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REVIEW ARTICLE

RETINOPATHY OF PREMATURITY IN HIGH RISK PRETERM: INCIDENCE, RISK FACTORS AND TYPE AND TIME OF INTERVENTION WITH OUTCOMES AT WESTERN REGIONAL INSTITUTE OF OPHTHALMOLOGY IN INDIA

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ABSTRACT

Purpose: To study the outcomes of various intervention in high risk preterm with retinopathy of prematurity along with its incidence and risk factors. **Materials and Methods:** High risk preterm infants with gestational age ≤ 34 weeks and birth weight ranging from 500 grams to 2.0 kg were examined for ROP. Neonates having unstable neonatal course along with risk factors were referred to ophthalmology department for screening and appropriate interventions were undertaken. **Results:** Amongst 208 high risk babies(102 female child, 106 male child) ROP was detected in 77.88% of babies. 29.62% had ROP with Zone I vascularization, 62.96% had ROP with Zone II vascularization and 07.40% had ROP with Zone III vascularization. After grouping and staging, 114 were kept under observation, 22 needed anti-VEGF (Vascular Endothelial Growth Factors) agents, 22 needed intervention with laser photocoagulation and 4 were referred after explaining the nil visual prognosis. **Timing of intervention** for anti-VEGFs: 12 of 22 were treated on presentation, 10 of 22 within 1 week. For laser treatment, 8 of 22 were treated on presentation, 4 of 22 between 1 to 2 weeks, 2 of 22 between 2 to 4 weeks and 8 of 22 after 4 weeks. **Conclusion:** Major risk factor in our study which contributed to high risk preterm were oxygen therapy, NICU admission with ventilation and multiple pregnancy which predisposed these babies to ROP. **Favourable outcomes:** Were noted in 87/114 babies under observation, 21/22 babies in anti VEGF treatment group and 18/22 in laser photocoagulation treated babies.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a retinal disease of low birth weight premature infants. It can be mild with no visual defects or it may become aggressive with new vessel formation and progress to retinal detachment and blindness (Zin, 2013). The risk factors for ROP are prematurity, low birth weight, high exposure to oxygen for prolonged period, sepsis, anemia, cardiac defects, multiple blood transfusion and respiratory distress syndrome (Senthil, 2015; GEBEŞÇE, 2016; Edy Siswanto, 2017). Prematurity and low birth weight are the most predictive risk factors for development of ROP. Timely screening and treatment of ROP can prevent blindness and minimize visual handicap. The principle of treatment is to remove the stimulus for growth of new blood vessels by ablating the peripheral avascular retina. This will in turn reduce the incidence of retinal detachment and consequent blindness. The treatment involves ablation of peripheral avascular retina and thereby abolishing hypoxic drive of retina mediated by overaction of vascular endothelial growth factor; VEFG. This results in regression of established ROP (Beharry *et al.,* 2016; Celebi *et al.,* 2014; Lee, 2018).

Objective: To study the outcomes of various intervention in high risk preterm with retinopathy of prematurity along with its incidence and risk factors.

METHODS AND MATERIALS

A prospective, observational and interventional study was carried out over 208 patients presenting for ROP screening including the patients referred from the NICU of Paediatric Department from December 2019 to December 2021.

Institutional Ethics Review Board approved the study and it was in accordance to the guidelines of Declaration of Helsinki. Screening of the patients was carried out for the infants with either of the following:

- Gestational age ≤ 34 weeks
- Birth weight ranging from 500 grams to 2.0 kg.
- Neonates with risk factors like prematurity, low birth weight, high exposure to oxygen for prolonged period, sepsis, anemia, cardiac defects, multiple blood transfusion and respiratory distress syndrome.
- Neonates with birth weight more than 2.0 kgs were also screened if they were under high risk category having unstable clinical course.

The screening was done at 4 weeks of birth or 34 weeks of post gestational age whichever was later. After instillation of 0.5% proparacaine eye drops for topical anesthesia, using a sterile wire speculum and scleral indentor, retinal examination was carried out with the indirect ophthalmoscope. Tropicamide (0.5%) with phenylephrine (2.5%) eye drops were used for pupillary dilatation. The findings were documented according to the ICROP classification into zones and stages. Those with ROP were either given anti VEGF injection on presentation/ within few days or examined every week till regression occurred. In few of these patients they were observed till they reached threshold for laser treatment and was offered the same. Those with no signs of ROP were observed till the retina was fully vascularized.

Time of intervention is as mentioned below

ZONE I

- Stage 1: Laser within 72 hours
- Stage 2: Laser within 24 hours
- Stage 3: Anti VEGF immediately/ within few days.
- Stage 4: Anti VEGF trial and referral for surgery with explained prognosis
- Stage 5: No intervention

ZONE II

- Stage 1: Observation
- Stage 2: Observation with Laser when threshold for laser treatment is reached
- Stage 3: Laser +/- Anti VEGF when indicated
- Stage 4: Refer for surgery
- Stage 5: No intervention

Zone III

No intervention/ Observation
AP ROP/ plus Disease: Immediate anti VEGF

Anti VEGF injection: Intravitreal injections were administered in operation theatre maintaining asepsis in less than five minutes, often without intubation. With minimal preparation and effort, it is an attractive and appropriate modality of treatment in places with absence of laser delivery system. A rapid response was observed in the cases where intravitreal anti-VEGF was administered as compared to those where laser was used as the antibody binds to VEGF immediately.

Laser treatment: Diode red wavelength laser was used using indirect ophthalmoscope delivery system. Laser burns were applied over the entire avascular retina anterior to the vascularized retina under topical anesthesia. Topical antibiotic eye drops were prescribed for 5 days. Subsequent examination was performed after 1 week and retreatment was done if skip areas were noted.

Follow up: The babies treated for ROP were followed up at 3 months and 6 months of age for cycloplegic refraction and detailed examination. IBM SSPS version 10.0 and chi square test were used for statistical analysis using multiple logistic regression analysis.

RESULTS

The **incidence** of ROP in the 208 high risk infants (106 male child; 50.96%, 102 female child; 49.03%,) who were screened was 77.88%. The incidence of ROP was also found to be significant in infants with birth weight of more than or equal to 2000g (Table 1) or more than 32 weeks gestational age (Table 2) when they had associated high risk course.

Table 1. ROP in patients with birth weight as risk factor

Weight category	ROP	No ROP	Odd Ratio (P value)
<1000 gms (28)	22	6	1 (ref)
1000 to 1500 gms (128)	104	24	1.23
1501 to 2000 gms (38)	28	10	0.76
>2000 gms (14)	8	4	0.54

Table 2. ROP in patients with gestational age as risk factor

Gestational Age category	ROP	No ROP	P value
<30 weeks (42)	36	6	1(ref)
>30 weeks (166)	126	40	0.52

Risk factors of ROP were oxygen therapy, maternal eclampsia or pre-eclampsia, intensive care admission with ventilation, exchange transfusion, infection, mechanical ventilation, hypoxia and multiple pregnancies (Table 3).

Table 3. ROP in patients with high risk factors

High risk factor	ROP	No ROP
Oxygen therapy (116)	92	24
Pre-Eclampsia/Eclampsia/ Seizures (4)	4	-
NICU admission/ Ventilation (152)	120	32
Exchange Transfusion (2)	-	2
Use of Blood Products (2)	2	-
PDA/ Cardiac defect (1)	1	-
Septicemia (2)	2	-
CPAP (2)	2	-
Apnea (6)	6	-
Multiple Pregnancy (73)	55	11

Out of the 162 infants who had ROP, 29.62% had ROP with Zone I vascularization, 62.96% had ROP with Zone II vascularization and 07.40% had ROP with Zone III vascularization. All ROP patients were grouped according to location and severity and then were administered with various types of treatment or were kept under observation, 114 (70.37%) were kept under observation with close follow ups, 22 (13.58%) needed anti VEGFs, another 22 (13.58%) needed intervention with laser photocoagulation and 4 (02.46%) were referred after explaining the nil visual prognosis (Table 4).

Table 4. Type of intervention in the patients with ROP according to grouping and staging

ROP Zone	Observation	Anti VEGF injection	Laser Photocoagulation	Referrals
Zone I (48)	16	20	8	4
Zone II (102)	86	2	14	-
Zone III (12)	12	-	-	-
Near Complete Vasularisation (46)	46	-	-	-

Table 5. Timing of intervention in patients with ROP and the outcomes

Time of intervention	Anti-VEGF inj (22)	Laser Photocoagulation (22)	Observation (114)
On Presentation	12	8	-
Within 2 weeks	10	4	-
2 to 4 weeks	-	2	-
4 to 12 weeks	-	8	-
Outcomes			
Favorable	21	18	87
Non-Favorable	1	3	-
Lost Follow-ups	-	1	27

Timing of intervention for anti VEGFs: 12 of 22 were treated on presentation, 10 of 22 within 1 week. And for laser treatment, 8 of 22 were treated on presentation, 4 of 22 within 2 weeks, 2 of 22 between 2 to 4 weeks and 8 of 22 after 4 weeks (Table 5).

DISCUSSION

International Classification of ROP (ICROP) is used for classifying ROP. ROP is categorised based on the severity of the disease into stages (0-5), location of the disease into 3 zones (Zone 1-3), extent of the disease based on clock hours (1-12) and the presence of plus disease.

Zone1: Defined by a circle whose radius is twice the distance from the centre of the optic disc to the centre of macula (Fovea).

Zone 2: Defined by a circle whose radius is the distance from the centre of the optic disc to the nasal margin of the retina (ora serrata)

Zone3: The remainder of the retina. This is crescent-shaped zone that largely involves temporal retina

Disease severity is determined by staging

Stage 1. Demarcation line: A thin but definite structure separating the avascular retina anteriorly from the posteriorly vascularized retina.

Stage 2. Ridge**:** A ridge arising from the demarcation line which has 3 dimensions (height and width) and extends above the retina.

Stage 3. Extra retinal fibro vascular proliferation: Extra retinal fibro vascular proliferation or neovascularization extends into the vitreous from the ridge. The posterior aspect of the ridge appears irregular as the proliferation becomes more extensive.

Stage 4. Partial retinal detachment: Retinal detachments are generally concave and most are circumferential. They are divided into 2 stages: 4A: extrafoveal, and 4B: foveal

Stage 5. Total retinal detachment: Retinal detachments are generally tractional but may occasionally be exudative. They are usually funnel-shaped.

Plus disease: Plus disease can be present as a major complicating factor at any stage. It is characterized by significant level of venous dilation and arteriolar tortuosity of the posterior retinal vessels. This reflects the increase of blood flow through the retina. Two quadrants of the eye retina must be involved for the changes to be characterized as plus disease. Associated changes may include iris vascular engorgement, poor pupillary dilatation (rigid pupil), vitreous haze and anterior chamber haze. Aggressive posterior ROP (AP-ROP): A rapidly progressing, severe form of ROP, if untreated, usually progresses rapidly to stage 5 ROP. The characteristic features of this type of ROP include its posterior location, prominence of plus disease, and the ill-defined nature of the retinopathy. This may not have classical ridge or extra retinal fibro vascular proliferation, but rather have innocuous looking retina and tortuous vessels forming arcades. This type of ROP is likely to get missed by inexperienced examiners. Observed most commonly in Zone I, it may also occur in posterior Zone II.

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

Type 1 ROP: Administer peripheral ablation treatment.

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

Type 2 ROP: Wait and watch for progression/regression

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

All the babies with high risk criteria were screened admitted to NICU.Screening was carried out for the infants with either of the following:

- Gestational age $\leq$ 34 weeks
- Birth weight ranging from 500 grams to 2.0 kg.
- Neonates with risk factors like prematurity, low birth weight, high exposure to oxygen for prolonged period, sepsis, anemia, cardiac defects, multiple blood transfusion and respiratory distress syndrome.

- Neonates with birth weight more than 2.0 kgs were also screened if they were under high risk category having unstable clinical course.

The screening was done at 4 weeks of birth or 34 weeks of post gestational age whichever was later. In previous studies, Chaudhary *et al.*[10]*and* Chawla, *etal.*[11] have suggested the same screening criteria.

Different authors suggested different screening criteria as followed:

- Babies having birth weightless than 1500g and a gestational age less than 35 weeks were screened by Maheshwari *et al*. (1996)
- Babies having birth weight of less than equal to 1500g and/or gestational age of less than 35 weeks were screened by Gupta *et al*. (2004)
- Vinekar, *et al.* (2007) found higher rate of incidence of ROP in gestationally elder infants in developing countries.
- Jalali, *et al*. (2003) recommended that in developing countries, the infants with gestational age of less than 37 weeks and/or birth weight of less than 2000g with other risk factors should be screened for ROP to prevent missing any threshold disease. We utilized similar criteria and named "high risk infants" in the study.
- Babies with birth weight more than 1250g were not screened by Goble *et al*. (1997)
- American Academy of Pediatrics (AAP) (Screening examination of premature infants for retinopathy of prematurity. Section on Ophthalmology, American Academy of Pediatrics, 2016) updated recommendations had used <30 weeks criteria. 77.8% is the incidence of ROP in our study which is almost comparable with the study by Gopal *et al.* (1995) in 1995 and much higher than Chaudhary. in 2009.

In our study ROP was significantly associated with risk factors like prematurity, low birth weight, high exposure to oxygen for prolonged period, sepsis, anemia, cardiac defects, multiple blood transfusion and respiratory distress syndrome.

- Chaudhary *et al.* (2009) had reported maximum association with oxygen administration, septicemia, and apnea.
- Septicemia was reported by Vinekar *et al*. (2007) having maximum association.
- Aggarwal, *et al*. (2006) concluded hypoxia and septicemia having maximum association.
- Seiberth, *et al*. (2000) concluded surfactant a significant risk factor

Favorable outcome was as following:

- 21/22 babies in anti VEGF treatment group (1 baby had worsening)
- 18/22 in laser photocoagulation treated babies (3 babies had worsening and 1 had lost follow up).

CONCLUSION

The major risk factors in our study were oxygen therapy, NICU admission with ventilation and multiple pregnancy predisposing to ROP in high risk preterm.

Favourable outcomes were noted in 87/114 babies who were kept under observation (27/114 lost follow up), 21/22 babies who were in anti VEGF treatment group (1 baby got worsened) and 18/22 who were in laser photocoagulation treated group (3 babies got worsened and 1 lost follow up) (Table 5). ROP is an asymptomatic disease in the early stages. Hence timely screening and treatment of ROP by an ophthalmologist can prevent blindness and minimize visual handicap in high risk preterm.

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