Prevalence of Retinopathy of Prematurity and Its Associated Risk Factors in Pre-Term Neonates - A Cross-Sectional Study Conducted in a Tertiary Care Hospital, Ahmedabad

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Abstract

Background: In this study, we wanted to estimate the prevalence of ROP in preterm neonates**,** to evaluate risk factors associated with the development of ROP in preterm neonates and to determine the treatment outcome of ROP in neonates. **Material & Methods:** This cross-sectional study was conducted for two years in the neonatal intensive care unit of a tertiary care centre. All data were collected in pre-structured and predesigned proforma, and prior informed consent was taken. To analyse the qualitative data, Fisher exact test or chi-square test was used as the test of significance. A P-value of < 0.05 was considered statistically significant with a confidence interval of 95 %. **Results:** Proportions of ROP increased significantly with an increase in gestational age. Oxygen therapy correlated significantly with the development of ROP. Hyperbilirubinemia requiring phototherapy (80 %), sepsis (73 %), NEC (Necrotizing Enterocolitis) (35 %), HMD (Hyaline Membrane Disease) (41 %), PDA (Patent Ductus Arteriosus) (25 %) and IVH (Intraventricular Hemorrhage) (3.5 %) were found to be statistically significant for ROP development. Laser treatment was found to be very effective in regression of ROP. **Conclusions:** By preventing prematurity, controlling, or minimizing risk factors and meticulous ophthalmic screening of at-risk preterms, it may be possible to reduce the incidence of ROP. Since ROP is essentially asymptomatic in the early stages, carefully timed retinal examination, and treatment of at-risk infants for ROP by an ophthalmologist are necessary.

Key words: Retinopathy of prematurity, Risk factors, Incidence, Stages, Birth weight, Gestational age

Introduction

The incidence of ROP in India has been reported to vary between 20 - 51.9 % in low birth weight infants.[1-4] Apart from increasing survival of preterm infants, use of unblended and unregulated oxygen, variable quality of neonatal care, paucity of trained manpower, and lack of awareness have been implicated for the high incidence of ROP.[5] Blindness due to ROP can be prevented by following an evidence-based screening protocol, detecting ROP in pre-threshold stage and providing time-bound

treatment.[6] The objectives of this study were to estimate the prevalence of ROP in preterm neonates, to evaluate risk factors associated with the development of ROP in preterm neonates and to determine the treatment outcome of ROP in neonates.

Material and Method

This is a cross-sectional study conducted for two years in the neonatal intensive care unit, civil hospital, Ahmedabad. Convenient sampling was adopted and as reported in a previous study the proportion of ROP was 27.7 %.[7] A sample size of 1098 was estimated based on the formula $n = z^2(pq/d^2)$, where, z = 1.96 at 95 % confidence interval, P = 27.7 % (proportion of ROP), q = 100 - p (72.3 %) and d = relative precision (10.0 % of 'p' i.e. 2.77 and hence $d^2 = 7.67$) sample size of 1002 was calculated. Considering 9.5 % of 1002 as a non-response rate, i.e. 95.2≈96, a total sample size of 1098 was estimated. The study was conducted among 1098 (488 intramural, 610 extramural) babies admitted at civil hospital Ahmedabad NICU (Neonatal Intensive Care Unit) with birth weight < 1.75 kg, gestational age < 34 weeks, selected preterm with 1.75 - 2 kg weight and/or 34 – 36 week gestation with following risk factors viz., required cardio-respiratory support (ventilator and inotropic support), oxygen therapy, blood transfusion, intraventricular haemorrhage, septicaemia, patent ductus arteriosus and hyperbilirubinemia requiring treatment. After obtaining, informed consent and ethical clearance from the institutional ethical committee, the screening of all the preterm neonates was done based on the evidence-based clinical practice guidelines and according to the national neonatology forum, India recommendation. Ophthalmological examination was carried out among all the study subjects. All the infants WHO developed threshold disease as per ICROP (International Classification of Retinopathy of Prematurity) classification[8] or earlier if aggressive progression was seen in zone 1 disease, were treated using laser photocoagulation and anti-VEGF (Vascular Endothelial Growth Factor). The follow up was done according to the national neonatology forum, India recommendation on the 3rd and 7th day after the treatment.

Statistical Analysis:

All the data were entered into a Microsoft Excel sheet and the data were expressed in proportions. The association of various risk factors with the ROP was analysed using chi-square test of significance or Fisher exact test. A P value of < 0.05 was considered statistically significant with a confidence interval of 95 %. Univariate analysis using the chi-square test was used where multiple causation factors were present.

Results

Out of 1098 babies screened, 586 (53.4 %) babies were males, and 512 (46.6 %) babies were females. The male: female ratio in the study group was 1.14:1 and the gestational age ranged from 26 to 36 weeks. The maximum number of babies was between 32 and 34 weeks of gestational age. The birth weight ranged from 700 g to 1800 g. The maximum number of babies had birth weight from 1000 to 1500 g. Out of 1098 babies, 550 babies were SGA (Small for gestational age) and 512 were AGA (Appropriate for gestational age). Out of 1098 babies, 610 babies were extramural and 488 were intramural.

Out of 1098 babies screened, 263 babies developed ROP and the overall incidence was 4 %. Out of 263 babies with ROP, 155 (25 %) were males and 108 (20 %) were females. The incidence of ROP was predominant in male babies but was not found to be significant statistically with a P-value of 0.054.

Out of 263 babies with ROP, 42 (16 %) babies had < 28 weeks of gestational age, 89 (52 %) babies had 28 - 30 weeks, 62 (20 %) babies had 30 - 32 weeks, 38 (10 %) babies had 32 - 34 weeks, and 32 (17 %) babies had 34 - 36 weeks of gestation. As the gestational age decreased, the incidence of ROP increased. This difference was statistically significant with P < 0.05. Thus, the occurrence of ROP was noted to be significantly associated with gestational age. Higher proportions of ROP were observed in preterm babies.

For babies with birth weight < 1000 g, the incidence of ROP was 100 %. Incidence of ROP with birth weight between 1000 - 1500 g was 19.2 % and 24.1 % was between 1500 -2000 g. As birth weight decreased, the incidence of ROP increased and this difference was found to be statistically significant (P = < 0.05).

The proportion of ROP was higher in SGA (30 %) as compared to AGA (19 %) and was found to be statistically significant with P < 0.00023.

Among various neonatal risk factors, hyperbilirubinemia requiring phototherapy (80 %), sepsis (73 %), NEC (35 %), HMD (41 %), PDA (25 %) and IVH (3.5 %) were found to be statistically significant for ROP development with P-value < 0.05. Though hyperbilirubinemia was seen in 202 (80 %) of the patients, it was not found as a single major risk factor for the development of ROP. All the patients with hyperbilirubinemia who had been treated had another single or multiple major risk factors like sepsis in 182 (90 %), oxygen therapy in 172 (85 %), anaemia in 98 (56 %) and HMD in 62 (50 %) patients with ROP. Out of 72 (27 %) patients who had not received oxygen therapies had other risk factors like septicaemia, hypoglycaemia, PDA, and birth asphyxia. All these patients were in the 1.5 - 2 kg birth weight group.

Table 1. Univariate analysis of risk factors in babies with ROP

Variables	Total number of babies with ROP (N = 263) ¥ (%)	Total number of babies without ROP (N = 835) ¥ (%)	P value
Risk Factors			
Hyperbilirubinemia requiring treatment	202 (80.8%)	277 (33%)	<0.05*
Sepsis	183 (73.2%)	147 (18%)	<0.05*
Anaemia	114 (45.6%)	81 (9.6%)	<0.05*
HMD	103(41.2%)	79 (9.3%)	<0.05*
Acidosis	93(35%)	32(4%)	<0.05*
NEC	87 (34.8%)	55 (6.5%)	<0.05*
PDA	63 (25.2%)	67 (7.9%)	<0.05*
Birth Asphyxia with HIE	49(19.6%)	71(8.3%)	0.0000075*
Apnoea	26(10.4%)	19(2.2%)	<0.05*
Hypoglycaemia	24(9.6%)	110 (13%)	0.1007
IVH	9(3.6%)	2(0.2%)	0.0000312*
Treatments			
Phototherapy	202(80%)	269(32%)	<0.05*
Oxygen therapy	191(73%)	73(8.7%)	<0.05*
Blood Transfusion	91(36.4%)	38 (4.5%)	<0.05*
HMD with Surfactant	56 (22.4%)	17 (2%)	<0.05*
Antenatal Steroid given	22(8.8%)	118 (13.9%)	0.0144*
Exchange Transfusion	0 (0%)	8(1%)	0.111

¥-'n' is for each row for respective columns *indicates a significant statistical association

Table 2. Different ways through which oxygen support was given

Ways of oxygen support given	Total number of babies with ROP (N = 191) (%)	Total number of babies without ROP (N = 73) (%)
O2 with nasal prongs	36 (18.8%)	14 (19.2%)
CPAP Support	31 (16.2%)	8 (10.9%)
Ventilator support	20 (10.5%)	5 (6.8%)
O2 with hood	104 (54.5%)	46 (63.1%)

Among the subjects with ROP, nearly 73.0 % required oxygen therapy and among those with no ROP, only 8.7 % required oxygen therapy. Oxygen therapy was associated significantly with the development of ROP ($P < 0.05$). Out of 263 patients, ROP was observed in 104 (54.5 %) patients who were given oxygen support with hood, 36 (18.8 %) received oxygen with nasal prongs whereas only 31 (16.2 %) CPAP and 20 (10.5%) patients on ventilator support suggesting that the use of oxygen blenders for oxygen therapy will decrease the incidence of ROP.

Out of 191 babies, 33 (17.3 %) had received for 24 - 48 hours, 52 (27.2 %) had received for 48 - 72 hrs and 106 (55.5 %) for > 72 hours. Babies who received more hours of oxygen were more prone to develop ROP ($P < 0.05$). Therefore, the duration of oxygen support was associated significantly with the development of ROP. An increase in the duration of oxygen support increases the incidence of ROP.

Table 3. Duration of oxygen support and ROP

Duration of Oxygen Support	Total number of babies with ROP (N = 191) (%)	Total number of babies without ROP (N = 73) (%)	P value
≤48 Hr	33 (17.3%)	44 (60.3%)	<0.00001*
48-72 Hr	52 (27.2%)	19 (26.0%)	
>72 Hr	106 (55.5%)	10 (13.7%)	
*indicates a significant statistical association			

Hyperoxia was noted in 55.1 % and 8.5 % of those with and without ROP respectively. Similarly, hypoxia was noted in 13.7 % and 1.7 % respectively. Acidosis was noted among 35.3 % of those with ROP and 3.8 % of those with no ROP.

Hyperoxia was found to be significant if there were > 3 episodes ($P < 0.05$). The proportions of those with ROP who had developed hypoxia (> 2 episodes) were higher compared to those who did not have ROP but it lacked significance. Acidosis was found as a significant risk factor for the development of ROP ($P < 0.05$). Therefore, frequent monitoring with ABGA was necessary.

Table 4. ABGA and ROP

ABGA	Total number of babies With ROP (%)	Total number of Babies Without ROP (%)	P value
Hyperoxia (No. of Episodes)	**(N = 145)**	**(N = 72)**	<0.0001 *
≤1	16 (11.0%)	17 (23.6%)	
2-3	57 (39.3%)	43 (59.7%)	
>3	72 (49.7%)	12 (16.7%)	
Hypoxia (no. of Episodes)	**(N = 36)**	**(N = 14)**	
1	13 (36.1%)	9 (64.2%)	0.07
2-3	23 (63.9%)	5 (35.7%)	
Acidosis	**(N = 273)**	**(N = 835)**	
Yes	93 (35.4%)	32 (3.8%)	<0.0001 *
No	170 (64.6)	803 (96.2)	
* indicates a significant statistical association			

Out of 263 babies with ROP, 151 (57 %) had stage 1 ROP, 78 (30 %) had stage 2 ROP, 20 (7 %) had stage 3 ROP, 6 (2 %) had stage 4 ROP, 1 (0.3 %) had stage 5 ROP. Maximum number of babies had stage 1 ROP.

Out of 78 babies with stage 2 ROP, 42 (54 %) had weight between 1 - 1.5 kg, 21 (27 %) had a birth weight less than 1 kg and 15 (19 %) had birth weight between 1.5 - 2 kg. All the babies whose ROP progressed to stage 2 plus and stage 3 plus belonged to either weight group < 1 kg or between 1 - 1.5 kg. The baby whose ROP progressed to stage 5 weighed less than 1 kg. Also, all the babies whose ROP

progressed to stage 4 had weight less than 1 kg further strengthening the significance of birth weight as a risk factor in the progression of ROP.

Out of 151 babies in stage 1, 88 (58 %) babies weighed 1 - 1.5 kg, 58 (39 %) babies weighed 1.5 to 2 kg. Out of 151 babies with stage 1 disease, 5 (3 %) were born in less than 28 weeks of gestational age, 48 (32 %) were born between 28 - 30 weeks, 44 (30 %) were born between 30 -32 weeks, 29 (19 %) were born between 32 - 34 weeks and 25 (16 %) babies were born between 34 - 36 weeks. Out of 78 babies with stage 2 disease, 13 (17 %) were born in less than 28 weeks gestational age, 37 (47 %) were born between 28 - 30 weeks, 12 (16 %) were born between 30 - 32 weeks, 9 (11 %) were born between 32 - 34 weeks and 7 (9 %) babies were born between 34 - 36 weeks.

Out of 20 babies with stage 3 disease, 14 (70 %) were born in less than 28 weeks gestational age, 4 (20 %) were born between 28 - 30 weeks and 2 (10 %) were born between 30 - 32 weeks. Out of 4 babies with stage 2 plus disease, 1 was born at gestational age less than 28 weeks, 1 was born between 28 - 30 weeks whereas 2 babies were born at 30 - 32 weeks gestational age. Out of 3 babies with stage 3 plus disease, 2 were born at gestational age less than 28 weeks, 1 was born between 30 - 32 weeks gestational age. The baby whose ROP progressed to stage 5 was born at gestational age lessthan 28 weeks. Also, all the babies whose ROP progressed to stage 4 had gestational age less than 28 weeks further strengthening the significance of gestational age as a risk factor in the progression of ROP.

Out of 263 babies, 53 babies were given treatment in the form of either laser photocoagulation therapy or intravitreal anti-VEGF. 32 (60 %) babies received laser photocoagulation and 14 (26 %) received anti-VEGF therapy. All the 53 babies showed regression following treatment. All babies withstood the procedure well and there was no post-laser complication other than reddening of the conjunctiva, which regressed in 2-3 days. Seven (7) babies who had stage 4 and 5 ROP were advised surgery.

Table 5. Treatment of babies with ROP

Treatment Modality	Number of Babies (N = 53) (%)
Laser Photocoagulation	32(60%)
Anti VEGF	14(26%)
Surgery	7(14%)

All babies with stage 1 ROP had regressed spontaneously. Out of 78 babies with stage 2 ROP, 58 (73.33 %) had regressed spontaneously. 12 babies received laser photocoagulation and 8 received the intravitreal anti-VEGF following which there was a regression. Out of 20 babies with stage 3 ROP, 17 received laser photocoagulation and 3 received the intravitreal anti-VEGF following which there was a regression. There were 4 babies with stage 4 ROP and 1 with stage 5 ROP. All these babies were advised for surgery. Out of 4 babies with stage 2 plus disease, 1 had regressed spontaneously and 3 babies regressed with treatment. Out of 3 babies with stage 3 plus disease, all regressed with treatment.

Table 6. Progress and outcome of babies with ROP

Stage of ROP	Number of Babies (N = 263)	Regressed Spontaneously Without treatment (%)	Regressed by treatment	Mode of treatment		
				Laser therapy	Anti-VEGF factor	Surgery
1	151	151 (100%)				
2	78	58 (73.33%)	20(26.7%)	12	8	
3	20	-	20(100%)	17	3	
4	6	-	-			6
5	1	-	-			1
2 3	4 3	1(25%) 0(0%)	3(75%) 3(100%)	2 1	1 2	

Discussion

Comparative analysis of occurrences of ROP:

The proportions of ROP in various Indian studies ranged from 20 % t o -51.8 %. Gopal et al. had reported 38 % incidence of ROP in 1995, Maheshwari et al. had reported 20 % incidence of ROP in 1996, Varughese et al. had reported 51.9 % incidence of ROP in 2001.[9-11] International studies had reported incidence of ROP in preterm babies ranging from 10 to 45.5 % and Schalij-Delfos et al. had reported incidence of ROP 27 % in 1996.[12] The overall incidence of ROP in the present study is 23.69 %, which was similar as reported in Chaudhari et al. a study in 2009 (22.6 %).[13]

Comparative analysis of P-value of risk factors and ROP:

In our study, there was a difference in the incidence of ROP among SGA and AGA. Shah et al. had not shown a significant difference of ROP among SGA and AGA.[14] It was proposed that compromisation of perfusion to organ can predispose to free radical injury that increases the risk of ROP. It has been reported that infants who are born SGA may be more likely to develop ROP.[15] In our study, oxygen therapy (65%), hyperbilirubinemia requiring phototherapy (80 %), sepsis (73 %), NEC (35 %), HMD (41 %), PDA (25 %) and IVH (3.5 %) were found to be statistically significant for the development of ROP with P-value < 0.05. Hyperbilirubinemia increases the risk of the opening of ductus arteriosus in preterm babies. Recently, phototherapy has been shown to increase mean cerebral blood flow velocity.[16] It is a significant risk factor in our study, still the association and positive influence of other risk factors can‘t be ruled out. The association of all other risk factors were similar to our study. In Chaudhari et al. study, oxygen support (60 %) and sepsis (52 %) were found to be statistically significant for ROP.[13] In addition, they found apnoea as a significant risk factor for ROP but it was not observed in our study.

Oxygen therapy and ROP:

Hussain et al. found the duration of oxygen as a factor predictive of ROP.[17] Similarly our study had also found oxygen as a significant risk factor. Our study had shown that oxygen supplementation for > 72 hours was highly significant for ROP. This reveals that the duration of oxygen therapy is directly proportional to the development of ROP.

Arterial blood gas analysis:

Shouhat et al. reported episodes of hypoxia as a risk factor for ROP. Other studies had shown hyperoxia and acidosis as risk factors for ROP.[18] Similarly in the present study, > 3 episodes of hyperoxia and acidosis were found to be significant risk factors for ROP.

Progress and outcome:

Babies with stage 1 and most of stage 2 without the plus disease had shown spontaneous regression of ROP. Sashidharan et al. had shown that most infants with initial stages of ROP had spontaneous regression of disease.[19] 7 out of 263 babies had the plus disease, out of which 4 babies had progressed from stage 2 and 3 babies had stage 3 plus disease. Similarly, Kumar et al. had reported a 4.7 % incidence of severe ROP.[20] It was noted that plus disease was more common in lower birth weight and gestation. One baby had shown spontaneous regression of ROP with plus disease and that baby had birth weight > 1000 g and gestational age > 30 weeks suggesting better outcome with higher gestational age and weight.

Treatment:

In our study, out of 263 babies with ROP, 32 (13%) babies received laser treatment and 14 (5%) received anti-VEGF therapy. There were 33.3% of babies given treatment with laser photocoagulation in the Chaudhari et al. study.[13] The profile and outcome of screened babies were similar to our study. Laser treatment was found to be very effective in regression of ROP. Ng et al. and Connolly et al. have reported that long term structural and functional outcome using a laser was superior to that obtained with cryotherapy.[21,22] Yetik et al. reported total regression in more than 95% of cases with the use of anti-VEGF therapy.[23] Wu w-c et al. reported a similar outcome with complete regression as observed in 88%.[24]

Conclusion

The present study highlights the magnitude of the problem due to ROP in Indian preterm babies. The incidence is likely to increase as smaller babies survive unless a parallel reduction in other risk factor occurs. By preventing prematurity, controlling or minimizing risk factors and meticulous ophthalmic screening of at-risk preterms, it may be possible to reduce the incidence of ROP. As the role of an obstetrician, neonatologist and ophthalmologist are vital; they should work in close co-operation. Since ROP is essentially asymptomatic in the early stages, standards of practice now demand carefully timed retinal examination and treatment of at-risk infants for ROP by an ophthalmologist to minimize the risk of visual loss in these infants. Various studies have been done to evaluate the factors contributing to the development of ROP. But there is a paucity of Indian data. This study was undertaken to shed more light on the subject.

Recommendations:

Birth weight of less than 1750 grams and/or gestational age of less than 34 weeks should be used as a cut-off for performing retinal screening examinations at all level 2 care newborn units. Babies with a gestational age of 34 to 36 weeks gestation or birth weight between 1750 and 2000 grams should also be screened if risk factors like prematurity, oxygen support, sepsis, acidosis, PDA, hyperbilirubinemia for developing ROP are present.

Limitations of Study:

The actual incidence of ROP can be higher as follow up of preterm's was not part of the study. ROP is considered a disease with multifactorial causations. Attributing a single risk factor for causation was not possible in this study. Multivariate logarithmic regression analysis should be done to attribute a single risk factor for causation.

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