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# Study of Retinopathy of Prematurity in a Tertiary Care Hospital

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**ABSTRACT**

**OBJECTIVES**

1. *To study the incidence of Retinopathy of Prematurity (ROP) in a tertiary care hospital, in a metropolitan city.*
2. *To study associated etiological risk factors for development of Retinopathy of Prematurity.*
3. *To study the outcome of Retinopathy of Prematurity, those treated with laser photocoagulation.*

**STUDY DESIGN:** *Prospective observational study which was conducted in a tertiary care center in a metropolitan city over a period of 2 years*

**METHODS:** *In this study 200 preterm babies were enrolled with gestational age less than 34 weeks or birth weight less than 1500 grams with or without risk factors admitted in our Neonatal intensive care unit which is a tertiary care hospital. The study aimed at studying risk factors, incidence and outcome of retinopathy of prematurity especially in those patients who were treated with laser photocoagulation.*

**RESULTS:** *The incidence of ROP was 24 % (48/200). Incidence was comparatively more in babies with gestational age less than 28 weeks and birth weight less than 1000 grams. Incidence of ROP was more in Small for gestational age (SGA) babies than in appropriate for gestational age (AGA) babies.*

*In this study group, gestational age less than 28 weeks, birth weight less than 1000 grams, oxygen therapy, apnea, septicemia and use of blood products were found to be significant risks factors by univariate analysis. Oxygen therapy, septicemia and use of blood products were significant risk factors for ROP by multiple analysis (stepwise logistic regression).*

*All 48 cases of ROP had symmetrical or bilateral involvement of eyes, 7.5% (15/200) had severe ROP and required laser therapy (five neonates with zone I and rest with zone II). Severe ROP who required laser therapy 9 (23.70%) were less than 28 weeks, and 7 (19.44%) were less than 1000 grams. The percentage of laser treatment increases in gestational age less than 28 weeks and birth weight less than 1000 grams.*

*After laser therapy, at corrected age of 6 months eyes were examined for structural outcome, only 1(6.67) infant had sequelae with discmacular drag. No any infants lost to follow up after laser and the disease had regressed in all 14 (93.33) cases. Outcomes were good after laser therapy.*

**Keywords:** *Retinopathy of prematurity, Laser photocoagulation, Prematurity, Oxygen therpy.*

**Introduction**

Retinopathy of prematurity (ROP) is a vaso-proliferative retinal disorder peculiar to premature neonates potentially leading to blindness and severe visual impairment. In the majority of neonates, ROP is a mild disease and undergoes spontaneous regression with no significant visual sequelae. However in a significant number of cases, progression to advanced ROP occurs, resulting in severe visual impairment [1].

ROP therefore is an important and preventable cause of childhood blindness all over the world. Hence detection of ROP require ongoing screening program. Advances in neonatology and improvements in quality of care have resulted in increased number of premature and extremely low birth weight neonates surviving in neonatal period leading to increase population at risk for developing ROP. Although there are other risk factors, the incidence of ROP is inversely related to gestational age and birth weight with the greatest at risk group being in the low birth weight babies less than 1500 grams, and especially neonates with very low birth weight of less than 1000 grams [2].

Although ROP has been recognized as an important cause of blindness in developed countries for some years, it is now becoming more significant in developing countries. The World Health Organization has identified ROP as a priority for control, through "WHO 2020 program" targets ROP as an avoidable disease requiring early detection and treatment to prevent blindness. As described by vision 2020, recent research has resulted in strategies that have been successful in reducing the incidence of ROP [3].

ROP begins to develop between 32 and 34 weeks after conception, regardless of gestational age at delivery and has two distinct phases [4]. During the acute first phase, the normal vasculogenesis of the retina is disturbed by the relative hyperoxia of the extra uterine environment. This causes vaso-obliteration and non-vascularization of some areas of the anterior retina [5]. The subsequent hypoxia causes a second chronicphase, characterized by the proliferation of vascular and glial cells arteriovenous shunt formation, occasionally leading to involution or permanent cicatricle changes and visual impairment [6,7].

Today it is well known that oxygen therapy is not the single causative factor, but many other significant risk factors like prematurity, low birth weight, apnea, sepsis, useof blood products, play a causative role in the pathogenesis of ROP [8, 9].

Essentially asymptomatic in the initial stages, a good screening program is essential for early detection and treatment of this condition [10]. The initial signs of ROP are detectable by a few weeks after birth, and the condition progresses rapidly thereafter. This means that screening has to be timely as there is only a very narrow window of opportunity for treating these babies and the condition can quickly progress to high risk pre-threshold or threshold stage. If not treated at this stage, ROP progresses rapidly to Stage 4 or 5 in approximately 50% of babies. The visual prognosis for babies with Stage 4 or 5 ROP is very poor. If not treated early, it results in severe visual impairment or blindness, and carry a high financial for the community but also a high Individual cost by affecting the normal motor, conceptual, and social development of the child.

Now a day's Laser photocoagulation therapy has emerged as savior for preventing retinal blindness in premature neonates. Although loner follow up of these neonates has shown myopia, and astigmatism. Despite a good laser and clinically good looking macula, the visual acuity remains subnormal in some cases. A longer follow up of these neonates therefore needed to access the structural & functional outcome of eyes in both treated &untreated ROP. Late referrals, inadequate laser, and progression of ROP despite laser further complicate this situation. Current treatment options are expensive and can have potentially serious complications, thus prevention is still the best strategy available at present to avoid visual deficits caused by ROP .In order to prevent severe ROP in very preterm neonates, multidisciplinary strategy is necessary,

obstetricians should prevent preterm births and intrauterine infections, neonatologists should reduce the occurrence of septic diseases and should carefully monitor neonates with oxygen exposure. In all NICUs, a pediatric ophthalmologist should periodically evaluate all very preterm neonates from the 28th day of postnatal age. The follow-up of neonates with Zone I and Zone II posterior ROP needs to be particularly scrupulous since these neonates are at high risk of surgical intervention and adverse outcome. With improving neonatal survival of very low birth weight neonates across the country, there is a likelihood of increase in cases of ROP. So we need to study the risk factors for ROP as addressing the same can be a major step to reduce the incidence of the disease and clinicians should be aware of the presence of the additional risk factors when monitoring preterm neonates.

**Materials and Methods**

All preterm babies who were born with gestational age less than 34 weeks or birth weight less than 1500 grams with or without risk factors admitted in our Neonatal intensive care unit were enrolled in this study.Those babies with gestational age greater than 34 weeks or birth weight greater than 1500 grams are excluded from this study.

After the approval of Institutional Ethics Committee was obtained, 200 preterm with a gestational age less than 34 weeks or birth weight less than 1500 grams, admitted to our NICU, with or without risk factors like oxygen requirement, use of surfactant, exchange transfusion, use of blood products, heart disease, apnea, septicemia, anemia, seizures, and hyperbilirubinemia were screened for ROP . They were followed up with detailed history, clinical examination and investigations to determine the etiology. The various clinical manifestations were studied by the following parameters:

**History**

Perinatal history is important in assessing a neonate for risk factors such as prematurity, sepsis (Meconium stained liquor, premature rupture of membrane >18 hours, maternal fever), maternal jaundice, maternal hypertension, maternal hemorrhage and perinatal asphyxia. Present history included the most common symptoms of respiratory distress requiring oxygen therapy, sepsis, phototherapy, congenital heart disease and blood transfusion.

**Clinical examination**

Birth weight was taken on an electronic weighing scale with naked neonates. Gestational age at birth was assessed by last menstrual period, ultrasono-graphy and new Ballard scores, weight for gestational age (AGA / SGA status), vital signs, neonatal reflexes, neurological manifestations, severity of respiratory distress syndrome by Silverman and Andersen score, with treatment by ventilation and circulatory manifestations with or without risk factors like oxygen requirement, use of surfactant, exchange transfusion, use of blood products, heart disease, apnea, septicemia, anemia, seizures, and hyperbilirubinemia during NICU stay were recorded. The initial examination was carried out at 4 weeks after birth or 31 to 33 weeks postconceptional age, whichever was later and follow up examination should be recommended by the examining neonatal ophthalmologist on the basis of retinal findings [11]. All the neonates were screened by the same neonatal ophthalmologist. The screening was done with a binocular indirect ophthalmoscope. Eyes were examined with an Alfanso eye speculum and a Kreissig scleral depressor, under topical anesthesia using 2% Proparacaine drops. The pupils were dilated by using 0.5% Tropicamide and 2.5% Phenylepherine eye drops two or three times, till full dilatation occurred. Retinopathy was graded into stages and zones as per the ICROP classification [12]. In this study the term severe ROP includes high risk pre-threshold, threshold and aggressive posterior ROP (AP-ROP), those required laser therapy. Neonates with normal vascularization up to the periphery were not examined again. Those with ROP were

examined every week till regression occurred or till they reached threshold for laser treatment. Any stage 3 ROP with Plus disease with 5 contiguous clock hours of disease or a total 8 noncontiguous clock hours in zone 1 or 2 was considered as threshold for treatment .

**Laser treatment**

Laser photocoagulation was advised for neonates who developed high-risk Prethreshold, Threshold disease and Aggressive Posterior (AP-ROP) or Type 1 as per results of ETROP trial. Laser was done using 810nm red laser (IridexSLx) with laser indirect ophthalmoscope as early as possible, at least within 7 days of diagnosis of threshold Plus disease. This was done under topical anesthesia, using an Alfanso eye speculum and sclera indentation in the NICU. The vascular retina beyond the ridge was ablated using confluent medium intensity burns over one session. Topical treatment with tobramycin and dexamethasone was given for 5 days and an oral analgesic was given for one day. If regression was found to be inadequate or skip areas were seen on subsequent examination, laser was repeated after one or two weeks.

**Follow up**

All neonates who had laser therapy were asked to come for regular follow up. At the corrected age of 6 months, they were called for a detailed ophthalmic examination and for structural and visual outcome.

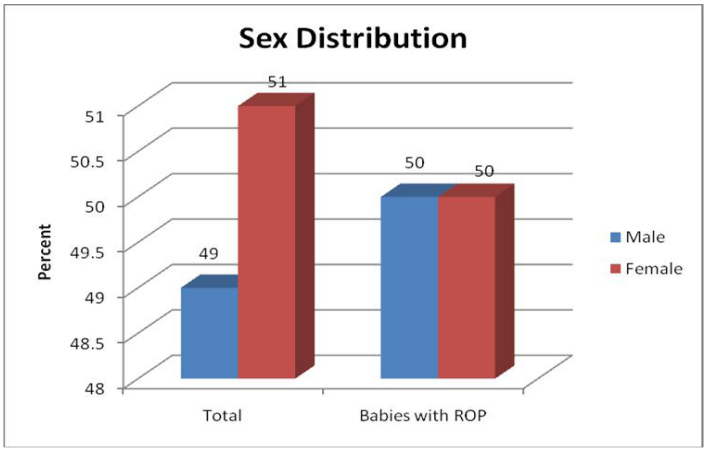
**Statistical Analysis**

Analysis was performed using SPSS version 16.0.Univariate analysis was conducted using Chi square test. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables as those variables which were significant in the univariate analysis.

**Results and Observation**

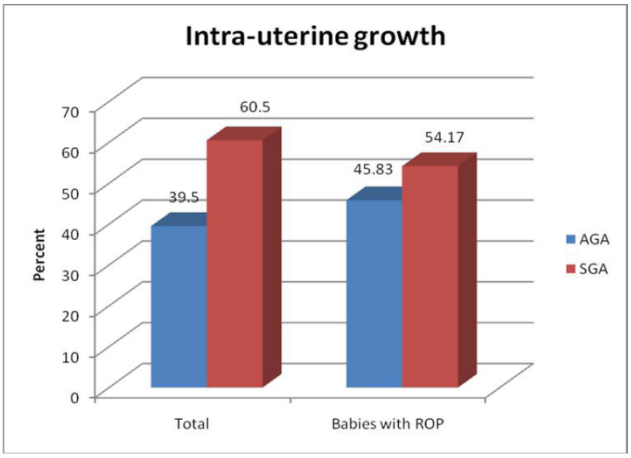
In this observational prospective study total 200 preterm with gestational age less than 34 weeks and birth weight less than 1500 grams with or without risk factors were studied in our NICU, a tertiary care hospital, to find out the incidence of ROP and associated etiological risk factors for development of ROP and to assess the outcome after laser photocoagulation. In this study 200 preterm were screened for ROP, their birth weight ranged from 600-1500 grams with a mean of 1241.13 +_202.13 grams and the gestational age ranged from 26-34 weeks with a mean of 30.99 +_2.2 weeks.

Amongst total patients 49% were females and 51 % were males while in patients developing ROP this percentage was 50% each for male and females (Graph 1)



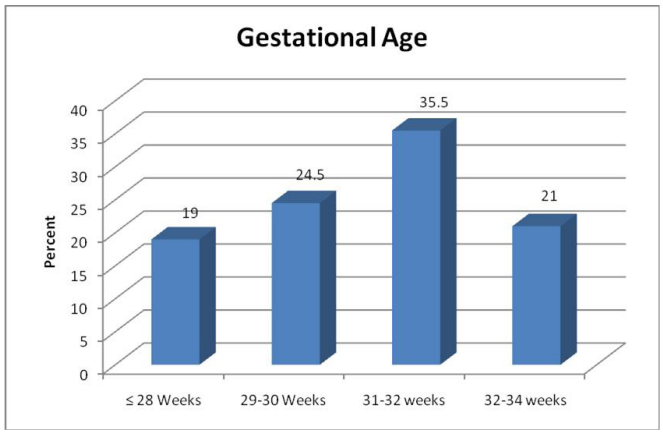

**GRAPH 1:** Bar Chart representing Percentage of cases with Sex distribution

Amongst babies who developed ROP 54.17 % were appropriate for gestational age and 45.83% were for small for gestational age. While this percentage was 60.5% and 39.5% respectively in total patients (Graph 2).



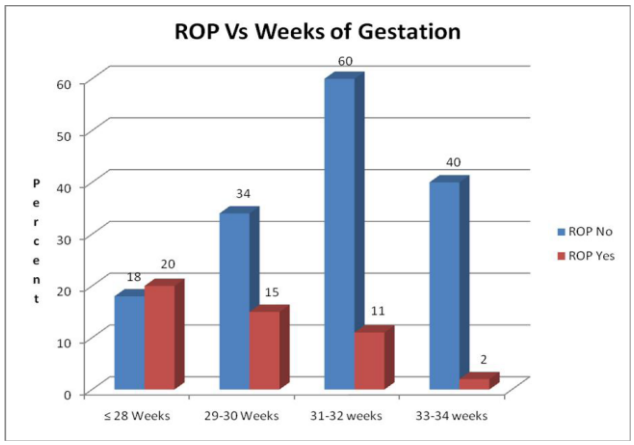

**Graph –2:** Bar Chart representing Percentage of cases with intrauterine growth distribution

The gestational age of the cases was less than 28 weeks in 19%, 29-30 weeks in 24.5% , 31-32 weeks in 35.5 % and 32-34 weeks in 21 % of cases (Graph 3).



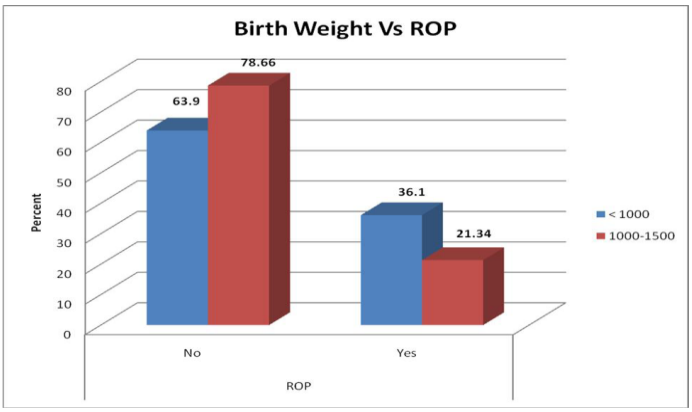

**Graph –3:** Bar Chart representing Percentage of cases with Age distribution

The incidence of ROP was most commonly seen in patients with gestational age less than 28 weeks (20%) while the incidence was least if the gestational age was more than 33 weeks (2%) (Graph 4).



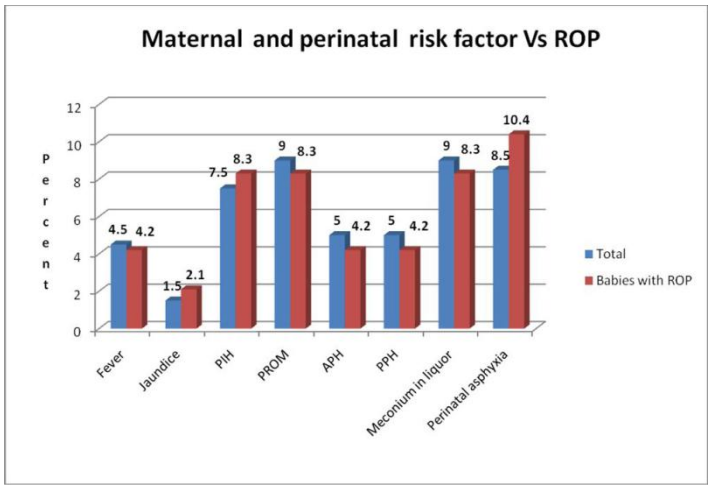

**Graph –4:** Bar Chart representing Incidence with Age distribution

In this present study, the incidence of ROP was 24 % (48/200, Graph 5), while that of severe ROP was 7.5 % (15/200) required laser therapy. There was no difference between male and female for the incidence of ROP. Incidence of ROP increases in gestational age less than 28 weeks and birth weight less than 1000 grams.



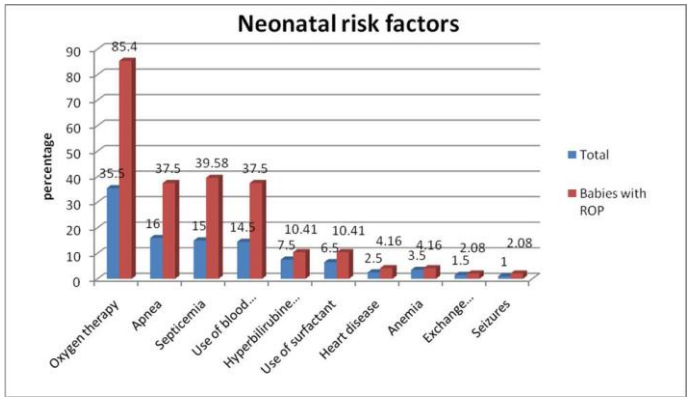

**Graph –5:** Bar Chart representing Incidence with birth weight distribution

Maternal risk factors associated with ROP were Fever (4.2%), Jaundice () Pregnancy induced hypertension (8.3%), Premature rupture of membranes (8.3%), Antepartum hemmorhage (4.2%), postpartumhemmorhage(4.2%),meconium stained amniotic fluid(8.3%) and perinatal asphyxia (10.4%)



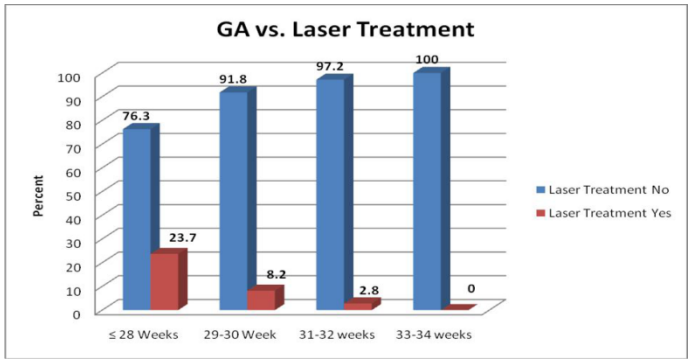

**Graph –6:** Bar Chart representing maternal and perinatal risk factors distribution

In this present study, gestational age less than 28 weeks, birth weight less than 1500 grams, oxygen therapy, apnea, septicemia and blood products used are significant risk factors by univariate analysis (Graph-7). Oxygen therapy, septicemia and blood products used were significant risk factors for ROP by multiple analysis (stepwise logistic regression)



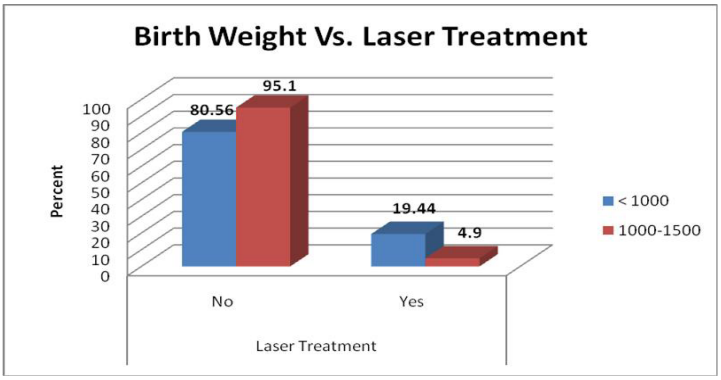

**Graph –7:** Bar Chart representing neonatal risk factor distribution

The requirement of laser therapy was inversely proportional to the gestational age while 23.7% of babies less than 28 weeks of gestational age required laser therapy this percentage was gradually reduced in babies with gestational age of 29-30 (8.2%), 31-32 weeks (2.8%) and in babies with gestational age more than 33 weeks no patient required laser therapy (Graph 8)



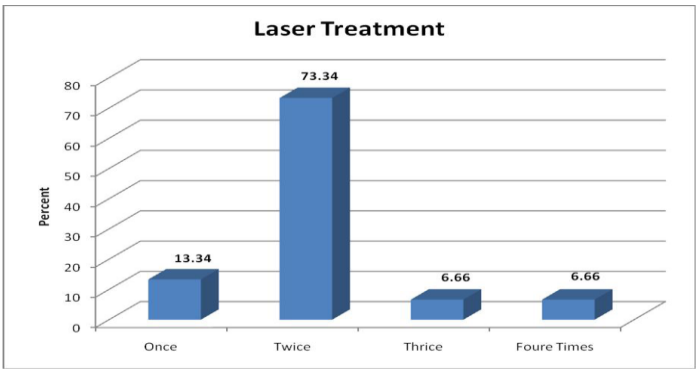

**Graph –8:** Bar Chart representing ROP with gestational age wise distribution required laser therapy

The relation of ROP was inversely related to birth weight. While 19.44% babies with birth weight less than 1 kg required laser treatment this percentage was reduced to 4.9% in babies with birth weight more than 1 kg (Graph 9)



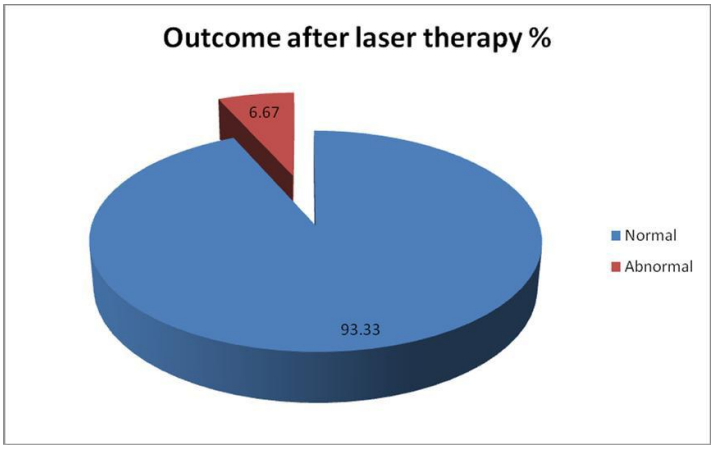

**Graph –9:** Bar Chart representing ROP with birth weight wise distribution required laser therapy

Most of the babies requiring laser therapy required it for 2 times (73.34%) while 13.34% patients required phototherapy only once. While laser theraphy was required for three and four times in 6.66% patients (Graph 10).




**Graph –10:** Bar Chart representing laser treatment with times wise distribution

After 6 months follow up for structural and visual outcome was normal in 14 cases (93.33%) and only 1case (6.67%) found abnormal with disc macular drag (Graph 11).




**Graph –11:** Pie Chart representing outcome after laser therapy

## Discussion

Retinopathy of prematurity is a serious vasoproliferative disorder seen in premature babies. Earlier the incidence of ROP was more in developed countries but with the availability of neonatal intensive care unit services and increased survival of premature and low birth weight babies the incidence of this disease is increasing even in developed countries like that of india [13]. ROP is one of the inevitable consequence of increased neonatal care. ROP may regress on its own but in many cases it may advance to cause severe disease resulting into blindness[14]. The blindness caused by ROP is different from the other causes of blindness seen in adult because it may cause various cognitive developmental disorders in children. Some of the studies have concluded that the children affected by blindness due to retinopathy of prematurity are prone to develop autism spectrum and deviant behavioral disorders [15].

There are many risk factors for development of retinopathy of prematurity. Important ones include prematurity, low birth weight , oxygen therapy, blood product infusion, multiple gestation, age more than 10 days to regain birth weight and resuscitation at birth were some of the important risk factors for development of retinopathy of prematurity[16]. Exposure of premature infant to oxygen causes down regulation of endothelial growth factor which in turn causes vasoconstriction and obliteration of retinal vasculature this stage of ROP is called stage I ROP. Growth of retina continues despite vaso-obliteration and this growth and consequent hypoxia causes vasoproliferation. This hypoxia coupled with vasoproliferation is constitutes stage II ROP. Stage III ROP consist of profileration of vasculature and its extension into other parts of eye. Stage IV and V consist of subtotal and total retinal detachment [17]. Premature infants treated by oxygen therapy and those with low birth weight and other risk factors should be screened to rule out this entity. American academyof pediatrics have a detailed schedule for screening of ROP. Other studies have suggested that the screening should be done at 4-6 weeks of age [18]. Identification of ROP should promptly be followed by treatment. Laser treatment and intravitreal bevacizumab are important treatment for ROP[19]. Surgical procedures like sclera buckling and vitrectomy may be required in some severe cases of ROP[20]. All patients who developed any stage of ROP must be under regular follow up to check for the progression of disease.

## Conclusion

In this study with 200 preterm, it was found that the incidence of ROP increases, as the gestational age and birth weight decreases. Oxygen therapy, septicemia and use of blood products were significant risk factors for development of ROP. As the gestational age and birth weight decreases, the percentage of laser treatment increases, after laser therapy with all followed-up there was regression of the disease and laser was effective in treatment of ROP and decreasing the progression of ROP.

Our study concluded that ROP is an important complication of prematurity for which screening should be started at 31-33 weeks or 4 weeks after birth which ever was later, associated risk factors for development of ROP are gestational age less than 28 weeks, birth weight less than 1000 grams, oxygen therapy, septicemia, use of blood products, apnea and outcome was good after laser therapy.

All units caring for babies at risk of ROP should have a written protocol inrelation for the screening and treatment of ROP. This should include responsibilities for follow-up of babies transferred or discharged from the unit before screening is complete.

**Conflict of interest**: NIL

## Learning points

- Earlier a disease of developed countries incidence of retinopathy of prematurity is

rapidly increasing in developing countries like India owing to improved neonatal care.

- Oxygen therapy , though one of the important determinants , is not the only cause of ROP.
- There is a narrow therapeutic window of treatment for cases of ROP and if treatment is not instituted in this "window" ROP progresses rapidly to Stage 4 or 5 in approximately 50% of babies.
- The prevention and treatment of ROP requires a multidisciplinary effort by obstetricians, neonatologists and pediatric ophthalmologists.
- ROP is a preventable cause of blindness and if it is not prevented, identified and treated properly then it may not only cause blindness in children but also affect normal motor, conceptual, and social development of the children.

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