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Research Article

RETINOPATHY OF PREMATURITY IN NEONATES WITH UNSTABLE CLINICAL COURSE

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ABSTRACT

Objective: The objective of this study was to determine incidence of development of retinopathy of prematurity (ROP) in infants with GA ≥34 weeks or BW ≥1750 g having unstable clinical course.

Methods: This was a cross-sectional study, all infants with GA ≥34 weeks or BW ≥1750 g having unstable clinical course were enrolled after taking informed consent from the parents. All these neonates were screened for ROP at 4 weeks of gestation age. Incidence of ROP was calculated and risk factors were also evaluated.

Results: Out of total 426 admissions to neonatal intensive care unit, 52 babies satisfied the inclusion criteria and were enrolled in study. Incidence of ROP in neonates ≥34 weeks was 4%. Among the various neonatal factors, the presence of Bronchopulmonary dysplasia, administration of blood transfusions, and surfactant therapy were having significant association with ROP.

Conclusion: ROP can even occur in babies with GA ≥34 weeks and normal birth weight neonates. Careful and timed retinal examination of all at risk infants will minimize the development of ROP and later on blindness which will lower the social and economic burden.

Keywords: Retinopathy, Neonates, Risk factors, Prematurity.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in premature newborns [1]. It generally occurs in those neonates who have received intensive care, especially prolonged oxygen therapy and those having several other risk factors. In ROP, retinal detachment and scarring are observed due to abnormal growth of blood vessels in the retina [2,3]. ROP mostly affects to neonates with birth weight of under 1500 g as per American Academy of Pediatrics (AAP) and 1750 g as per National Neonatal Forum (NNF) and gestational age less than 30 weeks and 34 weeks according to AAP and NNF, respectively [4].

However, ROP like retinopathy can occasionally occur in full-term infants. The factors such as low birth weight, oxygen administration, sepsis, multiple births, and hypoxia that cause retinopathy in premature neonates seems to be causative in term infants. However, there appears to be a complex interplay of factors which can potentially cause ROP like changes in term infants [5]. Some researchers have suggested full-term infants with high-risk factors such as hypoxic-ischemic encephalopathy (HIE) and neonatal asphyxia may be at risk of developing retinopathy, while there are some studies that suggest that factors which lead to retinopathy of high risk full-term infants are prenatal factors such as PRH, vevneonatal risk factors such as asphyxia, HIE, and low birth weight [6].

Risk factors for ROP in neonates with gestational age more than 34 weeks have not been clearly established. Multicenter studies are needed to determine the incidence, risk factors, and natural course of ROP in these infants. Thus, the objective of our study is to calculate incidence and evaluate various risk factors of ROP in neonates with gestational age ≥34 weeks.

METHODS

This was a cross-sectional study, conducted by Department of Pediatrics, SGRDIMSR, Amritsar in collaboration with Department of Ophthalmology, SGRDIMSR, Amritsar from December 2018 to May 2020. The study was conducted after taking permission from thesis and ethical committee of the institution. All infants with GA ≥34 weeks having unstable clinical course admitted in neonatal intensive care unit (NICU) of pediatrics department and those infants attending the outpatient department were enrolled in present study after taking informed consent from the parents. Baseline variables of all the enrolled neonates were recorded as per pro forma. Furthermore, maternal risk factors, neonatal problems, treatment given, procedures, and interventions done during stay in NICU were recorded as per the pro forma. All these neonates were screened for ROP at 4 weeks of gestation age. Incidence of ROP was calculated and risk factors were also evaluated.

Inclusion criteria

Infants with GA ≥34 weeks having unstable clinical course were in the study. The neonates with unstable clinical course were considered having presence of one or more of various risk factors enumerated below: perinatal asphyxia (PNA-considered history of delayed cry at birth or need for bag and mask ventilation or mechanical ventilation at birth), hyaline membrane disease (HMD), pneumonia, apnea, polycythemia, hyperbilirubinemia, sepsis (positive blood culture), thrombocytopenia, NEC, seizure, shock, acidosis, IVH, Bronchopulmonary dysplasia (BPD), oxygen therapy (through nasal prongs, hood, continuous positive airway pressure (CPAP), i.e., CPAP or mechanical ventilation), phototherapy for hyperbilirubinemia, blood transfusion, hypotension requiring vasopressor use, and days of stay in hospital. In this study, we considered maternal risk factors for ROP to identify association between risk factors with the development of various forms of disease. These variables were presence of meconium stained liquor, pregnancy-induced hypertension (PIH), maternal diabetes mellitus, maternal anemia, PPROM, and antenatal steroid use.

Exclusion criteria

Infants with gestation age >40 weeks, babies dying before completion of ROP screening, babies >34 weeks with uneventful post-natal period,

neonates with major congenital malformations, and neonates with suspected chromosomal anomalies were excluded in the study.

A comprehensive eye examination was performed in each case after explaining about the nature of the study, and obtaining the informed written consent from parents/guardians in their own vernacular language. Pupils were dilated with the help of a mixture of phenylephrine 2.5% and tropicamide 0.5% which were instilled 3 times at an interval of 10 min about 1 h prior to the procedure.

Procedure

Procedure was performed under topical anesthesia by instilling paracaine eye drops 0.5% such as to avoid systemic side effects of general anesthesia or sedation. The findings on screening were recorded as per the following table.

	No plus disease			Plus disease
	Zone 1	Zone 2	Zone 3	
Immature				
Stage 1				
Stage 2				
Stage 3				
Stage 4				
Stage 5				

Data so collected were compiled, which statistically analyzed and inferences were drawn.

RESULTS

This study was conducted in Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar for 18 months by Department of Pediatrics, SGRDIMSR, Amritsar in collaboration with the Department of Ophthalmology, SGRDIMSR, Amritsar from December 2018 to May 2020. All infants with GA ≥34 weeks or BW ≥1750 g having unstable clinical course admitted in NICU of pediatrics department were enrolled in the present study. Out of total 426 admissions to NICU, 52 babies satisfied the inclusion criteria and were enrolled in study. All these neonates were screened for development of ROP at 4 weeks of post-natal age. Incidence was calculated and inferences were drawn pertaining to various factors. Incidence of ROP in neonates ≥34 weeks was 4% (Table 1).

Among the various neonatal factors, the presence of BPD was having significant association with ROP (p<0.005). Whereas, other factors such as PNA, HMD, pneumonia, apnea, polycythemia, hyperbilirubinemia, sepsis, thrombocytopenia, NEC, seizures, shock, acidosis, and IVH did not show significant relation with ROP (p>0.005) (Table 2).

During hospital stay, neonates received oxygen inhalation through various modes such as nasal prongs, hood, bubble CPAP, venti CPAP, and mechanical ventilation. However, statistically no significant relation was noticed between ROP and these modes of oxygen inhalation (p>0.005) (Table 3). Apart from this, these neonates were given blood transfusions, surfactant therapy, vasopressor therapy, and phototherapy. However, only blood transfusion and surfactant administration had significant relation with development of ROP (Table 3).

Increased duration of stay in hospital also contributed to the development of ROP in the study group, as the results were statistically significant (p=0.003). Among the neonates who developed ROP, all had stage 2 zone two disease.

Table 1: Incidence of ROP

Total	Total	ROP Present		ROP Absent	
	n	n	%	n	%
Number of neonates	52	2	4%	50	96%

ROP: Retinopathy of prematurity

Various maternal risk factors such as Meconium-stained liquor (MSL), PIH, DM, anemia, PPROM, and antenatal administration of steroid were also analyzed as a predisposing factor to ROP. However, only MSL had statistically significant (p=0.039) relation with ROP, while all other showed statistically insignificant relation (p>0.005) (Table 4).

DISCUSSION

Worldwide ROP is among the leading causes for childhood blindness which is preventable.

ROP is a dynamic, time-bound disease which is not present at birth that makes screening an utmost important. The present study was

Table 2: Comparison of neonatal risk factors for ROP

Risk factor	n=52				p-value
	ROP present		ROP absent		
PNA	n	%	n	%	
Yes	0	0%	13	26%	0.405
No	2	100%	37	74%	
HMD					
Yes	0	0%	2	4%	0.773
No	2	100%	48	96%	
Pneumonia					
Yes	2	100%	20	40%	0.092
No	0	0%	30	60%	
Apnea					
Yes	0	0	3	6%	0.721
No	2	100%	47	94%	
Polycythemia					
Yes	0	0%	5	10%	0.638
No	2	100%	45	90%	
Hyperbilirubinemia					
Yes	2	100%	37	74%	0.405
No	0	0%	13	26%	
Sepsis					
Yes	2	100%	9	18%	0.260
No	0	0%	41	82%	
Thrombocytopenia					
Yes	1	50%	7	14%	0.166
No	1	50%	43	86%	
NEC					
Yes	0	0%	2	4%	0.773
No	2	100%	48	96%	
Seizures					
Yes	0	0%	7	14%	0.569
No	2	100%	43	86%	
Shock					
Yes	2	100%	18	36%	0.068
No	0	0%	32	64%	
Acidosis					
Yes	1	50%	18	36%	0.686
No	1	50%	32	64%	
IVH					
Yes	0	0%	1	2%	0.84
No	2	100%	49	98%	
BPD					
Yes	2	100%	2	4%	0.000
No	0	0%	48	96%	
Surfactant					
Yes	2	100%	3	6%	0.000
No	0	0%	47	94%	
Vasopressor					
Yes	2	100%	18	36%	0.068
No	0	0%	32	64%	
Blood Transfusion					
Yes	2	100%	4	8%	0.000
No	0	0%	46	92%	
Phototherapy					
Yes	2	100%	37	74%	0.405
No	0	0%	13	26%	

ROP: Retinopathy of prematurity

Table 3: ROP in relation to mode of oxygen inhalation in neonates

Mode of oxygen inhalation	Group B (n=52)			
	ROP Present		ROP absent	
	n	%	n	%
Bubble CPAP				
Required	2	100	41	82%
Not required	0	0	9	18%
p-value	0.765			
Mechanical ventilation	n	%	n	%
Required	2	100	26	52%
Not required	0	0	24	48%
p-value	0.354			
Venti CPAP	n	%	n	%
Required	1	50	12	24%
Not required	1	50	38	76%
p-value	0.405			
Nasal prongs	n	%	n	%
Required	2	100	50	100%
Not required	0	0	0	0%
p-value				
Oxygen via hood	n	%	n	%
Required	0	0	11	22%
Not required	2	100	39	78%
p-value	0.713			

CPAP: Continuous positive airway pressure, ROP: Retinopathy of prematurity

Table 4: Comparison of maternal risk factors for ROP

Risk Factor	n=52			
	ROP present		ROP absent	
Meconium-stained liquor	n	%	n	%
Yes	2	100	15	30
No	0	0	35	70
p-value	0.039			
PIH				
Yes	0	0	9	18
No	2	100	41	82
p-value	0.509			
MATERNAL DM				
Yes	0	0	3	6
No	2	100	47	94
p-value	0.721			
Maternal Anemia				
Yes	0	0	0	0
No	2	100	50	100
p-value	0.080			
PPROM				
Yes	0	0	4	8
No	2	100	46	92
p-value	0.677			
Antenatal steroid				

ROP: Retinopathy of prematurity

done at Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar in collaboration with the Department of Ophthalmology, SGRDIMSR, Amritsar. The neonates who satisfied the inclusion criteria were screened at 4 weeks postnatal age.

The incidence of ROP in neonates ≥34 weeks was 4%. In contrast to our study, for neonates >34 weeks gestation, higher incidence has been seen in a study by Sardar *et al*. [7], in which late preterm newborn (34 and $36^{6/7}$ weeks' gestation) were included and the incidence of ROP was 16.51%. This contrast could be attributed to inclusion of neonates >36 weeks gestation in our study. Although, lower gestational age is associated with higher incidence of ROP, it should also be taken into consideration that ROP can even occur in mature babies.

Among the maternal factors, MSL was found to be significant ($p<0.05$). Association of MSL with ROP can be explained on the basis of study by Ward and Aaron [8] that with MSL, as gestational age increases, the risk of meconium aspiration syndrome increases which can manifest as airway obstruction, chemical pneumonitis, and surfactant inactivation with decreased lung compliance. Thus with MSL, postnatal course of neonate could become unstable, leading to requirement for mechanical ventilation for respiratory failure, surfactant replacement, antibiotics, and hemodynamic support with inotropes. All these factors could contribute to development of oxidative stress in neonates and formation of free radicles that can lead to development of ROP. Other maternal factors such as diabetes mellitus, PIH, anemia, PPROM, and antenatal steroids were not having any significant relationship.

Among the neonatal factors BPD, surfactant administration and blood transfusion were significant risk factors. BPD was a significant risk factor associated with ROP in our study. In a study by Podraza *et al*. [9], newborn babies with BPD required more aggressive oxygen therapy and, thus, were significantly associated with advanced stages of ROP than newborns without BPD. It can be concluded that as oxygen plays a significant role in the development of both ROP and BPD, so both the diseases are significantly associated with each other.

Surfactant use in our study was contributing to the development of ROP in mature group of neonates. This could be attributed to the fact that in all ROP positive neonates in mature group surfactant use was done in view of their respiratory distress due to presence of MAS. Although the pathophysiology of MAS is very complex involving many factors, it includes inactivation of surfactant and impaired surfactant production [8].

In our study, blood transfusion was found to be significantly associated with the development of ROP in neonates. Similarly, in a study by Thomas *et al.* [10] , blood transfusion was significantly associated with the risk factor of ROP. In another study by Sundar *et al*. and Ali *et al*. [11], the use of blood transfusion was significantly associated with the development of ROP. In another study by Sathar *et al*. [12], it was observed that blood transfusion had a role in development of ROP and it was also discussed that as adult hemoglobin is used in the transfusions which releases more oxygen to tissues causing hyperoxia, generating free radical, and leading to the reflex vasoconstriction which plays role in development of ROP. On the other hand, vasopressor therapy and phototherapy did not demonstrated any statistically significant relation with ROP. The use of oxygenation was done in all neonates included in our study. However, statistically no significance was observed between the use of various modalities such as nasal prongs, oxygen hood, Bubble CPAP, Venti-CPAP, and mechanical ventilator.

In our study, prolonged stay (>20 days) was significant risk factor for the development of ROP. Similarly, in a study by Sahu *et al*. [13], prolonged stay >15 days was found to be risk factors for development of ROP. In another study by Braimah *et al*. [14], the of stay >4 weeks was significantly associated with the development of ROP. This association between length of hospital stay and ROP may be because of the proxy for fact that critically ill infants require longer hospital stays.

In mature group, among the neonates who developed ROP, all had stage 2 zone 2 and there was no case of plus disease.

CONCLUSION

We concluded in our study that ROP can even occur in babies with GA ≥34 weeks and normal birth weight neonates. Early screening for ROP is of great importance. Careful and timed retinal examination of all at risk infants will minimize the development of ROP and later on blindness which will lower the social and economic burden on the babies' family, society and the nation. Screening should be escalated in the presence of factors such as oxygen administration, pneumonia, sepsis, apnea, thrombocytopenia, NEC, shock, acidosis, IVH, BPD, vasopressor use, blood transfusion, and prolonged stay in hospital. By controlling and

minimizing the risk factors, and diligent management of sick babies, it may be possible to reduce the incidence of ROP.

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AUTHORS' CONTRIBUTIONS

Dr. Gursharan Singh conceptualized and supervised the study. In addition to this, Dr Kajaldeepkaur, Dr Gurmeet singh and Dr Ashwani kumar participated in data collection, review literature, and data analysis.

CONFLICTS OF INTERESTS

None declared.

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