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Original Article

Retinopathy of Prematurity: Frequency and Risk Factors in a Tertiary Care Hospital in Karachi, Pakistan

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Abstract

Introduction: To determine the frequency of Retinopathy of Prematurity (ROP) in the premature infants born in a tertiary care hospital and to determine the risk factors associated with it.

Methods: This was a retrospective analysis of premature infants with birth weight ≤ 1500 grams or gestational age ≤ 32 weeks, admitted to the Neonatal Intensive Care Unit of a tertiary care hospital in a three year period. The infants underwent eye examinations between their 4th and 7th week of life. Univariate and multiple logistic regression analysis were performed to determine the association between risk factors and ROP development.

Results: Sixty eight infants were included in the analysis. Out of these, 22 (32.4%) developed ROP (inclusive of all stages) and 14 (20.6%) developed threshold disease. Multiple logistic regression analysis revealed that low gestational age, sepsis and respiratory distress syndrome were independent predictors for the development of ROP.

Conclusion: The frequency of ROP in our hospital was on the higher side of the range reported in neighbouring developing countries. Low gestational age, sepsis and respiratory distress syndrome were independent predictors of ROP development. Our results suggest that ROP is an important emerging cause of preventable childhood blindness in urban areas of Pakistan like Karachi (JPMA 58:186;2008).

Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the eye affecting preterm infants which can progress to cause visual impairment or blindness. Recent advances in neonatal care in the last decade, have improved the survival rates for premature infants.[1] Consequently, the incidence of ROP has increased in parallel.[2,3] ROP is an important cause of childhood blindness in both developed[4] and developing countries.[3,5] This view is also expressed by the World Health Organization's "Vision 2020 programme".

Research has identified several factors which have been shown to have some causal association with ROP. However, three factors have shown consistent and significant association with ROP: low gestational age, low birth weight and prolonged exposure to supplementary oxygen following delivery.[6,7] Other putative risk factors include mechanical ventilation[8], sepsis[6,9], intraventricular haemorrhage[6], surfactant therapy[7,10], anaemia[11], high number of blood transfusions[11], apnoea[7,9], male gender and poor postnatal weight gain. It is difficult to determine whether these factors are actual predictors of ROP or if they reflect the severity of illness.

Although screening criteria have been suggested by various international institutions[12,13]; variations in quality of neonatal care facilities, socioeconomic status of patients, accessibility of services and awareness about ROP lead to variations in incidence of ROP in the same country. Therefore, it is imperative that studies be conducted to complement adapted screening programmes in each country. It is equally important to revise these criteria regularly. A number of studies, prospective as well as retrospective[6-8] have been done in developed countries to find out the frequency and specific features of ROP present in their own populations.

Pakistan is a developing country with poor health indicators. It is currently the sixth most populous country in the world.[14] The majority of the population (66%)[14] lives in rural areas. Intensive care facilities for premature infants are costly and specialized services are less likely to be established in remote and rural areas. Therefore, survival rates for premature neonates in these rural areas are low and ROP is not a significant cause of blindness there. However, in the urban cities where adequate neonatal care facilities are available, it can be predicted that ROP will emerge as an important cause of childhood blindness.

In the light of the above background, we decided to conduct a study to determine the incidence of ROP in the premature infants born in our hospital and to determine the risk factors associated with ROP.

Subjects and Methods

This retrospective study was conducted in the Aga Khan University Hospital (AKUH), a private tertiary care

hospital in Karachi. AKUH is located in the heart of the city and it draws patients from all over Karachi. AKUH has a busy Neonatal Intensive Care Unit (NICU) with excellent facilities. The Unit contains 10 intensive care unit cots.

This was a retrospective analysis of premature infants with birth weight ≤ 1500g and/or gestational age ≤ 32 weeks, admitted to the NICU of the AKUH between March 2003 and September 2006. These inclusion criteria were derived from the established screening criteria proposed by the British Royal College of Ophthalmologists.[13] However, we used the gestational age cut off of 32 weeks rather than 31 weeks.

Our exclusion criteria were defined as 1) infants who died before sufficient number of eye examinations could be done to diagnose ROP, 2) infants who were not referred for eye examination although they satisfied the inclusion criteria, 3) infants who were lost to follow up before sufficient number of eye examinations could be done to either rule out ROP or see the progression/regression of established ROP.

Perinatal and neonatal data on risk factors and course in hospital were retrieved from the infants' medical records.

The premature infants satisfying the above criteria underwent initial eye examinations on the 4th-7th week of life. All eye examinations were carried out by TAC. The stages of ROP were classified according to the International Classification of Retinopathy.[15]

If no ROP was noted, eye examinations were continued every 2 weeks until normal vascularisation of the retina had occurred. The infants with ROP were screened at intervals dictated by the severity of the disease, until the retinal vessels matured or the infant developed threshold ROP. All infants with threshold ROP were treated with argon laser therapy using indirect ophthalmoscopy. Follow-up examinations were done after laser treatment to confirm regression of disease.

Eyes were examined using 0.5% tropicamide and 2.5% phenylephrine eye drops after 3 insructions, 15 minutes apart. Binocular indirect ophthalmoscopy was performed using a 20 D lens. Lid speculum and scleral depressors were routinely used.

The data was entered in Epi Data version 3.1 and analyzed in Statistical Package for Social Sciences (SPSS) 14.0. Descriptive statistics were performed. Results were recorded as frequencies, means ± standard deviations (SD) and P values. Tables and figures were used for comprehensive viewing of the results.

Univariate comparison of the risk factors was done between the groups of infants who developed ROP versus those who did not by the Chi square test and Fisher's exact test for categorical variables and the independent samples t-test for continuous variables. The variables which achieved significance ($p<0.25$) on univariate analysis or were biologically meaningful were subjected to a stepwise multiple logistic regression analysis to determine which factors were independent predictors of the development of ROP. Unadjusted as well as adjusted odds ratios were recorded with a 95% confidence interval for each. Unless stated otherwise, a $p<0.05$ was taken as the criteria of significance for all purposes.

Results

At birth, a total of 164 infants fulfilled the screening criteria. Out of these, 48 expired before reaching the age for screening of ROP and 36 were not referred even though they fulfilled the screening criteria. After applying all the exclusion criteria, 68 infants were included in the analysis.

Of the 68 infants, 35 (51.5%) were male. The mean gestational age (GA) of the infants was 29.8 ± 2.2 weeks and the mean body weight (BW) was 1235 ± 281 grams. Out of the 68 infants, 22 (32.4%) developed ROP. Seventeen (77.3%) of the 22 ROP positive infants had pre-threshold disease at the initial screening while 5 (23.7%) had threshold disease. Eight (47.1%) of the 17 babies showed spontaneous regression in a mean period of 4 weeks, 9 (53.0%) progressed to threshold disease in an average of 2 weeks. Fourteen out of the 68 infants (20.6%) developed Stage 3 ROP. All patients who developed threshold disease underwent retinal photocoagulation within 72 hours of diagnosis except for one due to non-affordability. All of those treated with photocoagulation showed regression of disease on follow-up examinations and none of them therefore required another round of laser treatment.

Table 1. Incidence and stage distribution of ROP according to gestational age, birth weight and duration of supplemental oxygen.

Risk Factor	ROP+	ROP-	P value*	Stage		
				1	2	3
Gestational age (weeks)						
≤ 28	10 (66.7)	5 (33.3)		2	0	8
> 28	12 (22.6)	41 (77.4)	0.002	4	2	6
Birth weight (grams)						
≤ 1000	10 (71.4)	4 (28.6)		2	0	8
> 1000	12 (22.2)	42 (77.8)	0.001	4	2	6
Supplemental oxygen duration (days)						
0	1 (6.7)	14 (93.3)		0	0	1
≤ 5	5 (17.9)	23 (82.1)		0	2	3
> 5	16 (64.0)	9 (36)	<0.001	6	0	10

* The chi square test and Fisher's exact test were applied.
+ There were no infants with ROP at Stage 4 or 5.

Table 2. Univariate comparison of risk factors

Risk Factor	ROP+ (n=22) Mean+SD or n (%)	ROP- (n=46) Mean+SD or n (%)	Unadjusted OR*	95% CI+
Gestational age (P value < 0.001)				
	28.2 ± 2.0 wks	30.5 + 1.9 wks		
Birth weight (P value = 0.001)				
	1073 ± 274 g	1312 + 251 g		
Duration of supplemental oxygen therapy (P value < 0.001)				
	19.3 ± 18.9 days	3.2 + 4.1 days		
Mechanical ventilation (P value < 0.001)				
	18.6 ± 17.0 days	4.6 + 7.2 days		
Number of blood transfusions (P value < 0.001)				
	16.2 ± 12.0	6.2 + 9.6		
Gender (P value = 0.726)				
Female	10 (45.5%)	23 (50%)	1	
Male	12 (54.5%)	23 (50%)	1.2	0.4-3.3
Sepsis (P value = 0.001)				
No	6 (27.3%)	34 (73.9%)	1	
Yes	16 (72.7%)	12 (26.1%)	7.6	2.4-23.7
Respiratory Distress Syndrome (P value = 0.006)				
No	2 (9.1%)	22 (47.8%)	1	
Yes	20 (90.9%)	24 (52.2%)	9.2	1.9-43.8
Surfactant therapy (P value = 0.061)				
No	7 (31.8%)	26 (56.5%)	1	
Yes	15 (68.2%)	20 (43.5%)	2.8	1.0-8.1
Anemia (P value = 0.167)				
No	4 (18.2%)	16 (34.8%)	1	
Yes	18 (81.8%)	30 (65.2%)	2.4	0.7-8.3
Intaventricular haemorrhage (P value = 0.022)				
No	17 (77.3%)	45 (97.8%)	1	
Yes	5 (22.7%)	1 (2.2%)	13.2	1.4-121.7
Patent Ductus Arteriosus (P value = 0.154)				
No	13 (59.1%)	35 (76.1%)	1	
Yes	9 (40.9%)	11 (23.9%)	2.2	0.7-6.5
Patent Foramen Ovale (P value = 0.534)				
No	19 (86.4%)	42 (91.3%)	1	
Yes	3 (13.6%)	4 (8.7%)	1.7	0.3-8.1
Hypotension requiring ionotropic support (P value = 0.098)				
No	19 (86.4%)	45 (97.8%)	1	
Yes	3 (13.6%)	1 (2.2%)	7.1	0.7-72.7
Apnoea (P value = 0.623)				
No	15 (68.2%)	34 (73.9%)	1	
Yes	7 (33.8%)	12 (26.1%)	1.3	0.4-4.0

* OR = Odds ratio
+ CI = Confidence Interval
The independent samples t-test was used for continuous variables. The chi-square test and Fisher's exact test was used for categorical variables

Table 3. Multiple logistic regression analysis showing independent predictors of ROP development

Risk Factor	P value	Adjusted OR*	95% CI+
Gestational age	0.004	0.6	0.4-0.8
Sepsis	0.002	11.2	2.5-50.8
Respiratory distress syndrome	0.013	14.3	1.8-116.3

OR = Odds ratio
+ CI = Confidence Interval

The infants had their first screening in the 4th-7th day of life. ROP was first detected at 4-11 weeks (mean = 6.7 ± 1.5 weeks) of life. ROP stage 3 was first detected at a post-natal age of 5-11 weeks (mean = 7.9 ± 1.9 weeks).

Table 1 shows the incidence and stage distribution of ROP according to GA, BW and supplemental oxygen duration. A significantly higher proportion of infants of GA ≤ 28 weeks developed ROP compared to infants of GA > 28 weeks (66.7% vs. 22.6%, p = 0.002). When comparing birth weight, it was seen that a significantly higher proportion of infants with BW ≤ 1000 g developed ROP compared to infants with BW > 1000 g (71.4% vs. 22.2%, p = 0.001). When looking at the stage distribution, it was found that advanced cases of ROP occurred more frequently in the lower BW, lower GA and greater duration of supplemental oxygen therapy groups.

Table 2 shows the univariate comparison of risk factors between the group of infants which developed ROP versus those who did not. Based on the univariate analysis, the following risk factors were chosen to be included in the stepwise multiple regression model: GA, BW, supplemental oxygen duration, duration of mechanical ventilation, the number of blood transfusions, sepsis, respiratory distress syndrome, surfactant therapy, anaemia, patent ductus arteriosus, intraventricular haemorrhage and hypotension requiring ionotropic support. The final multiple regression model (Table 3) included three independent predictors of the development of ROP: low GA (AOR = 0.6, [95% CI: 0.4-0.8]), sepsis (AOR = 11.2, [95% CI: 2.5 - 50.8] and respiratory distress syndrome (AOR = 14.3, [95% CI: 1.8-116.3]).

Discussion

The present study showed that the incidence of ROP in the premature infants in our hospital was 32.4%. This value was within the range seen in other studies. In the developed countries, reported ROP incidence ranges from 13.2-46%.[6,16,17] There is a paucity of literature from developing countries as compared to developed countries, probably because ROP has just started emerging as an important cause of childhood blindness. In countries like Thailand, Philippines, Chile and west Africa, ROP is not reported in rural areas but causes 15-16.6% of visual loss in

the cities where better medical facilities are available.[18,19] In India, which is a comparable country to Pakistan in terms of socioeconomic and demographic aspects, reported rates vary from 20-47.3%.[9,20,21] The value of incidence (32.4%) in our study was on the higher side of the range reported in comparable developing countries. However, caution must be exercised when comparing with other studies due to differences in methodologies and selection criteria.

A high proportion of infants of GA ≤ 28 weeks developed ROP (66.7%). This was similar to a study done in India by Karna et al, which reported that 66% of infants of GA ≤ 28 weeks developed ROP[10] and another study done in Sweden which reported a rate of 65.5%.[22] A high proportion of infants with BW ≤ 1000g developed ROP (71.4%). This value was similar to those reported by a study done in Sweden[22] and one in Saudi Arabia[23] (72.2% and 76.9% respectively). However, it was higher than the incidence of 53.4% reported by a study done in Korea.[7] The CRYO-ROP study reported an incidence of 81.6% in infants with BW ≤ 1000g.[24] This wide variation in the incidence of ROP according to BW and GA could reflect racial and geographical differences. In addition, these variations can also be explained by differences in study designs and methodologies. It highlights the importance of conducting studies to find out the cost-effective screening cutoffs of GA and BW in each region.

Stepwise multiple logistic regression analysis revealed that only three risk factors were independent predictors of the development of ROP: low gestational age, sepsis and respiratory distress syndrome. It is well-established that prematurity is the most significant risk factor in the development of ROP and it has been shown to be an independent predictor.[10] Sepsis has been identified as an independent predictor of ROP development in many Asian studies including Indian studies.[9,20] Respiratory distress syndrome has also been shown to be an independent predictor of ROP development.[25]

It is imperative for studies to explore the association between ROP and risk factors other than the three well recognized risk factors: low GA, low BW and supplemental oxygen. This is especially important for developing countries because it is known that larger, more mature infants are developing advanced ROP in countries with low levels of development compared to developed countries.[5] A plausible explanation for this observation is that risk factors like sepsis which is more prevalent in developing countries, account for the advanced ROP in infants with relatively large GA and good BW.

While interpreting the findings of this study, the following limitations should be kept under consideration. A large number of infants (36) who satisfied the inclusion criteria were excluded mainly because they were not referred to an ophthalmologist for screening. Therefore, we could not determine whether they developed ROP or not. The sample size left in the end for analysis was consequently small. These factors could lead to an under- or overestimation of the true incidence of ROP. The present study had one disturbing revelation. Out of the large number of infants who satisfied inclusion criteria for screening but somehow remained unscreened, a few could have developed ROP and consequently blindness. This highlights the dire need for implementation of proper screening guidelines so that appropriate and prompt referral of high risk infants occurs. In order to develop cost-effective screening guidelines, prospective multi-centre studies need to be carried out in the country.

Conclusion

The incidence of ROP in our hospital was on the higher side of the range reported in neighbouring developing countries. Since the hospital caters to the population of Karachi, it can be postulated that ROP is an important emerging cause of preventable childhood blindness. It is imperative that screening guidelines be implemented in all hospitals with neonatal care facilities. ROP is currently under recognized and awareness needs to be increased among all doctors and parents of premature infants. There is a need for large prospective multi-centre studies to be conducted to determine the true incidence of ROP in Pakistan and to lay down cost-effective region specific screening guidelines for ROP.

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