THE EFFECT OF BLOOD TRANSFUSION ON THE DEVELOPMENT OF RETINOPATHY OF PREMATURITY IN SAMPLED EGYPTIAN NEONATES

Basma Samir Kamil Ismail Mostafa[1*], Esraa Ahmed Elmazzahy[1], Ahmed Reda Awadein[2], Heba Nabil Amin Baz[3], Aliaa Adel Ali[1]

Article History: Received: 10.06.2023 **Revised:** 25.07.2023 **Accepted:** 01.08.2023

Abstract

Background: Retinopathy of prematurity (ROP) is a leading cause of blindness. Current screening recommendations are mainly based on two risk factors: birth weight (BW) and gestational age (GA); however, many investigators have suggested other risk factors especially those related to treatment.

Aim: To determine the risk factors of ROP related to blood transfusion among preterm neonates admitted to the neonatal intensive care units (NICUs) of Cairo University Children Hospitals.

Patients and Methods: A prospective cohort study including 87 preterm neonates (GA ≤ 32 weeks and/or BW ≤ 1500 g). Documents from NICUs and investigation results were obtained, digital fundus photography and indirect ophthalmoscopy were used to examine the patients for presence of ROP. Scores for ROP were computed. Risk factors related to blood transfusion and development of ROP were documented.

Results: The majority of patients who had severe ROP needed to receive blood transfusions, plasma transfusions or platelet transfusions.

Highlights: Gestational age and birth weight are the two most well-established risk factors for ROP, in addition to other factors such as oxygen therapy.

The need for blood and plasma transfusions in preterm babies has established the need for studying the effect of blood transfusion and plasma transfusion as risk factors for the development of ROP. This study determines the relationship between these transfusions and ROP.

Conclusion: Blood transfusion and plasma transfusion and platelet transfusion were all risk factors for the development of severe ROP.

Keywords: Retinopathy of prematurity, risk factors, blood transfusion, plasma transfusion, neonates.

1 Pediatrics Department, Faculty of Medicine, Cairo University.
2 Ophthalmology Department, Faculty of Medicine, Cairo University.
3 Chemical Pathology Department, Faculty of Medicine, Cairo University.
***Corresponding author:** E-mail: basmasamir272016@yahoo.com

DOI: 10.31838/ecb/2023.12.9.176

INTRODUCTION

Retinopathy of prematurity (ROP) is a disorder affecting the retina in preterm infants. It is a serious condition that can lead to blindness. ROP can be affected by multiple factors, such as those related to the mother, delivery, infant and treatment factors **[1].**

In 2020, the World Health Organization's Vision program identified ROP as a leading cause of blindness in childhood, especially in low- and middle-income countries (LMIC). Almost 185 thousand infants born prematurely worldwide were estimated to have developed ROP of any stage, more than 10% of which developed blindness or severe visual impairment **[2].**

Eliminating the preventable blindness attributed to retinopathy of prematurity (ROP) continues to be an ongoing challenge for both ophthalmologists and neonatologists **[3].**

Fortunately, there is an increase in survival rates among very low birth weight preterm newborns who are at the greatest risk for developing ROP. Therefore, the disease has been extensively studied aiming to prevent development of the disease and its consequences. As a result, ROP has become the leading cause of preventable blindness in infants **[4].**

The normal relatively hypoxic conditions inside the uterus allow retinal vascularization. After birth, the hyperoxic environment, even room air, can suppress the growth of the vessels of the retina and this can result in improper vascularization of the retina (ROP Phase 1). With the growth of the retina and increasing demands with the impaired retinal vascularization, higher levels of retinal hypoxia occur (ROP Phase 2) **[5].**

Over time, a fibrous scar extending from the retina to the lens occurs. Retraction of this scar can separate the retina from the retinal epithelium, resulting in detachment and blindness. In a normal 40 weeks gestation, the most important weeks for

the development of the eyes are the last 12 weeks. In premature infants, the normal growth stops **[6].**

Although the incidence of ROP increases with decreasing gestational age and birth weight, not all preterm neonates develop ROP. There are many risk factors, prenatal and postnatal, which may increase the probability of ROP **[7].** The other factors being less significantly associated with ROP include oxygen therapy, history of transfusion, sepsis, and anemia.

A small subset of ROP infants require intervention. Therefore, it is important to better understand the risk factors of ROP to decrease the disease progression **[8].**

Most extremely preterm infants receive blood transfusions for anemia at some point during their hospitalization, based on hemoglobin levels and clinical indications, including oxygen requirements **[9].** The hypoxic avascular retina stimulates large increases in vascular endothelial growth factor (VEGF) and Erythropoietin (EPO), which results in uncontrolled retinal neovascularization in phase 2. Without timely treatment, neovascularization can lead to retinal detachment and blindness. In preterm infants, vitreous levels of EPO were elevated in infants that developed neovascularization during phase 2 ROP **[10].**

Of the risk factor for developing ROP, one of the most relevant in routine clinical practice is blood transfusion. A statistical correlation between the amount of blood transfused and the severity of retinopathy is established, but the potential causality of the relationship remains unclear. Transfusion of RBCs appears to be a risk factor for the development of ROP. The increased risk might be due to either the administration of adult hemoglobin or the iron overload resulting from the transfusions. Iron overload increases the risks of oxygen radicals. Adult hemoglobin causes a higher delivery of oxygen to tissues compared to fetal hemoglobin. Some studies found that anemia was related to an increased risk of ROP, as well as the administration of EPO **[11].**

Identifying the risk factors that accelerate the progression of ROP and knowledge of its etiology can help ophthalmologists and neonatologists screen carefully, make an accurate diagnosis, and reduce the disease complications **[12,13].**

PATIENTS AND METHODS

Aim of the Study:

Determine the relationship between blood transfusion and ROP in preterm babies admitted at the neonatal intensive care units.

Study Design:

A prospective cohort study including 87 preterm infants screened for ROP after they were admitted to the two Neonatal Intensive Care Unit (NICU)s run by Cairo University Hospitals: El Mounira NICU, and Al Kasr Al Ainy NICU. Preterm neonates were screened for ROP by cooperation between the Department of Neonatology and the Department of Ophthalmology.

Study participants:

Inclusion criteria:

- Preterm infants with gestational age (GA) ≤32 weeks.
- Preterm infants with birth weight (BW) ≤1500 g.

Exclusion criteria:

- Full-term neonates.
- Neonates suffering from hydrocephalus, or any congenital anomalies.
- Infants suffering from ocular media opacities that interfered with fundus examination or had any congenital retinal anomalies.
- Neonates who died or were lost to follow-up before development of ROP or full vascularization of the retina were excluded.

Sample size: The calculated sample size is 78 patients that will be increased to 87 patients with addition of 10% to compensate for dropout based on the detection of ROP by Eckert et al. **[14].**

Study location:

Neonatal Intensive Care Unit (NICU)s run by Cairo University Hospitals: El Mounira NICU, and Al Kasr Al Ainy NICU

Study timing: May 2020 to May 2021

Statistical analysis:

Data were analyzed using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Quantitative data was summarized using mean, standard deviation, median, minimum and maximum, while categorical data was summarized using frequency (count) and relative frequency (percentage). Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square/ Fisher's exact test was performed. Correlations between quantitative variables were done using Spearman's correlation coefficient. P-values less than 0.05 were considered statistically significant.

Ethical consideration:

Our study was carried out after approval by the ethical committee of the Faculty of Medicine, Cairo University. Informed consents were obtained from infants' parents. Strict confidentiality and privacy were maintained throughout the process of data collection, entry and analysis as the principles stated in the Declaration of Helsinki.

Methodology in details:

All neonates included in this study were subjected to the following:

1- Documentation of perinatal and neonatal data:

Data were extracted from daily neonatal progress notes throughout hospital admission on a weekly basis. The collected data included:

- Patient demographics (birth weight, gestational age, sex)
- Need and frequency of blood transfusion.

- Results of laboratory investigations (complete blood picture, chemistry, and C-reactive protein, INR)

2- Eye Examination:

The initial screening and follow-up examinations were performed in accordance with the timetable recommended by the American Academy of Pediatrics (AAP) and the American Association for Pediatric Ophthalmology and Strabismus (AAPOS) statement on screening of preterm newborns for ROP. The trained neonatal physician / ophthalmologist assessed patients in the NICU with the newborn in the incubator if they were hospitalized, or in the NICU follow-up clinic following release from the hospital.

A physician with experience in digital imaging screening (RetCam screening) for ROP conducted the first eye examination. An ophthalmologist interpreted the images and confirmed the zone, stage, and extent of the ROP by an indirect ophthalmoscope. If the newborn did not have ROP after the initial evaluation, he/she was reevaluated every two weeks until full vascularization. According to **Eckert et al.**, the ROPScore was applied at the sixth week of life **(2012).** The ROPScore was used to predict the severity of ROP. The presence or absence of blood transfusions up to the sixth week of life, BW, GA (evaluated by obstetric history, early obstetric ultrasound, and confirmed by newborn infant clinical examination), proportional weight gain measured at 6 weeks of life, and oxygen in mechanical ventilation were all necessary criteria for this process **[14].**

RESULTS

This study was conducted on 87 preterm neonates who were admitted to the Neonatal Intensive Care Units of Cairo University Hospitals.

Out of the 87 neonates, 51 (58.6%) were males and 36 (41.4%) were females. Regarding the birth weight, the neonates had a mean birthweight of 1302.41 gm (±170.20 gm) while the average gestational age at birth was 31.32 weeks (±0.90 wks.) (**Table 1**).

Table (1): Demographic data of the neonates included in the study (n = 87)

Numerical variables	**Mean ± Standard Deviation**	**Median**	**Range**
GA* (weeks)	31.32 ± 0.90	32.00	(29-32)
Birth weight (gm)	1302.41 ± 170.20	1300.00	(900 -1500)
Categorical variables		**Frequency**	**Percentage**
Gender	**Male**	51	58.6%
	Female	36	41.4%
Single/multiple gestation	**Single**	59	67.8%
	Multiple	28	32.2%

* **GA**: gestational age.

For statistical analysis, we divided the cases into two groups ROP not requiring treatment (mild ROP) and ROP requiring treatment (severe ROP).

Among our study participants, 45 patients received blood transfusions. All the patients (9/9, 100%) who developed severe ROP received blood transfusions, while (36/78, 46.2%) of the patients who developed mild ROP had blood transfusions, and (42/78, 53.8%) of them did not receive blood transfusions. This difference has been shown to be statistically significant (P = 0.003) (**Table 3**).

Regarding plasma transfusion, all the patients with severe ROP received plasma transfusions, while 56.4 % of those who had mild ROP received plasma transfusions. This difference was considered statistically significant (P=0.011) (**Table 3**).

More than two thirds of the patients with severe ROP received platelet transfusion (77.8%) while only 17.9% of the patients with mild ROP received platelet transfusion and this difference was statistically significant (P <0.001) (**Table 3**).

Table (3): Comparison of blood product transfusions between both groups

		ROP				P value
		ROP not requiring treatment (n=78)		ROP requiring treatment (n=9)		
		Count	%	Count	%	
Blood transfusion	**Yes**	36	46.2%	9	100.0%	0.003
	No	42	53.8%	0	0.0%	
No. of blood transfusions	**0**	42	51.3%	0	0.0%	< 0.001
	1	17	21.8%	0	0.0%	
	2	19	24.4%	2	22.2%	
	3	1	1.3%	7	77.8%	
	4	1	1.3%	0	0.0%	
Plasma transfusion	**Yes**	44	56.4%	9	100.0%	0.011
	No	34	43.6%	0	0.0%	
Platelet transfusion	**Yes**	14	17.9%	7	77.8%	0.001
	No	64	82.1%	2	22.2%	

After analyzing the relationship between the ROP score and blood transfusions we found a statistically significant difference when comparing the number of blood transfusions with the ROPscore (P<0.001). The correlation between these two variables has been shown to be a positive one, which means that whenever there is an increase in the ROP score there is also an increase in the number of blood transfusions received by the neonates and vice versa.

Table (5): Correlations between the ROPScore at 6th week of life and number of blood transfusions among the study group

	ROP Score at 6th week	
	Correlation Coefficient	**P value**
No. of blood transfusions	0.725	< 0.001

DISCUSSION

One of the main causes of childhood blindness worldwide is retinopathy of prematurity. There aren't many studies that show how serious ROP actually is as a healthcare problem in Egypt and other parts of Africa and the Middle East. Multiple factors, including race, geographical area, quality of NICUs, and the survival rate of newborns, affect the incidence of ROP. Due to differences in economic status, screening programs, and level of prenatal care at different institutions, the incidence of ROP differs between countries and within institutes within the same country **[15].**

Neonatal screening examination for ROP detection offers the highest possibility of treating the disease in those infants who are likely to develop permanent ROP-related complications when done between the fourth and sixth week after delivery in VLBW and ELBW preterm infants **[16].**

The incidence of mild ROP, not requiring treatment in our study was 89.7%, and the incidence of severe ROP, which required treatment was 10.3%. Treatment was performed successfully in the form of intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF).

Red blood cell transfusion during the early neonatal period has been associated with the development of severe ROP. In this study, blood transfusion was a risk factor for severe ROP, which is in agreement with the study by **Akkawi et al.** in 2019 **[17]**. **Lundgren et al. [18]** found that during the first postnatal week, infants with progressive ROP (28%) more frequently developed anemia (42.9% versus 8.0%, P = 0.003). However, **Hirano et**

al. [19] reported that it was controversial, and that overload of iron rather than blood transfusion frequency leads to ROP.

Similar to our findings, **Lust et al. [20]** related the use of transfusions during the first 10 days of life with the development of severe ROP. Similarly, **Schecter et al. [21]** observed that the number of red blood cell transfusions during the neonatal period in VLBW newborns is related to the development of more severe forms of ROP. All the patients with severe ROP in our study received blood transfusions compared to 46.2% of patients with mild ROP (P=0.003).

Bas et al. **[22]** suggested that limiting the number of transfusions can reduce the prevalence of ROP. Strategies such as late clamping of the umbilical cord and limiting the use of venipuncture for laboratory tests may reduce the need for red blood cell transfusion.

Dani et al. **[23]** observed a significant association between ROP and fresh frozen plasma transfusion, as the newborns in whom it was indicated were critically ill newborns with consumptive coagulopathy. Similar to these findings, patients with severe ROP in our study had a significantly higher INR value than patients with mild ROP and all of them received plasma transfusions compared to 56.4% of patients with mild ROP (p=0.011).

Infants with ROP requiring treatment in our study needed more blood transfusions than patients with mild ROP. There are many risk factors for the development of severe ROP, in our study we found an association between the transfusion of blood products and severe ROP. These results are similar to the findings of other lower- and middle-income countries **[24].**

The result of this study revealed a significant relation between thrombocytopenia and severe ROP requiring treatment (p=0.001). This finding is in agreement with studies which is suggest an association between thrombocytopenia and severe ROP including aggressive posterior ROP and zone I ROP by **Lundgren et al.**in 2017 **[25].**

Dani et al. [26] observed a significant association between ROP and fresh frozen plasma transfusion, as the newborns in whom it was indicated were critically ill newborns with consumptive coagulopathy. Similar to these findings, patients with severe ROP in our study had a significantly higher INR value than patients with mild ROP and all of them received plasma transfusions compared to 56.4% of patients with mild ROP (p=0.011).

Declarations of interest: none

REFERENCES

[1] Kim SJ, Port AD, Swan R, Campbell JP, Chan RVP, Chiang MF. Retinopathy of prematurity: a review of risk factors and their clinical significance. Survey of ophthalmology. **2018**;63(5):618–37.

[2] World Health Organization and the International Agency for the Prevention of Blindness Joint Initiative. Vision **2020**: Global Initiative for the Elimination of Avoidable Blindness: Action Plan 2006–2011. Geneva: World Health Organization, 2007 Access at: http://www.who.int/blindness/ Vision2020report.pd

[3] Fierson WM, Capone A Jr, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association of Certified Orthoptists. Telemedicine for Evaluation of Retinopathy of Prematurity. Pediatrics **2015**; 135: e238 -54.

[4] Lee TC, Chiang MF. Pediatric Retinal Vascular Diseases. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, editors. Ryan's Retina. 6th ed. New York: Elsevier; **2018**. p. 1246–67.

[5]Hartnett ME. Pathophysiology and mechanisms of severe retinopathy of rematurity. Ophthalmology. **2015**;122(1):200–210.

[6] Fleck BW, McIntosh N. Retinopathy of Prematurity: Recent Developments. NeoReviews **2009**; 10:20-30.

[7] Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center-incidence,risk factors and outcome. Indian Pediatr **2013**; 46:219-24.

[8] Port A. D., Chan R. V., Ostmo S., Choi D., Chiang M. F. Risk factors for retinopathy of prematurity: insights from outlier infants. Graefe's Archive for Clinical and Experimental Ophthalmology. **2014**;252(10):1669–1677

[9] Jopling J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system. Pediatrics. **2009**; 123: e333–7.

[10] Yang X, Ze B, Dai Y, Zhu L & Chen C The alteration and significance of erythropoietin serum levels in preterm infants with retinopathy of prematurity. Am. J. Perinatol. **2017**; 34, 1020–1025

[11] Rivera JC, Holm M, Austeng D, et al. Retinopathy of prematurity: inflammation, choroidal degeneration, and novel promising therapeutic strategies. J Neuroinflammation. **2017**; 14:165.

[12] Pivodic A, Hård AL, Löfqvist C, Smith LE, Wu C, Bründer M-C et al. Individual risk prediction for sight-threatening retinopathy of prematurity using birth characteristics. JAMA Ophthalmol **2020**; 138:21–29.

[13] Hellstrom A, Smith LE, Dammann O Retinopathy of prematurity. Lancet **2013**;382:1445–1457.

[14] Eckert G.U., Fortes Filho J.B., Maia M., Procianoy R.S.: A predictive score for retinopathy of prematurity in very low birth weight preterm infants. Eye (London, England), **2012**; 26:400–406.

[15] Gaber R, Sorour OA, Sharaf AF, Saad HA. Incidence and Risk Factors for Retinopathy of Prematurity (ROP) in Biggest Neonatal Intensive Care Unit in Itay Elbaroud City, Behera Province, Egypt. Clin Ophthalmol. **2021**;15:3467-3471.

[16] Bowe T, Nyamai L, Ademola-Popoola D et al: The current state of retinopathy of prematurity in India, Kenya, Mexico, Nigeria, Philippines, Romania, Thailand, and Venezuela. Digital Journal of Ophthalmology,**2019**; 25(4): 49–58.

[17] Akkawi MT, Shehadeh MM, Shams ANA, Al-Hardan DM, Omar LJ, Almahmoud OH et al. Incidence and risk factors of retinopathy of prematurity in three neonatal intensive care units in Palestine. BMC Ophthalmol **2019**; 19:189.

[18] Lundgren P, Lundberg L, Hellgren G, et al. Aggressive posterior retinopathy of prematurity is associated with multiple infectious episodes and thrombocytopenia. Neonatology **2017**; 111:79-85.

[19] Hirano K, Morinobu T, Kim H, Hiroi M, Ban R, Ogawa S et al. Blood transfusion increases radical promoting non-transferrin bound iron in preterm infants. Arch Dis Child Fetal Neonatal Ed **2001**; 84: F188–F193.

[20] Lust C, Vesoulis Z, Jackups Jr R, Liao S, Rao R, Mathur AM. Early red cell transfusion is associated with development of severe retinopathy of prematurity. Journal of Perinatology. **2019**;39(3):393-400.

[21] Schecter LV, Medina AE, Alexander JL, Sundararajan S. Impact of early postnatal exposure of red blood cell transfusions on the severity of retinopathy of prematurity. Journal of Neonatal-Perinatal Medicine. **2021**;14(4):527-35.

[22] Bas AY, Demirel N, Koc E, Isik DU, Hirfanoglu İM, Tunc T. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. British journal of ophthalmology. **2018**;102(12):1711-6.

[23] Dani, C., Poggi, C., Bresci, C., Corsini, I., Frosini, S. & Pratesi, S. Early fresh-frozen plasma transfusion decreases the risk of retinopathy of prematurity. Transfusion, **2014**; 54, 1002–1007.

[24] Keraan Q, Tinley C, Horn A, Pollock T, Steffen J, Joolay Y. Retinopathy of prematurity in a cohort of neonates at Groote Schuur Hospital, Cape Town, South Africa. S Afr Med J. **2016**; 107:64–9.

[25] Lundgren P, Lundberg L, Hellgren G, et al. Aggressive posterior retinopathy of prematurity is

associated with multiple infectious episodes and thrombocytopenia. Neonatology 2017; 111: 79-85.

[26] Dani, C., Poggi, C., Bresci, C., Corsini, I., Frosini, S. & Pratesi, S. Early fresh-frozen plasma transfusion decreases the risk of retinopathy of prematurity. Transfusion, **2014**; 54, 1002–1007.