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Original Research Article

Correlation between Anemia and Severity of Retinopathy of Prematurity in Preterm Infants in South Bihar

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Abstract

Introduction: Premature infants have avascular or incompletely vascularized retina at birth, and retinopathy of prematurity evolves over 4–5 weeks after birth. This relatively slow evolution gives a small window of opportunity to effectively conduct retinal examinations and timely interventions to improve visual outcome and avoid irreversible blindness owing to retinal detachment from progressive untreated ROP.

Aim and objectives: The aim of the study was to estimate the incidence, to identify the corelation of anemia to ROP, in preterm infants.

Material and methods: A retrospective analysis study was performed on the preterm infant with anemia in Narayan medical college Jamuhar, on 50 premature during July 2021 to june 2022 in the NICU on the neonates weighing <2000g and/or with a gestation ≤34 weeks admitted to our NICU. All the infants were screened by the same ophthalmologist. Ethical clearance was obtained from the hospital ethics committee and informed consent of the parents was also obtained.

Results: Incidence and severity of ROP in babies with anemia at 3 weeks of life was higher in those with severe anemia. 10 out of 14 study subjects in babies with Hb <8 mg/dl had stage 2 or higher ROP, 8 out of 19 study subjects in babies with 8-10 mg/dl, and 8 out of 17 study subjects with haemoglobin more than 10 had ROP grade more than 2.

Conclusions: On the basis of our study we can conclude that anemia and number of blood transfusions are significant risk factors in the development of retinopathy of prematurity.

Keywords: ROP, Anemia, Blood transfusion, Respiratory Distress syndrome (RDS)

Introduction

Retinopathy of prematurity (ROP) is a developmental retinal vaso- proliferative disease and a leading cause of blindness in children. It is characterized by the growth of abnormal vessels in the incompletely vascularized retina of preterm infants.[1]

The ICROP3 retains current definitions such as zone (location of disease), stage

(appearance of disease at the avascular-vascular junction), and circumferential extent of disease. Major updates in the ICROP3 include refined classification metrics (e.g., posterior zone II, notch, subcategorization of stage 5, and recognition that a continuous spectrum of vascular abnormality exists from normal to plus disease). Updates also include the definition of aggressive ROP to replace aggressive-posterior ROP because of increasing recognition that aggressive disease may occur in larger preterm infants and beyond the posterior retina, particularly in regions of the world with limited resources. ROP regression and reactivation are described in detail, with additional description of long-term sequelae.[2,3]

Anemia is extremely common in premature infants, especially in premature infants at a gestational age < 32 weeks. Timely blood transfusions to correct the anemia status might initiated the regression of ROP. However, some studies reported anemia status was related to decreased risk of ROP[5]. Other study suggested that blood transfusion in preterm neonates did not exhibit any influence on occurrence and development of ROP.[4]

Anemia is caused by immaturity of the haematopoietic system and is due to inadequate production of erythropoietin and iatrogenic blood loss due to frequent blood sampling . Most extremely preterm infants receive blood transfusions for anaemia at some point during their hospitalisation, based on haemoglobin levels and clinical indications, including oxygen requirements.[5]

Major risk factors for development of ROP include low birth weight, low gestational age, a history of cardiorespiratory support, prolonged oxygen requirement, respiratory distress syndrome, chronic lung disease, fetal haemorrhage, blood transfusion, sepsis, exchange transfusion, intraventricular haemorrhage, and apnoea. ROP screening is performed in infants with a birth weight of less than 2000 g or less and gestational age of equal to or less than 34 weeks.

Premature infants have avascular or incompletely vascularized retina at birth, and ROP evolves over 4–5 weeks after birth. This relatively slow evolution gives a small window of opportunity to effectively conduct retinal examinations and timely interventions to improve visual outcome and avoid irreversible blindness owing to retinal detachment from progressive untreated ROP.[6]

Screening of ROP should be done in a timely manner, as prompt treatment may reduce the risk of long term adverse visual outcomes[3]. However, the benefits of screening need to be balanced against the pharmacological risks of mydriatics and the stress of serial retinal examinations. Despite pre-existing guidelines for ROP screening, the vision-threatening sequelae of this developmental condition still affect a significant number of infants. Thus, there remains a need for improved screening criteria for ROP among premature infants.[7] In India, approximately, 1 in 1000 children is blind, and the incidence of ROP is reported between 24% and 47%.The aim of the study was to estimate the incidence, to identify the corelation of anemia to ROP, in preterm infants.

Materials and Methods

A retrospective analysis study was performed on the preterm infant with anemia in Narayan medical college Jamuhar, on 50 premature during July 2021 to june 2022 in the NICU on the neonates weighing <2000g and/or with a gestation ≤34 weeks admitted to our NICU. All the infants were screened by the same ophthalmologist. Ethical clearance was obtained from the hospital ethics committee and informed consent of the parents was also obtained. Neonates with birth weight ≤ 2000g or gestational age less than 34 weeks were screened if they had anemia as risk factors.

Retrospective analysis of data of 50 babies born premature less than 34 weeks for the development of Retinopathy of prematurity and its severity and for associated conditions. Study duration of 1 years between July 2021-june 2022. Factors analysed included Hemoglobin levels at 3 weeks of life, Number of blood transfusions, days on ventilator, gestational age, birth weight, duration of oxygen requirement, for the development of Retinopathy of prematurity. All babies screened for Retinopathy of prematurity at 3 weeks of age and further followed up for progression of ROP. Babies were grouped into those with no retinopathy of prematurity, with stage 1 ROP and those with stage 2 and above were clubbed into a single group. Other factors analysed included association of sepsis, Intraventricular hemorrhage, hypoglycemia with retinopathy of prematurity. Findings described in simple descriptive manner. All data analysed retrospectively not involving any ethical issues. SPSS version 20 was used for statistical analysis. Qualitative (categorical) variables were represented by frequency and percentage analysis. Quantitative (continuous/score) variables were represented by mean and standard deviation. Multinomial logistic regression was performed to find the association between ROP and other variables. A p-value less than 0.05 is taken as statistically significant.

Selection criteria for babies.

Inclusion criteria

All preterm babies born less than 34 weeks of gestation.

Exclusion criteria

Babies with congenital anomalies and babies requiring exchange transfusion for hyperbilirubinemia.

Results

Table 1: Sex distribution of study subjects

Sex	ROP>2	ROP<2	Total
Male	12	10	22
Female	18	10	28
Total	30	20	50

Table 1 shows sex distribution of study subjects. Out of 50 study subjects 22 subjects were male in which 12 had ROP stage more than 2 whereas 28 study subjects were female in which 18 subjects had ROP stage more than 2 whereas rest 10 subjects had ROP stage less than 2.

Table 2: comparison of the studied groups according to gestational age categories

Gestational age	ROP >2	ROP<2	Total
23-25	9	3	12
26-28	8	4	12
29-31	6	5	11
32-34	7	8	16
Total	30	20	50

Table 2 shows comparison of the studied groups according to gestational age categories. 12 study subjects had gestational age 23-25 weeks, in which 9 study subjects had ROP stage more than 2, whereas 3 study subjects had ROP stage less than 2. 12 study subjects had gestational age 26-28 weeks, in which 8 subjects had ROP stage more than 2 whereas 4 study subjects had ROP stage less than 2. 16 subjects had gestational age 32-34 weeks in which 7 subjects had ROP stage more than 2 whereas 8 subjects had ROP stage less than 2.

Table 3: Associations of RDS with ROP stage of study subjects

RDS	ROP		
	ROP>2	ROP<2	Total
With RDS	11	2	13
Without RDS	19	18	37
Total	30	20	50
Chi-square value- 4.44, p value- 0.01, significant			

Table 3 shows Associations of RDS with ROP stage of study subjects, out of 50 study subjects 13 subjects were with RDS whereas rest 37 study subjects were without RDS, Out of 13 study subjects with RDS 11 study subjects had ROP stage more than 2 whereas 2 study subjects had ROP stage less than 2. Out of 37 study subjects 19 study subjects had ROP stage more than 2 whereas 18 study subjects had ROP stage less than 2. On applying chi-square we found significant association with p value <0.05.

Table 4: Associations of Oxygen administration with ROP

Oxygen administration	ROP		
	ROP>2	ROP<2	Total
Given	28	12	40
Not Given	2	8	10
Total	30	20	50
Chi-square value- 8.33, P value< 0.01, non-significant			

Table 4 shows Associations of Oxygen administration with ROP, 40 study subjects were given oxygen therapy in which 28 study subjects had ROP stage more than 2 whereas 12 study subjects had ROP stage less than 2. Out of 10 study subjects who are not given oxygen therapy, 2 study subjects were had ROP stage more than 2 whereas 8 subjects had ROP stage less than 2. On applying chi-square it was significant with p value <0.05.

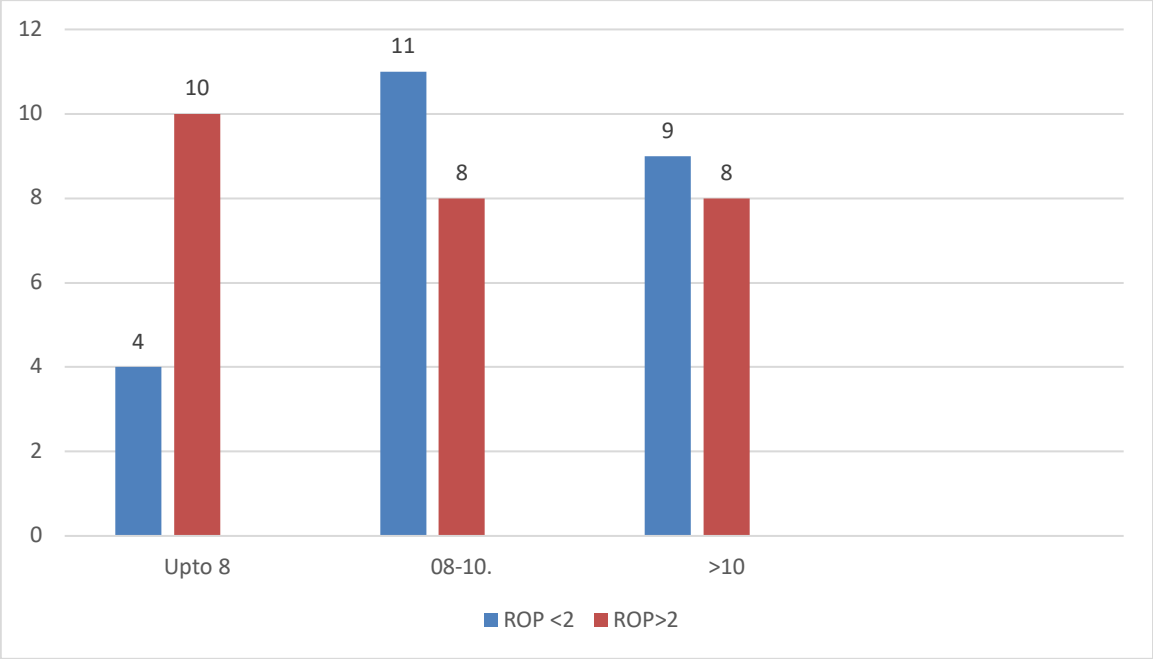

Figure 1: Association of stage of ROP with haemoglobin level

Incidence and severity of ROP in babies with anemia at 3 weeks of life was higher in those with severe anemia. 10 out of 14 study subjects in babies with Hb <8 mg/dl had stage 2 or higher ROP, 8 out of 19 study subjects in babies with 8-10 mg/dl, and 8 out of 17 study subjects with haemoglobin more than 10 had ROP stage more than 2.

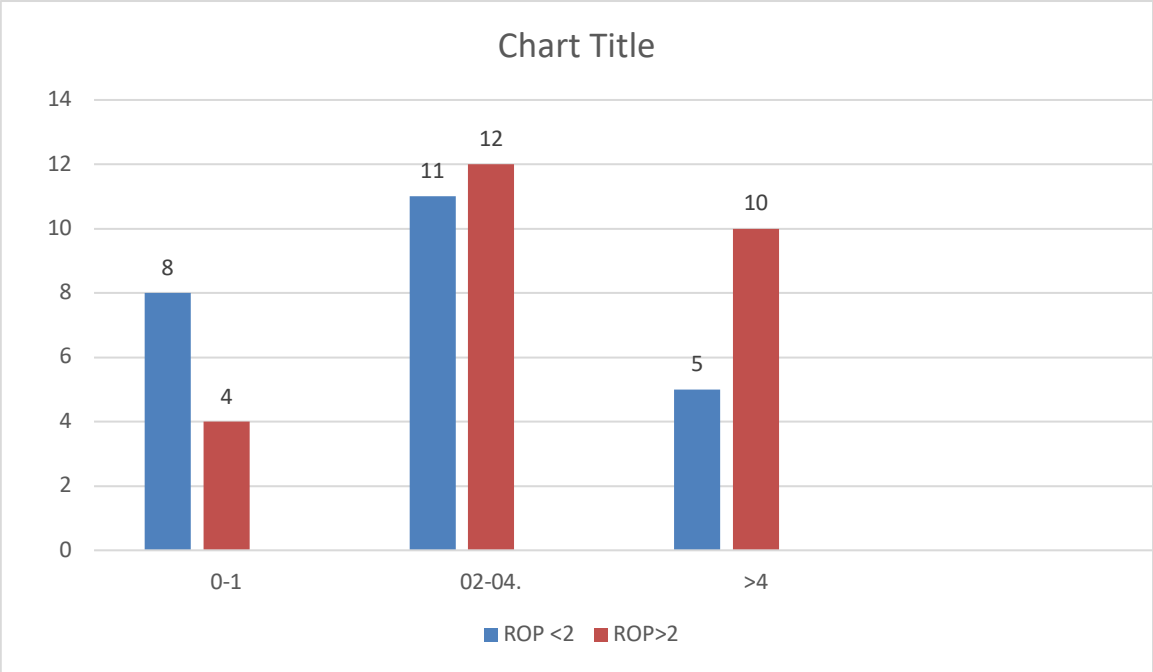

Figure 2: Association of stage of ROP with no of blood transfusion

Fig 2 shows Association of stage of ROP with no of blood transfusion. Analyzing correlation between number of blood transfusion with incidence and severity of ROP, stage II or more of ROP is significantly higher in cases with more than 4 blood transfusions(66.67%) and 2-4 blood transfusions (52.2%) compared to the cases with 0-1 blood transfusions (33.3%)

Discussion

In this study 50 babies born preterm less than 34 weeks were studied for the development of retinopathy of prematurity. Babies were screened for retinopathy of prematurity at 3 weeks of life and risk factors analysed for ROP including gestational age, birth weight, Anemia at 3 weeks, requirement of blood transfusions, Incidence and severity of ROP in babies with anemia at 3 weeks of life was higher in those with severe anemia.

In our present study 12 study subjects had gestational age 23-25 weeks, in which 9 study subjects had ROP grade more than 2, whereas 3 study subjects had ROP grade less than 2. 12 study subjects had gestational age 26-28 week, in which 8 subjects had ROP grade more than 2 whereas 4 study subjects had ROP grade less than 2. The incidence of ROP varies in different studies mainly due to the mean GA of the included infants and the percentage of extremely low birth weight (ELBW) in each study. Our findings are in complete agreement with all published data in the literature.[8,9] and also with the known association of low BW and low GA. Small for gestational age infants have been consistently associated with the development of ROP.

10 out of 14 study subjects in babies with Hb <8 mg/dl had stage 2 or higher ROP, 8 out of 19 study subjects in babies with 8-10 mg/dl, and 8 out of 17 study subjects with haemoglobin more than 10 had ROP grade more than 2. Similar results were found in a study by Doudou Xu et al (2022)[4] where they found that

hemoglobin during the postnatal first week had a nonlinear relationship with risk of ROP. As the hemoglobin level during the first week increased up to 140g/L, the risk of ROP was decreased. However, the risk of ROP was elevated when the concentration of hemoglobin increased after 140g/L. Therefore, anemia cannot be simply attributed to the protection or risk factors of ROP, but should be judged according to the hemoglobin level in different periods. However, as this study is a retrospective cohort study, and the occurrence of ROP is affected by oxygen consumption, gestational age, blood transfusion and other factors, more rigorous prospective studies are needed to further explore its correlation Edwin Pheng et al (2021)[7] observed that infants in the ROP group in their study had significantly lower mean haemoglobin levels in the first week of life compared to the group without ROP. Both groups (with and without ROP) experienced decreases in mean haemoglobin level from birth till the sixth week of life. These differences persisted even after adjusting for confounding factors. Banerjee et al.[10] likewise found an association between low haemoglobin at birth and ROP development. There were no significant differences in adjusted mean haemoglobin levels between infants with ROP requiring treatment and controls. Englert et al.[11] reported that infants with prolonged severe anaemia, with a haemoglobin of <80 g/L, developed milder ROP than those infants with anaemia with shorter duration who received frequent blood transfusions. That study showed that severe anaemia was associated with ROP severity. Anemia of prematurity is a common phenomenon in preterm infants. Whether anemia as risk factors for ROP have been inconsistent. Some evidence suggests that anemia was related to the development of ROP. Lundgren et al.[5] found the duration of anemia during the first week of life was an independent risk factor for ROP warranting treatment.

In our present study Analyzing correlation between number of blood transfusion with incidence and severity of ROP, stage II or more of ROP is significantly higher in cases with more than 4 blood transfusions (66.67%) and 2-4 blood transfusions (52.2%) compared to the cases with 0-1 blood transfusions (33.3%). Blood transfusion influences ROP mainly via two mechanisms. First, increased the oxygen availability in the developing retina. Fetal hemoglobin (HbF) was the main hemoglobin in early newborn. Unlike adult hemoglobin (HbA), HbF has a higher affinity for oxygen. Replacing HbF by HbA during transfusion possibly contributing to the development of ROP. Second, blood transfusion increases iron load. It is well known that transferrin saturates rapidly after transfusion, increased free iron may catalyze Fenton reactions, then produce free hydroxyl radicals from superoxide and hydrogen peroxide, which increase the risk of retinal damage . On the other hand, biologically active substances in blood products may also play a role. In the present study stage II or more of ROP is significantly higher in cases with more than 4 blood transfusions (80.0%) which coincides with Doudou Xu[4] study who concluded that both anemia and blood transfusions during the first gestational weeks of life, were associated with an increase of risk of ROP .

In study by Englert et al.[11] infants with ROP received 3.8 ±4.4 transfusions whereas babies without ROP received 2.5 ±3.7 transfusions ($p<0.01$). A decade later, Alter et al.[12] 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 ($P=0.059$) or number of blood transfusions ($p=0.072$)

Conclusions

On the basis of our study we can conclude that anemia and number of blood transfusions are significant risk factors in

the development of retinopathy of prematurity. Stage of ROP is significantly associated with haemoglobin level. These are in addition to other predisposing factors low gestational age, low birth weight, longer duration of ventilation and oxygen requirement, BPD as a risk factor for ROP.

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