. Risk factors in the development of mild and severe retinopathy of prematurity. J AAPOS. 2006 Oct; 10(5):449- 53.

115. Sudhachaudhari, VidyadharPatwardhan, UmeshVaidya, SandeepKadamandAartiKamat. Retinopathy of Prematurity in a Tertiary Care Center – Incidence,Risk Factors and Outcome. Indian pediatrics 2009 Mar 17 vol 46:219-224.

SUGGESTED PROFORMA FOR SCREENING OF ROP

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)

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

DELIVERY: _____ (1-NVD / 2-FORCEPS / 3-VACUUM / 4-LSCS)

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

a) PIH: _____
b) Placenta previa: _____
c) Abruptio placenta: _____
d) Fetal distress: _____
e) Meconium stained liquor: _____
f) IDDM: _____
g) GDM: _____
h) Fetalbradycardia: _____
i) Fetal tachycardia: _____

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 _____

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(paO2>100mmHg) _____
r. Hypoxia(paO2<50mmHg) _____
s. Hypercapnia(paCO2>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) : _____

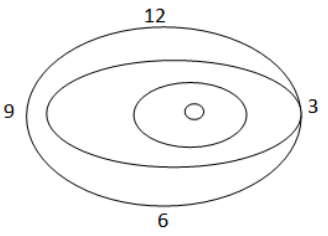
ANTERIOR SEGMENT EXAMINATION OF THE EYE:

	RE	**LE**
TUNICA VASCULOSA		
LENTIS		
PUPILLARY		
DILATATION		
LENS		
MEDIA CLARITY		

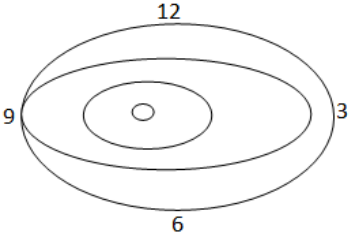
FUNDUS EXAMINATION:

RIGHT EYE	**LEFT EYE**
IMMATURE	IMMATURE
ZONE	ZONE
STAGE OF ROP	STAGE OF ROP
CLOCK HOURS INVOLVED (1-12)	CLOCK HOURS INVOLVED(1-12)
PLUS DISEASE	PLUS DISEASE
AP-ROP	AP-ROP

Right eye



Left eye



Impression

Follow up Examination :

Sl. No	Follow up	Gestational age	Post natal age	Stage of ROP	Next follow up Update