ACTA MEDICA LITUANICA. 2006. VOLUME 13 No. 3. P. 147–151

Analysis of risk factors for the development of retinopathy of prematurity in preterm infants at a tertiary referral hospital in South India

Krishna R. Murthy[1],

Nagendra[2],

Kalpana Babu[1],

Naveen Benakappa[2],

Niranjan[2],

Praveen R. Murthy[1]

[1] Department of Vitreo Retina and Paediatric Ophthalmology, Vittala International Institute of Ophthalmology, Bangalore, India

[2] Neonatal Intensive Care Unit, Indira Gandhi Institute of Child Health, Bangalore, India

Background: With the advances in neonatal care, more and more very low birth weight and short gestation age babies are surviving. Along with this population, the incidence and morbidity of retinopathy of prematurity (ROP) is increasing. Analysis of causative factors is imperative.

Materials and Methods: All preterm babies with gestational age ≤ 34 week and/or birth weight of ≤ 1750 g who were admitted in Neonatal Intensive Care Unit (NICU) of Indira Gandhi Institute of Child Health (IGICH) were enrolled. All babies underwent detailed ophthalmologic examination with indirect ophthalmoscope. A detailed history was taken regarding maternal risk factors during pregnancy, complications during delivery and early neonatal complications. Babies who developed threshold ROP underwent laser to avascular retina and those who progressed to stage IV or V underwent vitreous surgery.

Results: The incidence of ROP was 24%. Administration of oxygen, duration of oxygen delivery, apneic spells, short gestational age, hyaline membrane disease and exchange transfusion were significant risk factors for development of ROP. Sepsis, low birth weight, mechanical ventilation, twin pregnancies and maternal risk factors did not influence ROP. Laser was effective in regressing ROP.

Conclusion: Controlling ROP will need team effort and effective delivery of oxygen, quick recognition and management of apneic spells and proper treatment of hyaline membrane diseases.

Key words: retinopathy of prematurity, neonatal, prematurity

INTRODUCTION

ROP is the main cause of visual impairment in premature infants. Due to the advances in neonatal care, there has been an increased survival of very low birth weight infants, which has produced a population of infants at a high risk for developing ROP. Short gestation and low birth weight have been identified as the most important risk factors responsible for ROP, other recognized risk factors being sepsis, intraventricular haemorrhage, mechanical ventilation, oxygen therapy, blood transfusion and exposure to light (1).

Corresponding author: Dr. Krishna R. Murthy, Vittala International Institute of Ophthalmology, (A unit of the Sri Keshava Trust), CA Site 1, 2 Cross, 2 Main, 7th block, Banashankari 3rd Stage, Hosakerehalli, Bangalore 560 085, India. E-mail: viio@vsnl.net

Purpose of the study

To identify the antenatal and early neonatal factors in preterm infants, which could influence the development of ROP in these babies, and the effect of laser treatment in controlling this disease.

MATERIALS AND METHODS

The present study was a prospective study from the period of September 2004 till October 2005. The study population consisted of preterm babies with a gestational age of less than or equal to 34 weeks and / or birth weight less than or equal to 1750 g over a period of one year. Fifty consecutive infants admitted to the Newborn Intensive Care Unit at Indira Gandhi Institute of Child Health, who fulfilled the study criteria and who attended follow/up visits for eye examination were studied.

The various factors recorded in the study were gestational age, birth weight, sex, type of delivery, maternal risk factors like leaking per vaginum, hypertension and diabetes, and associated neonatal risk factors like blood transfusion, sepsis, apnea, exchange transfusion, hyperbilirubinemia, phototherapy, oxygen supplementation and mechanical ventilation.

Apnea was defined as cessation of respiration for >20 seconds, accompanied by bradycardia or cyanosis. Sepsis was diagnosed on the basis of clinical features and laboratory features of changes in leukocyte count, C reactive protein and positive blood culture. Anemia was taken as a hematocrit value below 40%. Babies requiring oxygen therapy or mechanical ventilation had continuous monitoring via pulse oximeter and arterial blood gases wherever possible.

Babies were examined by the same ophthalmologist each time. The first examination was done at 32 weeks post conceptional age or 4 weeks after birth. Gestational age of the babies was calculated from the date of the last menstrual period and the babies were assessed by modified Ballard's score for correlation. Clinical assessment by New Ballard's scoring correlated with gestational age by LMP in almost all the babies. Babies were examined in the NICU if they were hospitalised, or in the ophthalmology clinic after discharge from the hospital.

The pupils were dilated using 2.5% phenylephrine and 0.4% tropicamide eye drops instilled two times into each eye at intervals of 15 minutes. Resistance to dilatation was noted. Indirect ophthalmoscopy was performed using a 20 D lens. A pediatric wire speculum was used to keep the eyelids apart and a wire vectis was used as a scleral indenter to visualize the periphery of the retina. During examination, untoward neonatal complications were looked for. The examinations were done in the presence of a pediatrician to manage any untoward incidents during examination.

Infants were followed up till the retinal vascularisation was complete or till the disease was stable. Infants who had no ROP were followed up every 4 weeks till the retinal vascularisation was complete. Infants in whom ROP was detected were followed every week. Babies progressing to threshold stage were treated with laser photocoagulation.

Classification of ROP was done according to the International Classification of ROP (ICROP). Neonatal and maternal risk factors were entered into a prepared proforma. Babies who were diagnosed to have hyaline membrane disease of prematurity were given surfactant therapy only if the parents were able to afford the cost of the surfactant.

RESULTS

The total number of babies included in the study during the period from October 2004 to September 2005, fulfilling the criteria of less than 34-week gestation and / or birth weight less than 1750 g was 50.

Sex distribution in the study

Out of the 50 babies analyzed, 33 babies were male and 17 female. The ratio of male: female in the study group is 1:0.5 (Table 1).

Table 1. **Incidence of ROP**

Sex	No. of babies	Babies with ROP	Percentage of babies with ROP
Male	33	7	21.2%
Female	17	5	29.4%
Total	50	12	24%

The incidence of ROP in our study was 24%. 21.2% of male babies and 29.4% of female babies developed ROP. The difference between the male and female babies was not statistically significant ($p > 0.05$).

Incidence of ROP by gestational age

The incidence of ROP in babies with gestational age of 28 weeks or less was 60%, 34.78% in babies >28 to 32 weeks and 4.55% in babies with gestational age 33 and 34 weeks (Table 2).

Table 2. **Distribution of study group by gestational age**

Gestational age	< or equal to 28 weeks	> 28 to < or equal to 32 weeks	> 32 to 34 weeks
No. of babies	5	23	22
Percentage	10	46	44

A statistically significant correlation was found between gestational age and ROP ($p < 0.05$).

There was no such correlation between birth weight and ROP in our study ($p > 0.05$) (Tables 3–4).

Duration of oxygen administered and ROP

All the babies who had ROP in our study had received oxygen. 33.3% of babies with ROP had received oxygen for 2 days, 16.67% for 3 days and 25% for 4 days. There was a significant increase in the incidence of ROP in relation to the duration of oxygen administration. The correlation between the duration of oxygen administered and the incidence of ROP was found to be statistically significant (p value < 0.05) (Figure).

Individual risk factors and their univariate analysis are shown in Table 5.

Supplemental oxygen and ROP

Out of 50 babies in the study, 31 babies had received oxygen (62%).

Of 38 babies in whom ROP was absent, 50% had received oxygen. All the 12 babies who had ROP had received oxygen during their NICU stay.

Supplemental oxygen administration was a significant risk factor in the development of ROP ($p < 0.05$).

Duration of administration of oxygen in ROP and non-ROP babies

The mean duration of oxygen administration in ROP babies was 3.91 days and in non-ROP babies 1.21 days. The duration of oxygen administration is statistically significant ($p < 0.05$).

Apneic spells and ROP

Four out of 50 babies had apneic spells, and all but 1 went in for ROP. Of 12 babies with ROP, 3 babies (25%) had apneic spells.

A statistically significant relation was found between apneic spells and ROP ($p < 0.05$)

Sepsis and ROP

Seventeen babies in our study had sepsis.

Of 12 babies with ROP, 6 (50%) had sepsis. Of 38 babies who had no ROP, sepsis was seen in 11 babies (28.95%).

Table 3. **Incidence of ROP by birth weight**

Birth weight (grams)	No. of babies	No. of babies with ROP	Percentage
800–1000	4	2	50.00
1001–1200	4	1	25.00
1201–1400	8	4	50.00
1401–1600	5	0	0.00
1601–1800	17	4	23.53
1801–2000	10	1	10.00
2001–2200	2	0	0.00
Total	50	12	

Table 4. **Statistical significance of correlation between birth weight and ROP**

Statistic	DF	Value	P value
Chi-square	6	7.7367	0.2580

Sepsis was not a significant risk factor for ROP in our study ($p > 0.05$).

Blood transfusion and ROP

Eight out of 50 babies had received packed cell transfusions.

Of 12 babies with ROP, 4 (33.33%) had received packed cell transfusions.

Of 39 babies with no ROP, 4 babies (10.53%) had received packed transfusions.

Out of 42 babies with no packed cell transfusions, 8 had ROP (19.05%).

Blood transfusion was not found to be a statistically significant factor of ROP ($p > 0.05$).

Exchange transfusion and ROP

Five out of 50 babies had exchange transfusion in our study.

Of 12 babies with ROP, 3 babies (25%) had received exchange transfusion.

Of 38 babies with no ROP, 2 babies (5.26%) had exchange transfusion. Exchange transfusion was found to be a significant factor in the development of ROP on univariate analysis ($p < 0.05$).

Hyaline membrane disease and ROP

Fifteen babies in our study had HMD, out of which 7 babies had ROP.

Of 12 babies with ROP, HMD was seen in 7 babies (58.33%).

Of 38 babies with no ROP, HMD was seen in 8 babies (21.05%).

HMD was found to be a significant risk factor for development of ROP ($p < 0.05$).

Mechanical ventilation and ROP

Ten babies had received mechanical ventilation out of whom 4 babies developed ROP (40%).

Table 5. **Individual risk factors and their univariate analysis**

Risk factor	Total babies	Babies with ROP	p-value	Significance
Maternal hypertension	6	0	0.1423	NS
Maternal diabetes	1	0	0.5703	NS
PROM	13	3	0.9278	NS
Gest. age (LMP)			0.0170	S
NEC	2	1	0.3796	NS
Multiple births	3	0	0.3154	NS
Oxygen administration	31	12	0.0019	S
Duration of oxygen administration			0.0045	S
Ventilation	10	4	0.1853	NS
Apnea	4	3	0.0128	S
Sepsis	17	6	0.1796	NS
Blood transfusion	8	4	0.0603	NS
Exchange transfusion	5	3	0.0469	S
Hyaline membrane disease	15	7	0.0140	S
Anemia	11	4	0.1974	NS

Notes. S = significant, NS = not significant, Gest. age = gestational age by LMP.

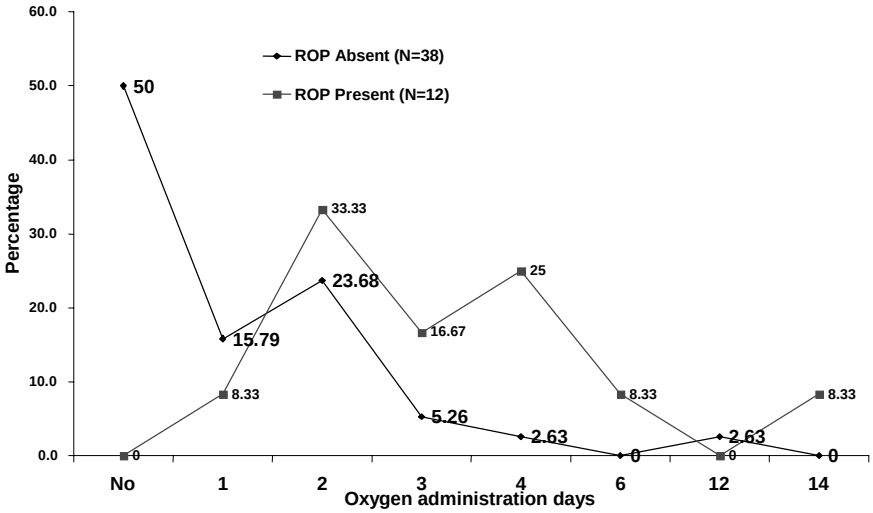

Figure. Distribution of Oxygen administration days among study population according to ROP

Of 12 babies with ROP, 4 babies (33.33%) had received mechanical ventilation. Six (15.79%) out of 38 babies who had no ROP had received mechanical ventilation.

Mechanical ventilation was not statistically significantly associated with ROP ($p > 0.05$).

Phototherapy and ROP

Thirty-three babies out of 50 babies had received phototherapy in our study.

Of 12 babies with ROP, 9 babies (75%) had received phototherapy. Of 38 babies who had no ROP, 24 (63.16%) had received phototherapy.

Our study did not show any statistically significant correlation between phototherapy and ROP ($p > 0.05$).

Maternal hypertension and ROP

Our study group had 6 mothers who had pregnancy-induced hypertension. None of the babies born to this group of mothers had ROP.

Of 12 babies with ROP, none of the mothers had hypertension. Of 38 babies who had no ROP, 6 mothers (15.79%) had hypertension.

Hypertension was not a statistically significant factor of ROP development in our study.

Maternal diabetes and ROP

Our study group had just one mother with gestational diabetes. Her baby did not have ROP.

Maternal PROM and ROP

There were 13 mothers who had prolonged rupture of membranes (PROM) in our study group. Of 12 babies with ROP, PROM was found in mothers of 3 babies (25%). Of 38 babies with no ROP, PROM was seen in 10 babies (26.32%).

There was no statistical association between leaking per vaginum and ROP ($p > 0.05$).

Our study found no statistically significant correlation between development of ROP and any of the maternal risk factors like PROM, hypertension and diabetes.

Twins and ROP

Our study had 2 sets of twins (4 babies). None of them had ROP.

There was no reliable difference in ROP between twins and singletons ($p > 0.05$).

Anemia and ROP

Anemia was found in 11 babies in the study. Four of these 11 babies had ROP, whereas 7 did not develop ROP. Of 39 babies who had no anemia, 8 developed ROP.

Anemia was not a statistically significant factor in the development of ROP in our study ($p > 0.05$).

NEC and ROP

NEC was seen in 2 babies. NEC was not a statistically significant factor of ROP in our study ($p > 0.05$).

Number of babies and different stages of ROP

The incidence of ROP in the present study was 24% (12 out of 50 babies had ROP). All the babies had a bilateral disease. Stage I was seen in 1 baby, Stage 2 in 1 baby, stage 3 in 9 babies, one baby had stage 4 disease when first seen and then went on stage 5 in spite of photocoagulation therapy being done. One baby had zone 1 disease, zone 2 disease was seen in 8 patients, and 3 had zone 3 disease.

Out of 12 babies, 9 developed threshold ROP and 3 didn't. One baby developed threshold ROP in one eye, while the remaining 8 babies developed bilateral disease (17 eyes had threshold ROP). Tortuosity of retinal vessels was seen in one ROP baby who progressed to threshold ROP.

Laser photocoagulation and ROP

Nine babies had threshold ROP. (There were 17 eyes with threshold ROP since one baby had threshold ROP in one eye). One baby with bilateral disease did not turn up for laser.

The remaining 15 eyes were subjected to laser photocoagulation. ROP regressed in all but one baby.

Mean gestational age of ROP and non-ROP babies

The gestational age of ROP babies varied from 28 to 34 weeks. The mean gestational age of the ROP babies was 30.8 weeks, whereas the mean gestational age of the non-ROP baby was 32.78 weeks.

On univariate analysis, gestational age, oxygen administration, duration of oxygen administration, apnea, exchange transfusion and hyaline membrane disease were significantly associated with ROP.

DISCUSSION

Retinopathy of prematurity is no longer a disease of the developed world as more and more very low birth weight babies in the developing countries are able to survive due to improvement in neonatal care. Short gestational age, oxygen supplementation (2,3), low birth weight, sepsis (4), apneic spells (3, 5), twin pregnancies, exchange transfusions (3), hyaline membrane disease (3, 4), mechanical ventilation, maternal risk factors (6) and anaemia (7) have been suspected to influence the incidence of ROP. Most of these studies have been done in developed countries and may not reflect the scenario in many of the developing countries.

The incidence of ROP in the present study (24%) compares favorably with the reported incidence from other studies.

In our study, oxygen administration and its duration was found to be a significant factor in the development of ROP.

Apneic spells, hyaline membrane disease, short gestational period and exchange transfusions were significantly associated with increased risk of ROP.

Sepsis, mechanical ventilation, twin pregnancy, low birth weight and all the maternal risk factors studied did not seem to significantly influence the incidence of ROP.

There was also no significant influence of the sex of the baby on the development of ROP. Out of 12 babies with ROP, 9 developed threshold ROP and 3 did not. One baby developed threshold ROP in one eye while the remaining 8 babies developed bilateral disease (17 eyes had threshold ROP).

Laser photocoagulation was found to be very effective in regressing ROP. One baby progressed to stage V in spite of laser, since the child has zone 1 disease.

CONCLUSION

In our opinion, the effective management of retinopathy of prematurity requires a team effort of the neonatologist, ophthalmologist and the NICU staff. Also, along with regular screening, an effective control of oxygen delivery, reduction of apneic spells and their early recognition and effective management of hyaline membrane disease are required. However, we could not study the role of surfactant because of its prohibitive costs.

Received 8 June 2006
Accepted 31 July 2006

References

1. Padmani Karna, Jyotsna M, Linda A. Retinopathy of prematurity and risk factors: a prospective cohort study. BMC Paediatrics 2005; 5:18.
2. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol 1995; 43: 123–6.
3. Ved P Gupta, Upreet Dhaliwal, Rohit Sharma, Piyush Gupta, Jolly Rohtagi. Retinopathy of prematurity – risk factors. Indian Journal Of Pediatrics Vol 71 – Oct 2004; 887–92.
4. Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari AK. Incidence and risk factors for retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J Ind 1996; 9(5): 211–4.
5. Rekha S, Battu RR. Retinopathy of prematurity: incidence and risk factors. Indian Pediatrics 1996; 33: 999–1003.
6. Holmstrom G, Thomason P, Broberger U. Maternal risk factors for retinopathy of prematurity – a population based study. Acta Obstet Gynecol Scand 1996; 75(7): 628–35.
7. Subina Narang, Sourabh Dutta, Anil Narang. Risk factors for threshold retinopathy of prematurity. Indian Pediatrics 2004; 41: 665–71.