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ORIGINAL ARTICLE

Risk of Retinopathy of Prematurity Among Preterm with Neonatal Sepsis in a Tertiary Care Hospital a Prospective Study

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ABSTRACT

Objective: To determine the risk of retinopathy of prematurity (ROP) among preterm with and without sepsis admitted in a neonatal intensive care unit of a tertiary care hospital of Karachi, Pakistan.

Methodology: In this prospective cross-sectional study conducted at Aga Khan University Hospital from October 2021 to March 2022. All the preterm born at gestation <32 weeks with birth weight of <1.5kg and were <28 days old of either gender was included. Examination for ROP was performed. Information about maternal and neonatal confirmed sepsis, risk factors predisposing to sepsis, ROP status were noted. Babies were followed in the outpatient clinics. The first examination was performed at 28th days and was subsequently followed at one or two week's interval as per the Ophthalmologist.

Results: Of 125 neonates, the mean age was 4.34 ±0.79 weeks. There were 72 (57.6%) males and 53 (42.4%) females. Stage 0 and 1 were most common stages reported as 49 (39.2%) and 55 (44%) neonates respectively. Zone 1 disease was observed in 15 (12.0%) whereas ROP plus disease in 7 (5.6%) neonates. Neonates with ROP stage <2 had significant association with maternal risk factors for sepsis (p-value 0.026), neonatal risk factors for sepsis (p-value 0.047), and neonatal culture proven sepsis (p-value 0.010). Similarly, zone 1 disease had a significant association with presence of maternal risk factors for sepsis (p-value 0.033), neonatal risk factors for sepsis (p-value 0.045), and antibiotics taken >48 hours (p-value 0.027).

Conclusion: A considerably higher risk of ROP was observed among hospitalized neonates with neonatal sepsis.

Keywords: Neonates, sepsis, retinopathy of prematurity, Preterm

INTRODUCTION

Retinopathy of prematurity (ROP) is a complex disease of developing retinal vasculature in preterm infants[1].clinical manifestations range from mild, usually transient changes of the peripheral retina to severe progressive Vasoproliferation scarring and retinal detachement.1 ROP has become the foremost cause of avoidable childhood blindness all over the world due to improvement in the survival rate of preterm babies.[2,3]

There are multiple risk factors associated with the development of different stages of ROP, including low birth weight, pulmonary disease, intraventricular hemorrhage, low gestational age, mechanical ventilation, and blood transfusions.[4,5] Neonatal infection leading to inflammation has recently been studied risk factor for ROP.[6] Both bacterial and fungal sepsis has been found to be associated to increase the risk of ROP in preterms.[7,8]

There is scarcity of data regarding incidence and association of ROP with sepsis from developing countries. Other than that, at Aga Khan University Hospital, practices including septic measures for infection control, feeding protocols and respiratory support management has considerably changed over the years especially in terms of preterm care. Screening all the preemies born <32 weeks of gestation or less than 1.5kg by an ophthalmologist is the standard of care at our setting. Furthermore, these babies have follow-up examinations weekly or fortnightly depending on the stage of previous exam until full retinal vascularization is achieved.

This prospective study was conducted at a large tertiary care private hospital to find out the association of sepsis with the development of ROP and the impact of advanced and updated management on the incidence of ROP among neonates admitted in neonatal intensive care unit.

METHODOLOGY

A prospective cross-sectional study was conducted among Neonatal Intensive Care Unit, Aga Khan University Hospital from October 2021 to March 2022. Ethical approval was obtained from Ethical review Committee of Aga Khan University Hospital. All data were kept confidential with no patient identifiers and secured in a password protected database. Access was only granted to the researchers involved in the study. All the preterm born at gestation <32 weeks with birth weight of <1.5kg and are less than 28 days old of either gender was included. Whereas all babies born with chromosomal abnormalities and congenital anomalies were excluded. Information about maternal and neonatal confirmed sepsis, risk factors predisposing to sepsis, ROP status was noted. Maternal risk factors were defined as presence of pyrexia (>38 OC), high leukocyte counts >12,000cells/mm3, foul smelling discharge, uterine tenderness, prolonged rupture of membrane (PROM) >18 hours as evident by leaking, maternal culture proven sepsis due to gram positive or gram-negative bacteria (either in blood or HVS). Neonatal risk factors were defined as low (<9,000cells/mm3) or high (>25000cells/mm3) white blood cells count, low platelet count <100,000/mm3, raised CRP >10mg/L or antibiotics taken >48 hours due to any clinical sign of systemic infection.

ROP was classified on the basis of international classification of ROP. Stage I was defined as a thin demarcation line develops between the vascularized region of the retina and the avascular zone. Stage II was defined as line develops into a ridge protruding into the vitreous, in which there is histologic evidence of an arteriovenous shunt. Stage III was defined as extraretinal fibrovascular proliferation occurs with the ridge. Neovascular tufts may be found just posterior to the ridge. Stage IV was defined as fibrosis and scarring occur as the neovascularization extends into the vitreous. Traction occurs on the retina, resulting in partial retinal detachment. While stage V was defined as complete retinal detachment. ROP plus disease was defined as when vessels posterior to the ridge become dilated and tortuous. Pre-threshold ROP was defined as any zone 1 ROP less than threshold, zone 2 stage 2 with plus, zone 2 stage 3 without plus or zone 2 stage 3 with plus but less than 5 contagious 0 or less than 8 cumulative clock hours of ROP. Threshold ROP was defined as ROP of more than 5 contagious or 8 cumulative clock hours of stage 3 plus ROP in zone 1 or zone 2. Initial ROP examination was done at the age of 28 days and subsequent examination was performed as per ophthalmologist at 1 to 2 weeks interval. Those who developed ROP were treated accordingly by the Ophthalmologist. For data analysis, Statistical Package for Social Sciences (SPSS) version 20.0 was used. For descriptive analysis, frequencies, percentages, means, and Standard Deviation (S.D) were reported. For inferential statistics, Chi-Square test/ Fisher's exact test was run to compare the risk of neonatal sepsis with and without ROP among Preterm infants. McNemar test was also applied to see the change in the ROP status at 28th day and 1-2 week after follow-up. The p-value of ≤0.05 was considered as significant.

RESULTS

Of 125 neonates, the mean age was 4.34 ±0.79 weeks. The minimum age of the neonates was 4 weeks while maximum age was 8 weeks. There were 72 (57.6%) males and 53 (42.4%) females. The mean birth weight was 1.24 ±0.19 kg. The minimum birth weight of the neonates was 0.87 kg while maximum birth weight was 1.6 kg. The mean gestational age was 29.82 ±1.29 weeks. The minimum gestational age of the neonates was 27 weeks while maximum gestational age was 32 weeks. Maternal risk factor for sepsis was observed in 23 (18.4%) neonates. Chorioamnionitis in 9 (7.2%), PROM in 22 (17.6%) while maternal culture proven sepsis was observed in none of the mothers. Intraventricular hemorrhage (IVH) was found in 12 (9.6%) patients, Necrotizing enterocolitis (NEC) in 37 (29.6%), Patent ductus arteriosus (PDA) in 17 (13.6%), and pneumothorax in 4 (3.2%) patients. Respiratory support was needed by 120 (96%) of the neonates, ventilatory support by 60 (48%), Continuous Positive Airway Pressure (CPAP) by 103 (82.4%), Hi-flow oxygen therapy by 103 (82.4%), while packed cell volume (PCV) transfusion was needed by 47 (37.6%) neonates. Neonatal risk factor for sepsis was observed in 46 (36.8%) neonates. Leukopenia was observed in 62 (49.6%), thrombocytopenia in 43 (34.4%), raised CRP in 55 (44%), antibiotics taken >48 hours due to any clinical sign of systemic infection in 60 (48%), whereas neonatal culture proven sepsis was observed in 15 (12%) neonates. The mean duration of ventilator stay was 3.39 ±2.11 days, mean duration of CPAP usage was 4.64 ±3.27 days, while mean duration of Hi-flow oxygen therapy was 2.96 ±1.72 days. Slow weight gain (<140gm/week) was reported by 23 (18.4%) patients. At 28th day, stage 0 was observed in 49 (39.2%), stage 1 in 55 (44%), stage 2 in 16 (12.8%), stage 3 in 3 (2.4%), whereas stage 4 in 2 (1.6%) of the neonates. Zone disease showed that zone 1 disease was observed in 15 (12.0%), zone disease 2 in 69 (55.2%), whereas zone disease 3 in 41 (32.8%) of the neonates. ROP plus disease was observed in 9 (7.2%) of the cases while majority of the patients were presented with pre-threshold, i.e., 102 (81.6%). Treatment was received by 15 (12%) of the neonates. A total of 74 individuals were followed up after 1 or 2 weeks. Of these 74 neonates, stage 0 was observed in 30 (40.5%), stage 1 in 27 (36.5%), stage 2 in 15 (20.3%), and stage 3 in 2 (2.7%) neonates. Zone disease showed that zone 1 disease was observed in 3 (4.1%), zone disease 2 in 57 (77.0%), and zone disease 3 in 14 (18.9%) of the neonates. ROP plus disease was observed in 11 (14.9%) of the cases. Comparison of ROP status at 28 days with maternal, neonatal and clinical characteristics showed that neonates with ROP stage <2 had significant association with presence of maternal risk factors (p-value 0.026), Chorioamnionitis (p-value <0.001), presence of neonatal risk factors for sepsis (p-value 0.047), leukopenia (p-value 0.033), neonatal culture proven sepsis (p-value 0.010), raised CRP (p-value 0.001), and use of Hi-Flow oxygen therapy (p-value 0.024). Zone 1 disease had a significant association with presence of maternal risk factors for sepsis (p-value 0.033), neonatal risk factors for sepsis (p-value 0.045), and antibiotics taken >48 hours (p-value 0.027). Threshold status had a significant association with presence of maternal risk factors for sepsis (p-value 0.036). (Table 1)

A significant difference was reported in ROP stages (p-value <0.001), and zone disease (p-value <0.001) at 28th day and at 1-2 weeks of follow-up. Whereas plus diseases and threshold status did not report significant difference at 28th day and at 1-2 weeks of follow-up. (Figures 1-4)

Comparison of slow weight gain with as a risk factor of ROP showed that weight gain was significantly associated with ROP stages (p-value 0.032) only. (Table 2)

Table 1: Comparison of ROP status at 28 days with maternal, neonatal and clinical characteristics (n=125)

	ROP Stage <2			Zone 1 Disease			Threshold Status		
	Yes (n=104)	No (n=21)	p-value	Yes (n=15)	No (n=110)	p-value	Pre-threshold (n=102)	Threshold (n=23)	p-value
Maternal Characteristics									
Presence of Risk Factor for sepsis	15 (14.4)	8 (38.1)	0.026	6 (40.0)	17 (15.5)	0.033	15 (14.7)	8 (34.8)	0.036
PROM	15 (14.4)	7 (33.3)	0.056	5 (33.3)	17 (15.5)	0.139	15 (14.7)	7 (30.4)	0.125
Chorioamnionitis	2 (1.9)	7 (33.3)	<0.001	2 (13.3)	7 (6.4)	0.327	5 (4.9)	4 (17.4)	0.059
Maternal Culture Proven Sepsis	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Neonatal Characteristics									
Presence of Risk Factor for sepsis	34 (32.7)	12 (57.1)	0.047	2 (13.3)	44 (40.0)	0.045	38 (37.3)	8 (34.8)	0.824
Leukopenia	47 (45.2)	15 (71.4)	0.033	6 (40.0)	56 (50.9)	0.428	50 (49.0)	12 (52.2)	0.821
Thrombocytopenia	32 (30.8)	11 (52.4)	0.078	2 (13.3)	41 (37.3)	0.067	36 (35.3)	7 (30.4)	0.658
Neonatal Culture Proven Sepsis	9 (8.7)	6 (28.6)	0.010	0 (0)	15 (13.6)	0.127	38 (37.3)	8 (34.8)	0.824
Raised CRP	39 (37.5)	16 (76.2)	0.001	4 (26.7)	51 (46.4)	0.149	44 (43.1)	11 (47.8)	0.817
Antibiotics taken >48 hours	49 (47.1)	11 (52.4)	0.811	3 (20.0)	57 (51.8)	0.027	52 (51.0)	8 (34.8)	0.175
Clinical Characteristics									
Respiratory Support	99 (95.2)	21 (100)	0.588	15 (100)	105 (95.5)	>0.999	97 (95.1)	23 (100)	0.583
Ventilatory Support	54 (51.9)	6 (28.6)	0.059	7 (46.7)	53 (48.2)	0.912	51 (50.0)	9 (39.1)	0.367
CPAP	84 (80.8)	19 (90.5)	0.363	10 (66.7)	93 (84.5)	0.139	86 (84.3)	17 (73.9)	0.238
HiFlow	82 (78.8)	21 (100)	0.024	12 (80.0)	91 (82.7)	0.727	83 (81.4)	20 (87.0)	0.763
PCV Transfusion	39 (37.5)	8 (38.1)	>0.999	6 (40.0)	41 (37.3)	0.838	37 (36.3)	10 (43.5)	0.519
IVH	12 (11.5)	0 (0)	0.216	0 (0)	12 (10.9)	0.357	12 (11.8)	0 (0)	0.121
NEC	31 (29.8)	6 (28.6)	>0.999	3 (20.0)	34 (30.9)	0.550	30 (29.4)	7 (30.4)	>0.999
PDA	13 (12.5)	4 (19.0)	0.485	0 (0)	17 (15.5)	0.220	15 (14.7)	2 (8.7)	0.736
Pneumothorax	2 (1.9)	2 (9.5)	0.131	0 (0)	4 (3.6)	>0.999	2 (2.0)	2 (8.7)	0.154

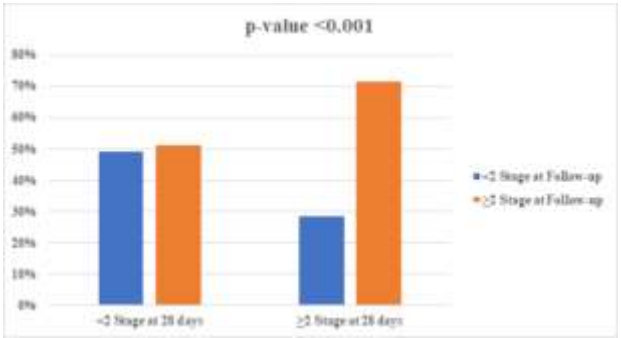

Figure 1: Comparison of ROP stages at 28 days investigation and follow-up at 1-2 weeks (n=74)

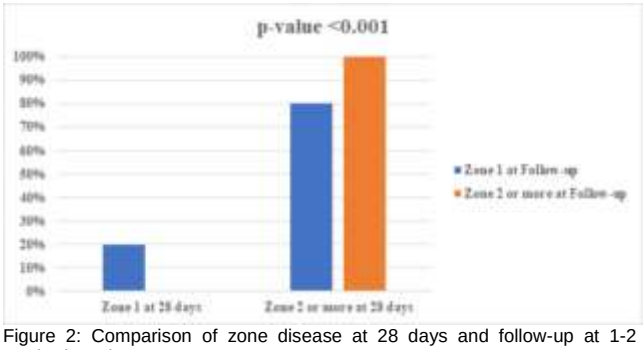

Figure 2: Comparison of zone disease at 28 days and follow-up at 1-2 weeks (n=74)

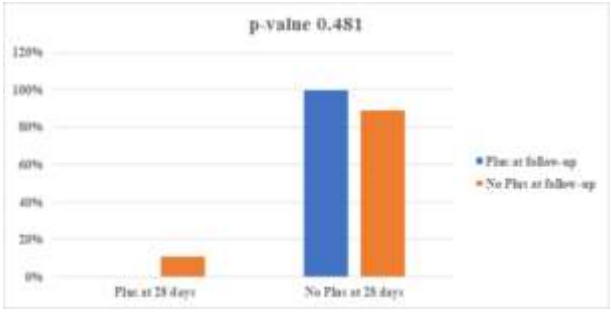

Figure 3: Comparison of Plus at 28 days and follow-up at 1-2 weeks (n=74)

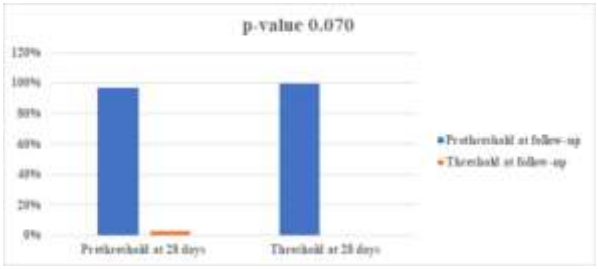

Figure 4: Comparison of threshold status at 28 days and at follow-up (n=74)

Table 2: Comparison of weight gain with ROP status of the patients (n=125)

Variables	Slow Weight Gain		p-value
	Yes (n=23)	No (n=102)	
Stages			
Stage 0	(9 (39.1)	40 (39.2)	0.032
Stage 1	8 (34.8)	47 (46.1)	
Stage 2	4 (17.4)	12 (11.8)	
Stage 3	0 (0)	3 (2.9)	
Stage 4	2 (8.7)	0 (0)	
Zone			
1	3 (13.0)	12 (11.8)	0.452
2	15 (65.2)	54 (52.9)	
3	5 (21.7)	36 (35.3)	
Threshold Status			
Pre-threshold	16 (69.6)	86 (84.3)	0.134
Threshold	7 (30.4)	16 (15.7)	
Plus Disease			
Yes	2 (8.7)	7 (6.9)	0.670
No	23 (100)	95 (93.1)	

DISCUSSION

The primary outcome of the study was to evaluate the association of sepsis with ROP while the secondary outcome was to assess the association of maternal, neonatal risks for sepsis and the effect of oxygen requirement, weight gain, transfusions, IVH, NEC, and PDA on development of ROP. Though reported incidence varies among the countries. One individual study suggested incidence of ROP in China as 18.5%, one Indian paper reported incidence of 33%, in Pakistan two publications reported 24.6% and 32.4% incidence.[9-12] One previously done study conducted in Aga Khan University Hospital Karachi evaluated the neonates by extending the screening criteria to 35 weeks of gestation and weight to 2000 gm and showed incidence of 9%.[13] In addition, a recent study from Lahore, Pakistan reported the frequency of ROP in 21% of the neonates.[14] On the basis of global data from 2010, approximately 2.6 million infants born <32weeks of gestation had an acute phase ROP ranging from ~20% in countries with low mortality rates (<5/1000 births) to nearly 40% in countries with higher mortality rates.[15]

According to the current study findings, neonatal risk factor for sepsis was observed in 36.8% neonates. Leukopenia was observed in 49.6%, thrombocytopenia in 34.4%, raised CRP in 44%, antibiotics taken >48 hours due to any clinical sign of systemic infection in 48%, whereas neonatal culture proven sepsis was observed in 12% neonates. Furthermore, neonates with ROP stage <2 had significant association with presence of maternal risk factors, chorioamnionitis, presence of neonatal risk factors for sepsis, leukopenia, neonatal culture proven sepsis, raised CRP, and use of Hi-Flow oxygen therapy. Most of the previously mentioned studies reported sepsis as an independent risk factor for ROP.[16,17] However, one study from Pakistan has reported insignificant association of sepsis with ROP.14 A study reported oxygen supplementation and respiratory distress syndrome to be significant for developing severe form of ROP.[18] In a recent study, sepsis and the duration of mechanical ventilation was reported as risk factors for more severe ROP in twins.[19] Similarly, another study has reported Respiratory distress, sepsis and apnea as independent risk factors.[20]

The findings of the current study could be highlighted in the light of limitations that this study was carried out in a single center with limited number of samples. Moreover, certain important predictor variables like vaginitis, urinary tract infection, aspirin use, NSAID use, acetaminophen use during pregnancy were not studied. In addition, hypocalcemia which was reported as significant risk factor for ROP in a study also not studied in the current study. Lastly, the observational nature of the study also limits strength of the study. Despite of these limitations, the current study has generated local study findings that are scarce on the topic in Pakistan. The identification of neonatal and maternal risk factors for sepsis as one of the indicators for prediction of ROP will be helpful in effective and timely management of the disease. Though introduction of isolation rooms for out born babies and culture proven and clinical sepsis, improved compliance of hand hygiene by the staff and visitors, strictly following the policy of cleaning incubators, warmers, suction machines, and other equipment's have controlled the sepsis rate in Aga Khan University Hospital as compared to other tertiary care hospitals. Despite of this, more rigorous studies are needed to prompt diagnosis of the disease.

CONCLUSION

In our cohort of preterm neonates, a considerably higher risk of ROP was observed among hospitalized neonates with neonatal sepsis. In particular, neonates with ROP stage less than 2 had significant association with maternal risk factors for sepsis, neonatal risk factors for sepsis, and neonatal culture proven sepsis. Similarly, zone 1 disease had a significant association with maternal risk factors for sepsis, neonatal risk factors for sepsis, and neonatal culture proven sepsis. Therefore, evaluation of risk factors of sepsis during pregnancy and appropriate management of newborn in health care setting with timely involvement of ophthalmologist taking care of ROP would definitely help in minimizing the risk of advanced retinopathy of prematurity, retinal detachment and subsequent blindness.

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