

Study By Screening Of High Risk Patients For Retinopathy Of Prematurity: Our Experience & Review

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Abstract: Retinopathy of prematurity (ROP) is a vasoproliferative disease of developing retina which occurs principally in premature (<32 weeks of gestation) or low birth weight (<1500-1600 grams) babies or infants who have been on oxygen for long time. It was initially identified way back in 1940-41 after second world war. However, it has suddenly become an important focus point in today's context because of its increased incidence not only in western, but also in developing countries like India due to advancement of neonatal care facilities, causing national as well as global emphasis on this disease. Another important reason is the number of blind years, which in children is about 60 years as compared to 10-20 years in adults. This plays an important role in economic and social structure and productivity of any community and Nation. That is why we conducted this study by screening of high risk patients for ROP.

Key Words: ROP, Low birth weight, Prematurity

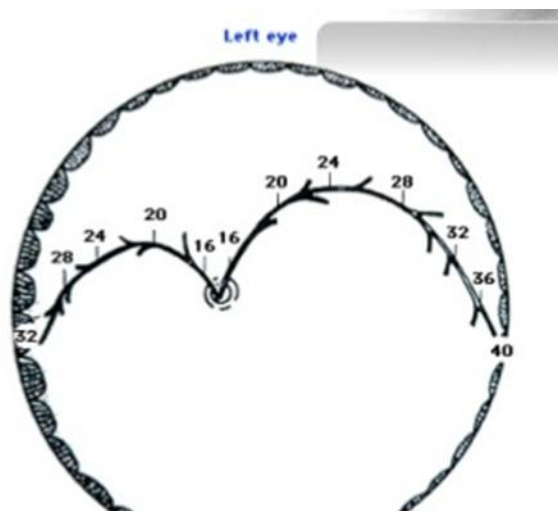
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I. Introduction

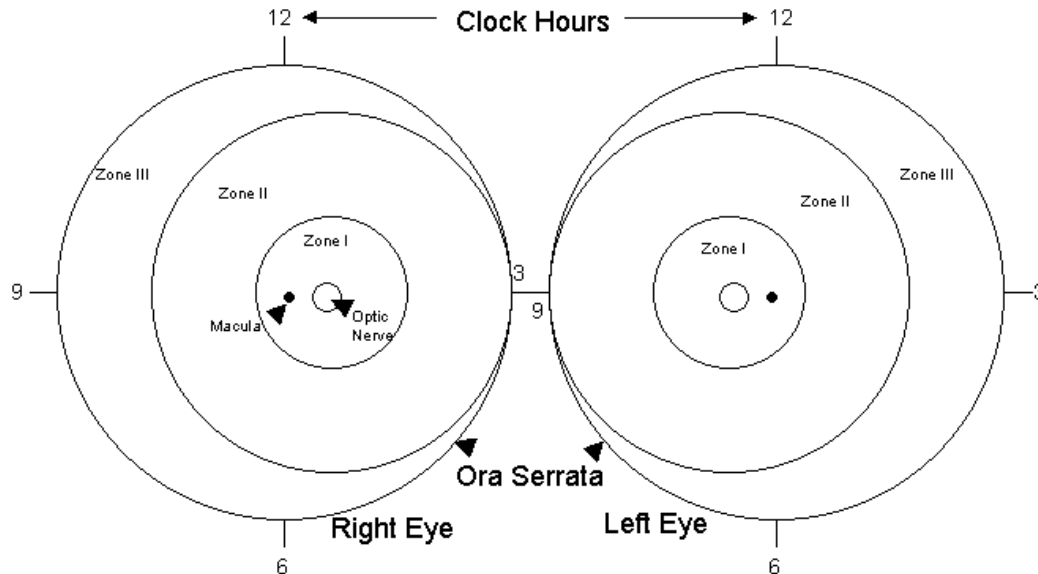
Retinopathy of prematurity (ROP) occurs when abnormal blood vessels grow and spread throughout the retina, the tissue that lines the back of the eye. These abnormal blood vessels are fragile and can leak, scarring the retina and pulling it out of position. This causes a retinal detachment. Retinal detachment is the main cause of visual impairment and blindness in ROP¹.

Several complex factors may be responsible for the development of ROP. The eye starts to develop at about 16 weeks of pregnancy, when the blood vessels of the retina begin to form at the optic nerve in the back of the eye. The blood vessels grow gradually toward the edges of the developing retina, supplying oxygen and nutrients. During the last 12 weeks of a pregnancy, the eye develops rapidly. When a baby is born full-term, the retinal blood vessel growth is mostly complete (The retina usually finishes growing a few weeks to a month after birth). But if a baby is born prematurely, before these blood vessels have reached the edges of the retina, normal vessel growth may stop. The edges of the retina—the periphery—may not get enough oxygen and nutrients.



Scientists believe that the periphery of the retina then sends out signals to other areas of the retina for nourishment. As a result, new abnormal vessels begin to grow. These new blood vessels are fragile and weak and can bleed, leading to retinal scarring. When these scars shrink, they pull on the retina, causing it to detach from the back of the eye.

In addition to birth weight and how early a baby is born, other factors contributing to the risk of ROP include anemia, blood transfusions, respiratory distress, breathing difficulties, and the overall health of the infant.



Staging the Disease (As defined by the ICROP)

Stage 1 (Demarcation line): This line is a hint but definite structure that separates the avascular retina anteriorly from the vascularised retina posteriorly. There are recognizable abnormal branching or arcading of vessels leading up to it. It is relatively flat, lies within the plane of the retina and is white color.

Stage 2 (Ridge) : The line of stage 1 now has grown, has height and extends up out of the plane of the retina. The ridge may change in color from white to pink and describe location and extent of retinopathy of prematurity.

Stage 3 (Ridge with extraretinal fibrovascular proliferation) : To the ridge of stage 2 is added the presence of extraretinal , fibrovascular proliferative tissue.

Stage 4 (Retinal detachment): It may be caused by exudative effusion of fluid, traction, or both, even in this early stage

Stage 4a. Subtotal retinal detachment not involving the macula

Stage 4b. Subtotal retinal detachment involving the macula²

Stage 5 : Total tractional retinal detachment is always funnel shaped and is based on configuration of the funnel³
Plus disease

Additional signs of increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels which can increase in severity to include iris vascular engorgement, poor pupillary dilatation, and vitreous haze was referred to as plus disease in the original classification. Subsequent clinical trials have used a "standard" photograph to define the minimum amount of vascular dilatation and tortuosity required making the diagnosis of plus disease.⁴

Pre-Plus disease

There is a spectrum of abnormal dilatation and tortuosity of which Plus disease is the severe form. A pre-plus disease was later described as 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.⁵

Aggressive Posterior ROP (AP-ROP)

An uncommon, rapidly progressing, severe form of ROP is designated AP-ROP was later added to the classification.^[8] Characteristic features of this type of ROP are a posterior location, plus disease, and the ill-defined nature of the retinopathy, which usually progresses to stage 5 if untreated. This rapidly progressing has also been referred to as "type II ROP" and "Rush disease".

Prethreshold ROP

Prethreshold ROP is defined as :-

1. Any stage of ROP in zone I with plus disease

2. ROP stage 3 with plus disease with 3 contiguous or 5 interrupted clock hours of involvement of retina in zone II and plus disease but less than threshold

It is important to understand this situation since it can rapidly progress to disease which requires treatment. As the timeframe for the therapy is narrow, once prethreshold ROP is detected, one is obliged to make frequent examinations to detect progression to threshold disease

Threshold disease

This is defined as: Zone I or II stage 3 ROP more than 5 contiguous or 8 cumulative clock hours with plus disease present.

This is the stage in which the treatment is mandatory since the chance of progression to retinal detachment is 50% if left untreated.

Regressed ROP

A significant number of patients with active ROP undergo partial regression. The residual changes have been divided in the classification into those affecting the retinal periphery and those affecting the posterior fundus. Each location has been further subdivided to describe separately the vascular alterations and the residual retinal changes.

Peripheral Changes

Vascular

- Failure to vascularise peripheral retina
- Abnormal, non-dichotomous branching of retinal vessels
- Vascular arcades with circumferential interconnection
- Telangiectasia.

Retinal

- Pigmentary changes
- Vitreoretinal interface changes
- Thin retina
- Peripheral folds
- Vitreous membranes with or without attachment to retina
- Lattice like degeneration
- Retinal breaks
- Traction or rhegmatogenous retinal detachment

Posterior changes

Myopia - In the very low-bright-weight infants who are born weighing less than 1251g, 20% develop myopia in the first two years of life. The lower the birth weight, the higher the chance of myopia. In addition, among the infants with the ROP, the incidence of myopia increases, having the direct relationship to the severity of ROP, e.g. in patients who develops zone II, stage 3 ROP have a 13% incidence of myopia.

Other refractive and muscle defects are:

Amblyopia, nystagmus and strabismus

Lens and corneal changes – Cataract, keratoconus, irregularities in corneal curvature, band keratopathy and acute hydrops

Glaucoma is a serious complication of ROP in both the acute and regressed phase of the disease

Pathogenesis of ROP

Concept of retinopathy of prematurity has dramatically changed over since terry first described it in 1942. Supplemental oxygen administration which was for a long time considered as the most important causative factor is now considered as only a risk factor. Low bright weight and decreased gestational age are now considered primary causative factors.

Two important hypotheses described are:

- (i) The classical theory
- (ii) Spindle cell theory

The classical theory

Arhton and Patz proposed the classical pathogenesis of ROP. According to this theory which was one widely accepted, supplemental oxygen administration was considered as the main causative factor. Elevated arterial PO₂ causes retinal vasoconstriction, leading the vascular closure and if vasoconstriction is sustained subsequent permanent vascular occlusion occurs. Endothelial cell proliferation adjacent to closed capillaries is followed when neonate returns to room air thus leading to neovascularisation . subsequent extension of this

neovascularisation may reach vitreous, producing hemorrhage leading to fibrosis and causing vitreous traction and retinal detachment.

Spindle cell Thoery

This theory which was proposed by Kretzer et al postulates the induction of retinal and vitreal neovascularisation by spindle cell insult. In premature newborn the peripheral retina is avascular and thin. After birth the spindle cells are exposed to hyperoxic environment because of increased oxygen diffusion through this retina from choroidal vasculature. Oxygen free radical: a cytotoxic agent attacks compromised spindle cells, which has deficient anti-oxidative defence mechanism . This abnormal spindle cells stop migration and canalization.

Growth factors in ROP

Vasoformative factors play a vital role in the normal development of retinal vasculature. Many vasoformative factors have been described but vascular endothelial growth factor (VEGF) was among first to be identified and cloned. VEGF is produced anterior to the vascular area. Adequate amount of VEGF is required for retinal growth. If the avascular zone is larger and when this is exposed to the hyperoxic state, VEGF expression is decreased leading to vaso-obliteration. This causes hypoxia and ischemia in non-perfused area if insult is sustained. This again stimulates VEGF production and thus neovascularisation. Over the time if VEGF production decreases, ROP will regress. If VEGF production increase or persist, ROP will progress. The manipulation of these factors could be beneficial therapeutically.

The overall status of the eye will read either

I) Mature II) Immature III) ROP

I) Mature : Signifies that the vessels have now reached at /or within one disc diameter of both nasal and temporal ora serrata. This child does not require further follow up.

II) Immature : Signifies that though there is no ROP, yet the vasculature has not matured fully. Immature vasculature is defined as vessels which are short of 1 DD of the nasal or temporal ora. Thus they could terminate in zones I/II/III and are designated accordingly immature I,II or III. A potential for developing ROP exists till the vessels are still immature. Therefore an exact record of the zones in which the tip of these immature vessels have reached must be kept in seqal examinations. They are then followed up till maturity as given in the screening protocol.

III) ROP : Presence of ROP is to be recorded meticulously in relation to:

- a. Zone and stage of ROP in each clock hour
- b. Presence or absence of plus disease

For recording of findings in an universally acceptable way, we recommend the use of graphic representations and standard notations of the STOP-ROP study. These help to depict various stages of ROP along with ancillary findings.

Selection of Eyes for Ablative Management

How does peripheral Retinal Ablation helps in Treating ROP?

Vasoformative factors are produced anterior to the vascular area, which causes neovascularisation at the junction of avascular and vascular area. The larger the avascular area, more is the production of vasoformative factors and more is the neovascularization. So the aim is to eliminate the source of vasoproliferative response i.e., avascular area by ablation.

Cryo ROP Study

The most detailed and comprehensive data regarding the safety and efficacy of ROP was made available by the multicenter trial of cryotherapy for retinopathy of prematurity. This study was carried out in 23 centers across USA.

The CRYO ROP results indicated an unfavourable outcome in 25.7% of the eyes that received cryotherapy compared with 47.4% of the control eyes. Though this data signifies a definite advantage of treatment over no treatment but the rate of 25% blindness is still very high.

How to do Cryotherapy

Cryotherapy spots are applied in a contiguous manner anterior to the ridge and then to the entire avascular retina with the end point as a creamy white intensity spot and an average number 21 spots ranging from 15 to 30.

Photocoagulation Treatment for Retinopathy of prematurity

Photocoagulation has largely supplanted cryoablation established as standard treatment by the CRYO-ROP trial

Diode laser with an indirect ophthalmoscopic delivery system is used to deliver an average number of 1500-1800 spots of 100micron size placed one half burn width apart and the end point for laser burns is a grade II gray burn, and is applied to the entire avascular retina, up to the ora serrata, avoiding the mesenchymal ridge.

Surgery For Retinal Detachment

The surgical options for treatment of eyes that develop partial retinal detachment and total retinal detachment including sclera buckle, combined lensectomy and vitrectomy, vitrectomy with lens conservation, and observation. No single approach can be applied to all patients. Each procedure has distinct advantages and disadvantages.

Scleral buckling is done for progressive stage IVA and stage IVB. Vitreoretinal surgery is reserved for cases that further progress to stage IV and stage V. All these infants are operated under general anaesthesia.

STOP – ROP STUDY (supplemental therapeutic oxygen for prethreshold ROP)

It concluded that USE OF SUPPLEMENTAL oxygen at pulse oxymetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery.

Supplemental oxygen increased the risk of adverse pulmonary events including pneumonia and exacerbations of chronic lung disease and the need for oxygen, diuretics and hospitalisation at 3 months corrected age.

Light ROP study

Light reduction in ROP study shown no benefit of preterm infants from a reduction in light exposure from birth to postmenstrual age 32 weeks.

ETROP (Early treatment of retinopathy of prematurity)

This project has been initiated to prove scientifically the benefit of treatment in ROP, earlier than is recommended by the CRYO-ROP study. It was indeed the high failure rate in even the treatment group of the CRYO ROP study, which has resulted in initiation of such a study.

Results: Grating acuity results showed a reduction in unfavourable visual acuity outcomes with earlier treatment from 19.5% to 14.5% (p=0.001) and unfavourable structural outcome were reduced from 15.6% to 9.1% (p<0.001) at 9 months. Further analysis supported retinal ablative therapy for eyes with type 1 ROP defined as zone 1 ROP, any stage ROP with plus disease, zone 1, stage 3 ROP without plus disease; or zone 2 stage 2 or 3 ROP with plus disease. The analysis supported a wait and watch approach to type 2 ROP defined as zone I stage 1 or 2 ROP without plus disease or zone 2, Stage 3 ROP without plus disease. These eyes should be considered for treatment only if they progress to type 1 or threshold ROP.

II. Material & Methods

The present clinical study was conducted in the Upgraded Department of Ophthalmology, JLN Medical College & Hospital, AJMER (Rajasthan), India.

All cases from 1st September 2015 to 30th March 2017 under 12 months of age were included in the study. During this period 644 patients were screened for posterior segment pathology among which 14 were diagnosed as having ROP.

After taking informed consent, all the subjects were asked a detailed ocular and systemic history and they had undergone a thorough ophthalmic examination. All the patients were referred to higher centre for timely management.

III. Results

S N o	NAME	AGE (MONT HS)	SE X	EY E	BIRTH HISTORY	MATERN AL HISTORY	PERSON AL HISTOR Y	INVESTIGATI ONS	DIAGNO SIS
1	B/O SHILPA	3	F	BE	PREMATU RE			USG- RD WITH VITREOUS HAEMORRHA GE	ROP 4
2	B/O SAPNA	6	M	BE	FTND		JAUNDIC E		ROP 2
3	PARI	1	F	BE	PREMATU RE				ROP 2
4	B/O ANJA	2	M	BE	PREMATU RE				ROP 3
5	B/O SUSHEELA	2	F	BE	PREMATU RE	1ST BABY DIED	OXYGEN THERAP Y		ROP 1
6	B/O KOMAL	2	M	BE			MAS, OXYGEN THERAP Y		ROP 1

7	SITARA	48	F	BE	FTND		OXYGEN THERAPY		ROP 4
8	B/O JASHODA	1	M	BE	PREMATURE				ROP 3
9	B/O SABINA	4	M	BE			IUGR, OXYGEN THERAPY		ROP 2
10	B/ONAHEED	8	M	BE	PREMATURE		IUGR, OXYGEN THERAPY		ROP 2
11	B/OMONICA	7	F	BE			IUGR, OXYGEN THERAPY		ROP 3
12	B/OVIJAYLAKSHMI	7	M	BE	PREMATURE TWIN		IUGR, OXYGEN THERAPY		ROP 2
13	B/OVIJAYLAKSHMI	7	M	BE	PREMATURE TWIN		IUGR, OXYGEN THERAPY		ROP 2
14	B/O SANJU	7	M	BE			IUGR, OXYGEN THERAPY		ROP 2

Table 1: Epidemiology of all ROP positive patients in our study

Table 2 : According to Prematurity

Premature babies	Full term babies
8	6

Out of 14 patients found to be positive with ROP, 8 were premature and 6 were full term which explains prematurity is the main risk factor for development of ROP.

Table 3 : Distribution of ROP positive patients according to Gender

Gender	No. of Patients
Male	9
Female	5

Of all the ROP patient 9 were males and 5 were female, which shows male preponderance.

Table 4 : According to Oxygen therapy

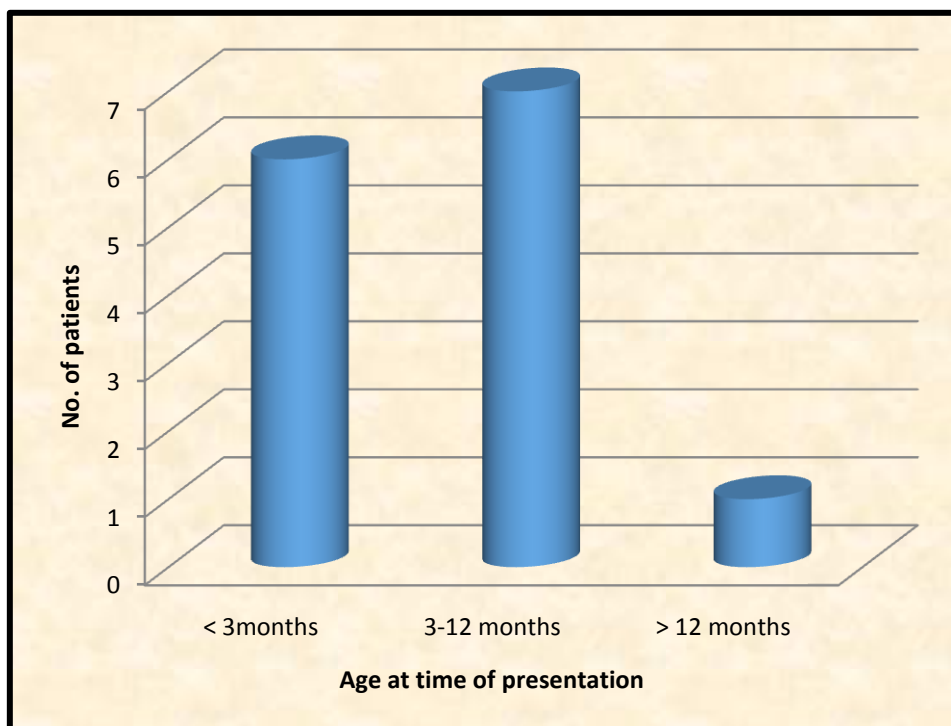
Children with history of Oxygen therapy	No history of oxygen therapy
9	5

Among these ROP patients 9 patients had history of oxygen therapy which supports the fact that Oxygen therapy to neonate can be a associated risk factor for ROP

Table 5 : According to Age Of Presentation

Age at time of presentation	No. of patients
< 3months	6
3-12 months	7

Most of the patient presented before the age of 12 months. Only 1 patient presented late i.e after 1 year of age.



Graph 1: Age of ROP positive patients at presentation

Table – 6 : Distribution according to Stage of ROP

Stage	No. of patients
1	2
2	7
3	3
4	2

Table 7 : According To Other Related Factors

Associated factors like MAS, IUGR, Jaundice	No associated factor
8	6

In 8 patients out of 14 patients other associated factors were also present like Meconium aspiratin syndrome (MAS), sepsis, Intra Uterine Growth Retardation, jaundice.

IV. Discussion

In 1942, Terry⁶ first described retrolental fibroplasia with implication of oxygen therapy as the causative agent. However, reports have found ROP in cases without oxygen therapy and even after oxygen therapy, not all premature infants develop ROP. Three factors have shown consistent and significant association with ROP: low gestational age, low birth weight and prolonged exposure to supplementary oxygen following delivery. Other putative risk factors include mechanical ventilation, surfactant therapy, anaemia, frequent blood transfusions, and apnea. The precise roles of these factors individually in the progression of the disease have not yet been determined.

DEMORGRAPHIC PROFILE

Different birth weight criteria have been taken in different studies.: Birth weight <2000 grams by Gopal L⁷ et al 1995, Birth Weight < 1750 grams by Shivaprasad B⁸ et al 2011, Birth Weight <1700 grams by Charan K et al 1995, Birth Weight < 1500 grams by Maheshwari R⁹ et al 1996, Rekha S¹⁰ 1996, Varughese S¹¹ 2001, Agarwal R¹² 2002, Gupta P¹³ 2004.

The criteria for gestational age is also different in different studies: Gopal L 1995 and Charan K 1995 did not include gestation in inclusion criteria; Maheshwari R 1996, Rekha S 1996, Agarwal R 2002, Gupta P 2004 and Shivaprasad B 2011 kept gestational age < 35 weeks as inclusion criteria; Varughese S kept GA < 34 weeks as inclusion criteria; Chaudhary S 2009 kept <32 weeks as inclusion criteria.

INCIDENCE OF ROP

While earlier studies Gopal L 1995, Charan K 1995, Varughese S 2001 and Rekha S 1996 estimated a higher incidence of ROP from 38 – 52%. However, Gupta P 2004 has found the incidence of 21.70%, Chaudhary S 2009 has found the incidence to be 22.3% and Shivaprasad B 2011 has found an incidence of

ROP of 13%. In our study we found that among all the 151 patients who were diagnosed for any posterior segment eye pathology, 14 of them were the patients of ROP. Thus the incidence of ROP in our study is 9.27%.

INCIDENCE OF SEVERE ROP

In an earliest study by Gopal 1995 the incidence of Threshold ROP was found to be 16%. After that Maheshwari R 1996 found incidence of Threshold ROP to be 9.1%, Rekha S 1996 found it to be 9%, Varughese S 2001 reported it as 6.3%, Chaudhary S 7.4%. However, Agarwal R 2004 and Shivaprasad B 2011 found incidence to be 2.6% and 3% respectively

BIRTH WEIGHT AND GESTATIONAL AGE

Low-gestational age on occurrence of ROP, is a significant risk factor in ROP. This was in support with the results of studies done by Shah¹⁴ et al., Karna¹⁵ et al. and Fortes et al. This was explained by immaturity of vascularization that induces an increased susceptibility of the retina to oxidative damage and to a number of perinatal factors which include hyper and hypoxia, blood transfusions, and sepsis. Present study found a significant relationship between gestational age and the severity of ROP, this was similar to the other studies, showing that lower gestational age was significantly associated with severe ROP.

Birth weight was a significant risk factor for the development of ROP that is in agreement with many studies which reported that lower birth weight was significantly associated with development of ROP, and explained that by more susceptibility for oxygen therapy, prolonged ventilation, sepsis, and blood transfusion in very low birth weight infants.

The mean birth weight associated with ROP by Maheshwari¹⁶ et al found as 1222 grams (SD = 304g)

OXYGEN THERAPY

Oxygen therapy was not an independent risk factor for the development of ROP, which is in disagreement with several studies who found them to be independent risk factor (i.e. Result was drawn by Chaudhary S 2009, Shivaprasad B 2011 and Gupta VP 2004.) On the other hand, Palmer¹⁷ et al, and R Agarwal et al 2004, reported that oxygen therapy was a non-significant factor for occurrence of ROP. They reported that ROP may develop in those cases also who did not receive oxygen therapy.

Other risk factors

Mechanical ventilation was a significant risk factor for ROP and this agreed with Shah VA and Chaudhary S 2009, and explained by, the increased exposure to Oxygen, Sepsis, IVH and blood transfusions. However, Murthy¹⁸ et al. observed that ventilatory support and CPAP were not significantly associated with development of ROP.

Packed cell transfusions is a significant risk factor for development of ROP, and this agreed with Chaudhary S 2009, Dutta S 2004 and Rekha S 1996. This can be explained by the fact that, adult RBCs are rich in 2, 3 DPG and adult hemoglobin which binds less firmly to oxygen, thus releasing excess oxygen to the retinal tissue. While Hirano et al. stated that it is controversial and iron overload rather than number of transfusions may contribute to the development of ROP.

Sepsis was not significantly associated with the development of ROP. This was in agreement with the results of Chaudhari et al and Smith. On the other hand, this was in disagreement with Shah et al. and Vinekar et al. which may be due to the effect of endotoxins on retinal blood vessels. Significant relationship occurs between apnea and occurrence of ROP. This was in support with S. Rekha 1996, Agarwal R 2002, Gupta P 2004, Chaudhary S 2009 and Shivaprasad B 2011 and was attributed to hypoxia of retinal vasculature leading to stoppage of normal angiogenesis followed by neovascularisation. However Kim TL found apnea as an independent risk factor for ROP which was not seen in this study.

No significant relationship shown between sex and occurrence of ROP, in contrast to Darlow¹⁹ et al. and Agarwal R 2002 who found that male sex is a significant risk factor.

A significant relationship noted between phototherapy and ROP however this was in disagreement with Chaudhari et al.

V. Summary And Conclusions

Retinopathy of prematurity (ROP) has become more common in developed countries with an improvement in survival of very premature infants. Though previously rare, it is likely to emerge as a major problem in India because of improving outcome of 'at-risk' preterm infants. It is a potentially blinding illness which can be treated successfully if recognized on time. Infants with birth-weights ≤ 2000 grams and Gestational Age ≤ 32 weeks and infants with gestational age of more than 32 weeks with sickness like need of cardio-respiratory support, prolonged oxygen therapy, need for phototherapy, apnea of prematurity, anemia, blood transfusion and neonatal sepsis are at high risk²⁰. These infants were subjected to periodic

ophthalmological evaluation for detection of ROP until full retinal vascularization occurred. The factors which were not found to be associated with ROP were male gender, and culture proven sepsis.

The study provided data for incidence of ROP in Central Rajasthan and the patient found positive for the disease were referred to higher centre on time for further evaluation and treatment so that their remaining visual potential can be saved from this sight threatening disease.

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