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Study of the effect of anemia and blood transfusion on the severity of retinopathy of prematurity

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ABSTRACT

Introduction: The incidence of ROP is reported to be around 20-25% in the screened preterm babies. The relationship of anemia with ROP is difficult to study due to many factors affecting blood hemoglobin values, especially blood transfusions. Once an infant has received a blood transfusion, the anemia is temporarily resolved and hemoglobin values increase.

Aim & Objective: A review of literature showed a scarcity of data on the association of anemia in the progression of ROP from the Indian subcontinent. Hence this study was undertaken to evaluate the effect of anemia on the progression and severity of ROP.

Materials and Methods: After getting clearance from the institutional clearance committee this hospital based observational study was done in the Nursery of SVP PG Institute of Pediatrics & SCB Medical College, Cuttack from October 2019 to September 2021.

Observation: Out of 200 patients 70 patients (35%) were anemic and 130 patients (65%) were non anemic. The mean number of blood transfusion was 0.53±0.85 ranging from 0-4. 130 patients did not receive any blood transfusion. 1-2 blood transfusions while 9 patients received 3-4 blood transfusions. In 129 patients (54.5%) the severity of ROP regressed while 71 patients (35.5%) developed severe ROP.

Conclusion: EGA at birth strongly correlated with severity of ROP ($p<0.001$). the prevalence of anemia, the primary parameter in question, to be significantly higher in the group that developed severe ROP.

1. Introduction

Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative disorder that affects the retina of preterm infants. The disease is entirely asymptomatic in its early phase and has the potential to progress to severe visual impairment. Long term morbidity manifests across a spectrum ranging from mild myopia to blindness. 90% of cases of ROP go on to regress spontaneously with little or no visual loss; fewer than 10% of the involved eyes progress to significant visual loss.[1]

ROP manifestation has changed through the years, encompassing different "ROP generations", with increased and reduced ROP incidence.[2,3] In high- and middle income countries, the improvement of neonatal care has led to a constant increase in the survival rate of extremely premature babies, giving rise to a new increase in ROP incidence, that may be hypothetically considered as a new ROP "epidemic", with higher incidence of posterior and more aggressive forms, usually more prone to rapid worsening.[4–6]

Various studies from India have reported the incidence of ROP as 20-25% of the screened neonates. Given the huge birth cohort in the country, this may translate to substantial numbers. Keeping in view the severity of the problem,

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guidelines for Universal Eye Screening including ROP in newborns were developed. These guidelines place greater emphasis on comprehensive eye screening of the newborn with particular focus on ROP screening in high risk babies.[1]

The pathophysiology of ROP has been widely investigated, and prematurity itself is the primary unavoidable risk factor for the development of ROP. In addition, low gestational age (GA) and birth weight (BW) are the main drivers in the setting of prematurity.[7] Many other risk factors have been correlated to ROP worsening, such as persistently elevated oxygen saturation, bronchopulmonary dysplasia, sepsis, ventricular hemorrhage and genetic components.[7–9] Therefore, ROP can be defined as a multifactorial disorder, where prematurity does not represent the only explanatory driver. Indeed, in apparently equal premature newborns, different ROP outcomes may exist, suggesting that some partially known genetic factors (such as those related to the Wnt transduction pathway) and other unknown factors may influence ROP course.[9]

The pathophysiology of ROP, even if widely investigated, remains partly unknown. One reason may be the co-existence of several concomitant systemic diseases, or concurrently administered medications and necessary interventions such as surgical procedures, which may confound the correlation between risk factors and ROP in premature infants. In the last years, some blood parameters of premature infants have been investigated to detect possible correlations with ROP development and progression.[10–12] These parameters have been measured at different times in the natural history of ROP, but very early postnatal biomarkers possibly predictive of ROP outcome have not clearly been detected yet. Although systemic conditions have a great impact on the development of ROP, the identification of the earliest factors influencing ROP progression may be helpful for both ophthalmologists and neonatologists, to plan efficacious prevention and/or therapeutic strategies aiming to reduce the need for more invasive treatment for ROP.

Among these factors, anemia and red blood cell (RBC) transfusion may play an important role.[13,14] Due to the immature hematopoietic system and iatrogenic phlebotomy losses, preterm infants frequently undergo transfusion.15 Reports have found that approximately 90% of extremely low birth weight (ELBW) infants receive at least one RBC transfusion.[15] In general, RBC transfusions are able to improve anemia, increase tissue oxygenation, promote growth and reduce mortality.[16] However, considerable evidence suggests that RBC transfusions are related to several preterm disorders, including the development of ROP.[16] According to a national survey by Ludwig, the incidence of ROP in the transfusion group was 1.68-times as high as that in the non-transfusion group.[17] Other studies did not identify a close relationship between RBC transfusion and ROP, especially after adjusting for other risk factors[18,19]. Moreover, the most severely ill infants receive more RBC transfusions, making it difficult to identify the effect of RBC transfusion on ROP.[20]

Few studies have addressed the effect of anemia on the severity of ROP. Bossi et al found no association between hemoglobin levels and development of ROP, but did identify a greater frequency of blood transfusions in infants who developed ROP using univariate analysis.[21] A recent report by Brooks et al showed no difference in transfusions to maintain high hematocrit levels (>40%) and infants receiving blood transfusions only when clinically symptomatic.[21] Other reports have not addressed anemia specifically. However, they did suggest that frequency of blood transfusion may be a riskfactor in the development of ROP in infants weighing less than 1500 g, although this correlation was not substantiated using logistic regression.[21]

In the light of existing divided opinion, the present study was undertaken to assess, evaluate and understand the role of anemia and blood transfusion in the progression of ROP with greater clarity.

2. Aim & Objective

The present observational study was carried out in the newborn nursery of Department of pediatrics, SCB Medical college & SVP PG Institute of pediatrics, Cuttack from October 2019 to September 2021.

Target population-All preterm neonates admitted to SVPPGIP or SCBMCH who were screened positive for ROP during the period of study.

Sample size – 200. Sample size was calculated using convenience sampling.

2.1. Inclusion criteria

Preterm babies(<37 weeks) who were screened positive for ROP were included in the study.

2.2. Exclusion criteria

1. Preterm babies who did not develop ROP.
2. Preterm babies lost to follow-up or died before final stage of ROP could be examined.

3. Materials and Methods

Detailed history and risk factors were documented using a structured proforma. Sepsis was clinically suspected and confirmed by blood culture. Anemia was defined as hemoglobin less than 10 g/dl. The hemoglobin of these babies was checked at the time of admission during the first week of life, thereafter every week, in between as and when required till the baby was discharged. The decision to transfuse blood was not only determined by the hemoglobin

level, but also took into account the presence of lung disease, respiratory effort, oxygen therapy and overall health of the infant.

Gestational age was assessed by First trimester fetal ultrasound, LMP, or by New Ballard Score (Annexure I) if ultrasound was not done or LMP could not be recalled. Neonates were best examined in the neonatal unit itself under supervision of attending pediatrician. Babies were examined by the same ophthalmologist each time (Monday/Friday). Feeding was avoided 30 minutes before examination; neonatologist was present during examination of unstable babies. Pupils were dilated using 2.5% Phenylephrine and 0.5% Cyclopentolate eye drops instilled two times into each eye at intervals of 15mins. The first indirect ophthalmoscopic examination was performed in SNCU between the 3rd week and 4th week of life, and for babies born less than 1200 grams the first examination was between the 2nd and 3rd week. Each baby also underwent wide field digital imaging (WFDI) with the Retcam Shuttle (Clarity MSI, CA, USA) with the 130 ROP lens. Images were stored and compared using the software of the machine at each visit by the ophthalmologist. All aseptic precautions were taken and speculum used in all cases. A Flynn infant sclera depressor was also used in all cases when indirect ophthalmoscopy was performed in all quadrants to ascertain any peripheral zone 3 disease. Depression was not required in most cases when the Retcam was used. If no ROP was detected at initial examination the infants were re-evaluated every 2 weeks until complete vascularisation of retina. If ROP was detected frequency of follow up was decided by ophthalmologist depending on the stage of ROP. Details of ROP were recorded in the proforma as per International Classification of ROP.

Statistical methods:-Data was analyzed using SPSS statistical package version 22. Univariate analysis was performed for the variables. Students' t-test was used for continuous variables and Pearson chi square, Fishers exact probability test and Odds ratio were applied to categorical variables wherever required. Risk factors were analyzed by multi nominal logistic regression analysis to establish relationship with ROP.

Ethical issues:-Informed consent of parents was taken after explaining in detail about the disease, methods and procedures involved in the study in their own vernacular language. Institutional ethical committee clearance was taken.

4. Observation

The mean gestational age of patients in our study was 30.29±2.17 weeks ranging from 26 to 35 weeks. Out of 200 patients 82(42%) were female and 118 (59%) were male. The mean weight of patients was 1177.53±265.31 grams ranging from 600-2000 grams. Out of total 200 babies under study, 70(35%) were anemic and 130(65%) were non -anemic. The mean number of blood transfusion was 0.53±0.85 ranging from 0 to 4.130 patients did not receive any blood transfusion. 61 patients received 1-2 blood transfusion while 9 patients received 3-4 blood transfusions. BPD (also known as chronic lung disease), defined as supplement oxygen dependence beyond 28 postnatal days. Out of 200 patients, 30 developed BPD while 170 did not develop BPD. Culture proven sepsis was documented in 78 patients which accounted to 39%. The mean duration of O2 therapy was 17.67±8.95 days ranging from 3 to 42 days. 170 patients (85%) received oxygen therapy via nasal prongs while 30 patients (15%) needed mechanical ventilation. Mean duration of hospital stay was 41.42±11.67 days ranging from 25 to 80 days. Out of 200 patients, in 129 patients (54.5%) the severity of ROP regressed while 71 patients (35.5%) developed severe ROP. The final outcome of ROP in our study was as follows: Mature retina in 68 patients (34%), ROP regressed in 61 patients (30.5%) and Severe ROP requiring treatment in 71(35.5%). Out of 200 patients, 129 did not require any treatment for ROP while 69 patients were treated with anti-VEGF injection and 2 were treated with laser ablation.

5. Observation

5.1. Mean gestational age

Englert et al[21] identified estimated gestational age(EGA) at birth as a strong predictor of severity of ROP (p=0.0001). In the present study too, EGA at birth strongly correlated with severity of ROP (p<0.001). The mean gestational age among the patients who did not develop severe ROP was 30.75 (2.27) weeks as compared to the severe ROP group where it was 29.46 (1.72) weeks.

5.2. Sex distribution

In the previous study male infants were more likely to progress to more severe ROP (p=0.03).However in the present study, we did not find sex to be a significant predictor of ROP severity. In the group that did not develop severe ROP, male to female ratio was 1.48:1 as compared to the severe ROP group where it was 1.36:1.

5.3. Birth weight

In the previous study birth weight was not correlated with ROP severity, perhaps because the range of birth weights in the study group was narrow (508 to 800g). In our study, lower birth weight correlated well with severity of ROP (p=0.033).

The mean birth weight was 1207.56 (275.35) grams in the group that did not develop severe ROP, as compared to a lower mean birth weight of 1122.96 (238.29) grams in the severe ROP group

Table 1: Socio-demographic & clinical profile of the study participants (n=200)

Parameter		Number	Percentage
Gestational age	<28 wks	26	13
	28-30 wks	76	38
	30-32 wks	62	31
	32-34 wks	28	14
	34-36 wks	8	4
	>36 wks	0	0
Sex	Female	82	41
	Male	118	59
Birth weight	<800gms	6	3
	800-1000gms	68	34
	1001-1500gms	118	59
	1501-2000gms	8	4
Anemia	Present	70	35
	Absent	130	65
Blood transfusion	No	130	65
	1-2	61	30.5
	3-4	9	4.5
BPD	Absent	170	85
	Present	30	15
Sepsis	Absent	78	39
	Present	122	61
Duration of oxygen Therapy	<7days	13	6.5
	7-14 days	68	34
	15-21 days	56	28
	22-28days	39	19.5
	29-35days	20	10
	>35days	4	2
Days of oxygen therapy	Mean	17.67 (8.95)	
	Range	3.00-42.00	—
Mode of oxygen therapy	Nasal prong(NP)	198	94.5
	NP& M V	11	4.5
Duration of stay	Mean (SD)	41.42(11.61)	—-
	Range	25.00-80.00	—-
Outcomes	Severe	71	35.5
	Non-severe	129	61.5
Final outcome	ROP requiring treatment	71	35.5
	Matured retina	68	34
	Regressed ROP	61	30.5
Treatment	Anti-VEGF	69	34.5
	Leser	2	1
	No treatment	129	64.5

Table 2: 2: Socio-demographic factors associated with severity of ROP

Parameter		Non-severe N=129	Severe N=71	Total N=200	p-value
Gestational age in weeks	Mean	30.75 (2.27)	29.46 (1.72)	30.29 (2.17)	<0.001
	Range	26.00 - 35.00	27.00 - 34.00	26.00 - 35.00	
Sex	Female	52 (40.3%)	30 (42.3%)	82 (41.0%)	0.79
	Male	77 (59.7%)	41 (57.7%)	118 (59.0%)	
Birth weight in grams	Mean (SD)	1207.56 (275.35)	1122.96 (238.29)	1177.53 (265.31)	0.031
	Range	600.00 - 2000.00	600.00 - 1600.00	600.00 - 2000.00	

Gestational age and birth weight plays a role in development of severe ROP

Table 3: 3: Clinical factors associated with severity of ROP

Parameter		Non-severe N=129	Severe N=71	Total N=200	p-value
Anemia	No	93 (72.1%)	37 (52.1%)	130 (65.0%)	0.005
	Yes	36 (27.9%)	34 (47.9%)	70 (35.0%)	
No. of BT	Mean (SD)	0.23 (0.54)	1.07 (1.03)	0.53 (0.85)	<0.001
	Range	0.00 - 3.00	0.00 - 4.00	0.00 - 4.00	
Days_O2	Mean (SD)	15.88 (8.39)	20.93 (9.07)	17.67 (8.95)	<0.001
	Range	3.00 - 39.00	5.00 - 42.00	3.00 - 42.00	
Mode_O2	NP	122 (94.6%)	67 (94.4%)	189 (94.5%)	0.95
	NP &MV	7 (5.4%)	4 (5.6%)	11 (5.5%)	
BPD	No	121 (93.8%)	49 (69.0%)	170 (85.0%)	<0.001
	Yes	8 (6.2%)	22 (31.0%)	30 (15.0%)	
Sepsis	No	53 (41.1%)	25 (35.2%)	78 (39.0%)	0.42
	Yes	76 (58.9%)	46 (64.8%)	122 (61.0%)	

ROP has been significantly observed in number of blood transfusion, duration of oxygen therapy, bronchopulmonary dysplasia.

Table 4: Logistic regression analysis

Parameter		Non-severe N=129	Severe N=71	Odd ratio	p-value
GA (Weeks)		30.7 (2.27)	29.5 (1.72)	0.74 [0.63;0.86]	<0.001
BW (Grams)		1208 (275)	1123 (238)	1.00 [1.00;1.00]	0.033
Anemia	No	93 (72.1%)	37 (52.1%)	Ref.	Ref.
	Yes	36 (27.9%)	34 (47.9%)	2.36 [1.29;4.35]	0.005
BT_Class:	No B T	105 (81.4%)	25 (35.2%)	Ref.	Ref.
	1-2 BT	23 (17.8%)	38 (53.5%)	6.83 [3.50;13.7]	<0.001
	3-4 BT	1 (0.78%)	8 (11.3%)	29.1 [4.90;756]	<0.001
Oxygen	Day-O2	15.9 (8.39)	20.9 (9.07)	1.07 [1.03;1.10]	<0.001
BPD:	No	121 (93.8%)	49 (69.0%)	Ref.	Ref. <0.001
	Yes	8 (6.20%)	22 (31.0%)	6.64 [2.85;17.0]	

Logistic regression was used to evaluate the odds ratio of various significant factors (p<0.05) on severity of ROP among children

5.4. Oxygen therapy and duration of hospital stay

The previous study reported severity of ROP to be associated with greater number of ventilator days (p=0.004) but not with number of oxygen supplementation days (p=0.12). However, longer duration of oxygen therapy was a significant predictor of ROP severity in our study (p<0.001).The mean duration of oxygen therapy was 15.88 (8.39) days in the group that did not develop severe ROP as compared to a longer duration of oxygen therapy i.e.20.93 (9.07) days in the severe ROP group.

Longer hospital stay was identified as a significant predictor of ROP severity (p=0.01) which is in concordance with our study results (p<0.001). Mean duration of hospital stay was 47.77 (11.82) days in the severe ROP group as compared to a shorter duration of hospital stay i.e. 38.08(10.13) in the non severe ROP group.

5.5. Bronchopulmonary dysplasia

In the previous study BPD was significantly associated with ROP severity (p=0.001). Our study too identified BPD as a significant predictor of ROP severity (p<0.001). The odds of BPD patients developing severe ROP were 6.64 times that of patients who did not have BPD.

5.6. Sepsis

Englert et al[21] did not identify sepsis as significant factor in development of severity of ROP. In our study too, no correlation was obtained between sepsis and development of severe ROP.

5.7. Anemia

The previous study by Englert et al found no correlation between frequency of anemia (Hb<10g/dl) and ROP severity. However, they showed that severe anemia (Hb<8g/dl or hematocrit<25%) was significantly associated with ROP severity (p=0.03).

Another study by Brooks et al[22] found no difference between infants with ≤stage 2 ROP and infants with ≥ stage 3 ROP when evaluating hemoglobin levels during the first week of life(p=0.059).

Brooks et al[23] found no association between anemia or blood transfusions and ROP incidence or severity in 34 infants evaluated during a 6 week period (day of life 29 to 71).

Our study showed the prevalence of anemia, the primary parameter in question, to be significantly higher in the group that developed severe ROP. In the group that did not

develop severe ROP, prevalence of anaemia was found to be consistently lower. This difference was calculated to be statistically significant, with a p-value of **0.005**. The odds of an anaemic patient developing severe ROP were 2.36 times the odds of non-anaemic patients.

5.8. Blood transfusion

Englert et al[21] found that infants who received a greater number of blood transfusions developed more severe ROP (p=0.0007). Alter et al. did not find any association of severity of ROP with the number of blood transfusions.

In our study, babies who received 1-2 blood transfusions had 6.83 times the odds of developing severe ROP than the ones who did not receive any blood transfusion. In addition, the odds of developing severe ROP was significantly higher i.e. 29.1 times in the babies who received 3-4 blood transfusions, indicating higher frequency of blood transfusions was significantly associated with ROP severity (p<0.001). There were no identifiable trends regarding infant age at the time of blood transfusion and severity of ROP. However, the decision to transfuse was not determined solely by hemoglobin/ hematocrit levels but also by respiratory rate and effort, ventilator/ oxygen status, sepsis and overall health of the infant.

Although the association of blood transfusions and ROP development has been shown in some studies, this does not prove a cause-and-effect relationship. However there is speculation that transfusions containing adult hemoglobin with lower affinity for oxygen than fetal hemoglobin (HbF) cause greater oxygen delivery to retina, increasing the risk for developing ROP. In addition, packed RBC transfusions contain large amounts of iron, which can rapidly increase serum iron levels in premature infants. Free iron can produce free radicals, which have been enzymatically linked to ROP development.

6. Conclusion

70 patients (35%) were anemic and 130 patients (65%) were non anemic. The mean number of blood transfusion was 0.53±0.85 ranging from 0-4. 130 patients did not receive any blood transfusion. 61 patients received 1-2 blood transfusions while 9 patients received 3-4 blood transfusions. EGA at birth strongly correlated with severity of ROP (p<0.001). The prevalence of anemia, the primary parameter in question, to be significantly higher in the group that developed severe ROP. The odds of an anemic patient developing severe ROP were 2.36 times the odds of non-anemic patients. Higher frequency of blood transfusions was significantly associated with ROP severity (p<0.001). In 129 patients (54.5%) the severity of ROP regressed while 71 patients (35.5%) developed severe ROP.129 patients did not require any treatment for ROP while 69 patients were treated with anti-VEGF injection and 2 were treated with laser ablation.

7. Limitation

This hospital based observational study could not able to compare with comparison with other author as limited data is available .

8. Authors Contribution

All authors were involved in research design, data analysis, and manuscript preparation and editing.

9. Source of Funding

None.

10. Conflict of Interest

None.

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