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Original Research Article

Retinopathy of prematurity: incidence and risk factors: a hospital based study from Shimla, Himachal Pradesh, India

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ABSTRACT

Background: The blindness due to retinopathy of prematurity (ROP) is avoidable, if it is detected in time by screening. With increasing survival of preterm and low birth weight newborns in neonatal units, who are on prolonged oxygen therapy and mechanical ventilation; ROP is bound to affect these babies. This study was planned to investigate the incidence and the risk factors of ROP in a tertiary care institute in Himalayan region of north India.
Methods: This was a hospital based prospective study, conducted at neonatal intensive care units at IGMC, Shimla, from June 2011 to July 2012. 64 premature and low birth weight neonates born or admitted for neonatal intensive care unit (NICU) were screened for ROP using indirect ophthalmoscope. Cases found positive for ROP were closely followed up and managed as per international guidelines.
Results: Out of 64 neonates, 14 were lost to follow up and 50 babies were enrolled in the study. Out of them 21 were males and 29 were females. Among them 3 male and 5 female newborns developed ROP. Mean gestational age of babies with ROP was 30.63 weeks. ROP was significantly associated with oxygen administration (p=0.027), RDS (p=0.003), septicaemia (p=0.028) and exchange transfusion (p=0.003). Apneic spells, surfactant administration, hyperbilirubinemia, phototherapy, blood transfusion and maternal factors were not associated with increased risk of ROP.
Conclusions: For premature infants with birth weight less than 1200 grams, who has received prolonged oxygen therapy, associated respiratory distress and had received exchange transfusion the screening of ROP should be done at most appropriate time that is 32 - 40 weeks of gestational age. Timely referral of detected ROP cases for early treatment prevents blindness. There is a need for the obstetricians, neonatologist and ophthalmologist to work in close co-operation to prevent blindness due to ROP.

Keywords: Gestational age, Low birth weight, Premature infants, ROP

INTRODUCTION

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the retina, which principally occurs in premature children during vascular development and maturation stage. It was first identified by Terry in 1942 and named it retrolental fibroplasia.[1] ROP is multifactorial disorder, having various risk factors including prematurity, low birth weight, oxygen therapy.[2] In many cases it may undergo spontaneous regression or may progress to blindness. If detected early and timely intervention is done, the blindness is preventable.

There are approximately 50 million blinds in the world today out of them 30% are in Asia. Of this total blindness 4% (2 million) are children. India shares 20% of the world childhood blindness, important causes include congenital cataract, glaucoma and ocular injuries. ROP is one of the important causes of childhood blindness in India. It is estimated that out of 100 preterm infants, 20 to

40 develop ROP, out of which 3-7 can progress to blindness.[2]

There has been a marked increase in incidence of ROP in India due to better survival rate of low birth weight and preterm babies availing modern neonatal facilities and care.[3] As baby and attendant can never complain about any symptoms until it is too late, so it is responsibility of the health system to prevent its development (monitored oxygen therapy and its danger), detection (screening) and treatment.

Screening programs in India are inadequate because of lack of trained manpower and infrastructure, non-referral from paediatricians and lack of awareness about the disease in general. Thus, there is a need to know the exact prevalence of this disease and good screening programs. Timing is one of the important factors that ensure successful treatment in ROP, because the disease can progress very fast and delayed treatment often reduces the chances of success.[4]

The present study was conducted with an objective to determine the incidence and the risk factors of ROP in a tertiary care institute in Shimla situated at an altitudinal height of 2000 meter, where oxygen concentration of air is lower 80-90%.

METHODS

This was a hospital based prospective study to know the incidence of ROP, conducted at neonatal intensive care units at IGMC, Shimla, from June 2011 to July 2012. Sixty four premature and low birth weight neonates born /or admitted for different ailments in neonatal intensive care unit (NICU) were screened and followed up for a period of one year.

The children born before 35 weeks of gestation and birth weight of <1500 gms were taken up for the study. The babies having ocular disorders interfering with the fundus examination and those with congenital retinal abnormalities, who died or did not complete the follow-up, were excluded or dropped from the study. All eligible babies were screened at NICU where temperature was well controlled and the place to handle any emergencies existed. One cabin in NICU was converted to dark room for indirect ophthalmoscopy. Informed consent was obtained from parent or guardian of baby after being explained the procedure of screening for ROP.

Table 1: ICROP II classification of ROP.

1. Location	Zone I	Circle with optic nerve at center and radius of twice the distance from optic nerve to macula.
	Zone II	From edge of zone I to nasal orraserrata on nasal side and equator on temporal side.
	Zone III	Lateral most crescent shaped area from zone II to orraserrata temporally.
2. Severity	Stage 1	Presence of thin white demarcation line separating vascular from avascular retina.
	Stage 2	The line becomes more prominent because of lifting of retina forming a ridge with a height and width.
	Stage 3	Presence of extra retinal fibro-vascular proliferation with vessels and fibrous tissue arising from the ridge and extending into vitreous.
	Stage 4	Partial retinal detachment: A) not involving macula, B) involving macula.
	Stage 5	Complete retinal detachment.
3. Plus disease		Presence of dilatation and tortuousity of posterior retinal vessels.
4. Extent		Extent of involvement of retina expressed as clock hours (30° sectors).
5. Pre-plus disease		Vascular changes in posterior retina not sufficient for diagnosis of plus disease but showing more arterial tortuosity and more venous dilatation than normal retina.
Threshold ROP	Threshold ROP is present if five or more contiguous or eight cumulative clock hours (30-degree sectors) of stage 3 with plus disease in either zone 1 or 2 are present.	
Pre-threshold ROP	Pre-threshold 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.	

The pupils were dilated using 2.5% phenylephrine and 0.5% tropicamide eye drops instilled three times into each eye at intervals of 15 minutes about one hour before the scheduled examination. Care was taken to wipe off any eye drops with sterile cotton that come out of eyes to cheeks and not to feed the baby immediately before examination as the child could vomit or aspirate. The examination was carried out with indirect ophthalmoscope using convex 20 D lens along with paediatric wire speculum and scleral indenter. ROP was

classified based on international classification of ROP (ICROP II) as given in Table 1.[5]

For babies born before 28 weeks, the first examination was conducted at 4 weeks postnatal age or 32 weeks post-conceptional age, or whichever was earlier. For this purpose, gestational age was calculated from the last menstrual period, where available, or based on new Ballard score (taken from records). Babies born after 28 weeks of gestational were seen at two weeks after birth.

Follow up protocol

If no ROP was detected at initial examination, the infants were re-evaluated once every two weeks until vascularisation was complete. If ROP was detected, it was staged and details of extent and severity were recorded on retinal chart according to ICROP classification. Indirect ophthalmoscopic examinations were performed weekly for stage 1-2 disease and twice weekly for stage 3 diseases till the disease started resolving or progressed to threshold stage. Babies showing evidence of regression were followed up till vascularisation was complete. Babies with ROP were managed depending on the stage of disease as shown in Table 2.

Table 2: Management of ROP at different stages.

Stages of ROP	Management
Stage 1 & 2	Observation & close follow up
Stage 3	Laser photocoagulation
Stage 4 & 5	Vitrectomy

Data collection

Genders of newborn, birth weight (BW) and gestational age (GA) were recorded. The perinatal variables documented included presence of fetal distress, maternal supplemental oxygen administration before and during delivery. The following risk factors occurring during the first 4 weeks after birth were recorded: respiratory distress syndrome, surfactant administration, intraventricular hemorrhage, hyperbilirubinemia, blood transfusion, exchange transfusion, sepsis, duration of oxygen and duration of continuous positive airway pressure.

Statistical analysis

GA and BW in different groups were compared using t-test. Chi-square tests were used to compare the rate of ROP in different groups. Univariate analysis was used to explore variables associated with ROP with the appropriate significance of P <0.05, and those found to be significant were included in a logistic regression model using a backward stepwise method. The odds ratio (OR) and 95% confidence interval (CI) for each possible risk factor were also calculated.

RESULTS

A total of 1281 newborns were admitted in the hospital during this period. 241 had birth weight of less than 1500 gms and gestational age <35 weeks. Among them 64 were listed for the study but 14 babies lost to follow up, hence 50 were included in the study. Out of 50 neonates screened for ROP, 21 (42%) were male and 29 (58%) were females.

Incidence of ROP in this study group was 16% i.e. eight of the 50 neonates had evidence of ROP. Among males, 3 (14.3%) of 21 and in female newborns 5 (17.2%) of 29 developed ROP. Out of 8 babies who developed ROP, 5 (62.5%) were in stage 1 while 3 (37.5%) were in stage 2. However none of the neonates developed higher stage disease. The birth weight of the ROP babies ranged from 850-1500 grams (mean =1043.75 gms), while that of non-ROP babies ranged from 1000-1500 gms (mean =1333.52 gms). This difference was significant (p=0.000) using independent sample t- test. The incidence of ROP was 38.9% in babies weighing ≤1250 gms at birth.

Table 3: Distribution as per birth weight (range).

BW (gm)	Total	ROP	%
801-900	4	3	75.0
901-1000	6	2	33.3
1001-1100	3	1	33.3
1101-1200	6	1	16.6
1201-1300	5	0	0.0
1301-1400	11	0	0.0
1401-1500	15	1	6.0
Total	50	8	16.0

Mean BW of babies with stage 1 ROP was 1080grams and that of stage 2 ROP was 983.3gms. There was statistically significant (p=0.001) difference with non ROP group (mean BW= 1334.52gms). One way ANOVA test was used for statistical analysis.

Table 4: Distribution according to gestational age.

Gestational age	ROP		Total	% age
	Yes	No		
28 weeks	2	1	3	66.6
29 weeks	0	2	2	0.0
30 weeks	2	3	5	40.0
31 weeks	1	4	5	20.0
32 weeks	2	18	20	10.0
33 weeks	0	6	6	0.0
34 weeks	1	6	7	14.3
35 weeks	0	2	2	0.0

Mean gestational age of babies with ROP was 30.63 weeks and that of non ROP babies was 32.10 weeks, which was statistically significant (p=0.024) using independent sample t- test.

Table 6 demonstrates the incidence of ROP on oxygen administration. In total oxygen therapy was given to 33 (66%) babies out of 50. All the 8 (24.2%) babies who developed ROP had received oxygen (>24 hours), while no ROP was seen in babies not requiring oxygen. The association was statistically significant with p value 0.027.

Table 5: Mean gestational age of babies with and without ROP.

	ROP	No.	Mean	SD	Min	Max	p-value
GA	Yes	8	30.63	2.07	28	35	0.024
	No	42	32.10	1.54	28	35	

Table 6: Oxygen administration and incidence of ROP.

Oxygen administration	ROP		Total	Chi square value with 1d/f	p-value
	Yes	No			
No	0	17	17	4.906	0.027
	0%	100%	100%		
Yes	8	25	33		
	24.2%	76.8%	100%		
Total	8	42	50		
	16%	84%	100%		

Various risk factors and their statistical significance with ROP were given in Table 7. Exchange transfusion, respiratory distress syndrome (RDS) and septicaemia were the risk factors that showed significant association with ROP (P <0.05). No statistically significant relation was found between apneic spells, surfactant administration, blood transfusion, hyperbilirubinemia, phototherapy, septicaemia and ROP. None of the maternal factors like pregnancy induced hypertension (PIH), anti-partum haemorrhage (APH), hypoxic ischemic encephalopathy (HIE), premature rupture of membrane (PROM) or antenatal steroids did not show any significant association with ROP (p=0.686).

Table 7: Various Risk factors and their statistical significance with ROP.

Risk factor	Total babies	Babies with ROP	Odd's ratio		p-value
			OR	95% CL	
Oxygen	33	8	-	-	0.027
RDS	20	7	0.064	0.007-0.575	0.003
Septicemia	26	6	0.118	0.013-1.046	0.028
Exchange transfusion	3	2	0.073	0.006-0.936	0.003
Blood transfusion	9	3	0.278	0.052-1.479	0.117
Apnoea	5	1	0.316	0.047-2.118	0.797
Surfactant	8	1	1.400	0.148-13.242	0.768
Hyper-bilirubinemia	37	5	1.920	0.388-9.489	0.131
Phototherapy	37	5	1.920	0.388-9.489	0.131
HIE	1	0	-	-	0.659
APH	3	0	-	-	0.436
PIH	8	1	1.400	0.148-13.242	0.768
PROM	28	5	0.726	0.153-3.439	0.686
Antenatal steroids	12	1	2.484	0.274-22.536	0.406

Babies were kept on close follow up till complete vascularisation in non ROP group and till regression of ROP in ROP group and two babies were to be followed up even after completion of the study.

DISCUSSION

Retinopathy of prematurity is a bilateral vaso-proliferation in retina of premature baby or low birth weight babies which sometimes progresses to cause visual impairment or blindness. It is an avoidable cause of childhood blindness and its control is given priority in "WHO Vision 2020" programme. Its secondary prevention, i.e. its early treatment to prevent blindness, requires qualified ophthalmologists to screen babies at risk soon after birth.

The overall incidence of ROP in the present study was 16%. Various Indian and International studies had reported overall incidence 17.5% to 51.9% and 10.0% to 45.4% respectively.[6-8]

A study by Patil et al on 40 babies <32week or <1250grams had reported overall incidence of ROP 17.5% and none with severe ROP, while other studies on babies <35week or <1500grams have reported overall incidence around 20% and severe ROP in 7%. However, in most instances it is not possible to compare studies, as the inclusion criteria are different. Some centres include only smaller preterm babies, while others have more liberal inclusion criteria.

The mean birth weight of the ROP babies was 1043gms while that of non-ROP babies 1334gms. Lower birth weight was significantly associated with increased incidence (p=0.007) and severity (p=0.017) of ROP. The incidence of ROP was 38.9% in babies weighing ≤1250 gms at birth. The mean gestational age of the ROP babies was 30.63 weeks while that of non- ROP babies 32.1 weeks. The incidence of ROP was 33.33% in babies born ≤32 weeks of gestational age. No ROP seen after 34 week of gestation.

Oxygen is the prime factor for causation of the initial insult leading to ROP.[10,11] The concentration and fluctuation of oxygen administration are the key factors. Sudden discontinuation of oxygen and duration of oxygen therapy are also incriminated in the pathogenesis of ROP. Oxygen acts partly through vascular endothelial growth factor, plays a central role in retinal vessel development and in ROP. It is important to note that other biochemical mediators are also involved in the pathogenesis of retinopathy. Oxygen therapy was given to 33 (66%) babies. All the 8 (24.2%) babies who developed ROP had received oxygen, while no ROP was seen in babies not requiring oxygen. The association was statistically significant with p value 0.027.

Respiratory distress syndrome (p=0.003), exchange transfusion (p=0.003) and septicaemia (p=0.028) were other significant factors associated with the development of ROP. All these situations require oxygen administration and so could be indirectly associated with ROP. Out of 8 babies who developed ROP 5 (62.5%) were in stage 1, 3 (37.5%) were in stage 2 and no baby developed stage 3 or higher disease. So no severe ROP was seen in the study group. Possible causes could be monitored and judicious use of oxygen and earlier screening. Other causes could be smaller sample and relatively lower number of extremely premature babies. Similar results have been seen in other studies also.[12]

Though gender did not significantly influence the incidence but female predominance of ROP was seen (p=0.778) in the present study. On univariate analysis birth weight, gestational age, oxygen administration, RDS, sepsis, exchange transfusion and mechanical ventilation were found to be significant factors. Hence, meticulous fundus examination with indirect ophthalmoscopy in all preterm babies with birth weight ≤1500gms is essential non-invasive method for early detection of ROP and its progression.[13,14]

Limitations of the study

The sample size was small and may not represent all premature babies. To know the true incidence and risk factors involved it is advisable to undertake larger study over a period of years.

CONCLUSION

This study concludes that ROP is an important complication of prematurity. In most of the cases it does not require treatment but close follow up. Screening should be intensified in the presence of factors like oxygen administration, RDS and exchange transfusion. Better management of risk factor may reduce the chances of progression to visual threatening disease. Timely referral of detected ROP cases for treatment prevents blindness. There is need for the obstetricians, neonatologist and ophthalmologist to work in close co-operation to prevent blindness due to ROP.

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