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ORIGINAL ARTICLE

Blood products transfusion and retinopathy of prematurity: A cohort study

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Abstract

Aim: The aim of the study was to assess the influence of blood product transfusions on the development and severity of retinopathy of prematurity (ROP).

Methods: A retrospective cohort study was conducted of very low birth weight (VLBW) newborns with less than 32 weeks gestational age (GA) admitted to the neonatal unit of a tertiary care hospital during the period from 1 January 2008 to 31 December 2021. Data on the degree of ROP and the transfusions received were obtained and analysed. Both univariate and multivariate analyses were performed, by logistic regression.

Results: A total of 565 VLBW newborns were recruited, of whom 263 received a red blood cell transfusion prior to 36 weeks corrected GA. The newborns with ROP received significantly more red blood cell transfusions than those not presenting this condition. After adjusting for oxygen therapy and GA, the risk of ROP was found to be 2.77 times higher (95% CI 1.31–5.88) after receiving three or more transfusions, with a 3.95 times higher risk (95% CI 1.40–11.1) of developing severe ROP. Having received the first red blood cell transfusion before 32 weeks corrected GA is associated with an increased risk of ROP (OR 2.18; 95% CI: 1.09–4.36).

Conclusion: In VLBW neonates, the number of red blood cell transfusions and their administration before 32 weeks corrected GA are important risk factors for ROP.

KEYWORDS
platelets, red blood cells, retinopathy of prematurity, transfusion

1 | INTRODUCTION

Retinopathy of prematurity (ROP) is a fibrous vasculoproliferative vitreoretinopathy that occurs as a consequence of abnormal retinal vascularization in premature infants (<1500 g weight at birth, or <32 weeks' gestation). It can cause a loss of visual acuity or even blindness (Recchia & Capone, 2004). The increased survival of children of low gestational age (GA) is accompanied by a corresponding increase in cases of severe ROP among newborns of lower GA, who also present more comorbidities (sepsis, ductus and apnoea) and have a greater need of supplemental oxygen to achieve a proper oxygenation (Chan et al., 2018; Gilbert, 2008).

Red blood cell transfusions are more frequently given to premature newborns, being indicated for approximately 40% of those with low birth weight and in 90% of those weighing <1000 g at birth. Although red blood cell transfusion may be crucial to the survival of these infants, it is also associated with higher rates of complications, such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), ROP and, possibly, abnormal neurological development (Villeneuve et al., 2021).

In preterm infants, diminished foetal haemoglobin is related to the number of transfusions received. In these

situations, there is an increase in haemoglobin A, which has lower affinity for oxygen and greater capacity to release oxygen, possibly exposing immature tissues to higher concentrations of oxygen and posing a greater risk of endothelial injury from the toxicity of oxygen free radicals (De Halleux et al., 2002). Stored red blood cells contain both pro- and anti-inflammatory mediators that could play a role in the pathophysiology of certain comorbidities in premature newborns (Collard et al., 2005; Patel et al., 2019), and there is a higher risk of this occurring when larger volumes of transfused blood are received.

Increased oxygen pressure after birth can trigger ROP in very low birth weight (VLBW) infants through two consecutive phases. The first phase, vaso-obliterative, is initiated at birth with supplemental oxygen treatment, which usually occurs at 32 weeks corrected GA. After delivery, the newborn loses growth factors of maternal and placental origin and is exposed to high extrauterine oxygen tension. Hyperoxia suppresses the expression of angiogenic factors that maintain physiological angiogenesis. Phase 2, vaso-proliferative, begins with hypoxia of the retina due to the increasing metabolism of the growing retina, usually from 32 weeks corrected GA. During this phase, there is hypoxia in the avascular retina, which increases vascular growth factor (VEGF) which causes increased vascularization at the edge of the vascularized and avascular retina (Sarlos et al., 2003).

The transfusion of red blood cells may expose premature newborns to a higher risk of developing ROP (Bas et al., 2018), the severity of which is related to the number of transfusions (Valieva et al., 2009), while the need for transfusion is associated with the clinical severity of the newborn.

Platelets are of crucial importance to tissue repair, endothelial maintenance and vascular tone. Among other functions, they accumulate, transport and release various key regulators of angiogenesis, such as vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and platelet-derived growth factor (PDGF) in locations of pathological angiogenesis (Italiano et al., 2008; Klement et al., 2009). Furthermore, Fresh-frozen plasma (FFP) from adult donors may be an actual source of IGF-1 and play a main role in the pathogenesis of ROP (Dani et al., 2014).

We hypothesize that the number of transfusions of blood products, or the early transfusion of such products for VLBW infants, might be associated with the development of ROP (moderate or severe). The objective of this study is to evaluate the impact of blood product transfusions on the development and severity of ROP in this population of infants.

2 | METHODS

A retrospective observational cohort study was conducted of newborns with GA <32 weeks or birth weight <1500 g, born between January 2008 and December 2021. The dependent variable in this analysis is the degree of ROP, and the independent variables are the moment at which a red blood cell transfusion was performed and the numbers of red blood cell, platelet and fresh plasma transfusions performed. The maternal and perinatal variables shown in Table 1 are taken as adjustment variables.

2.1 | Assessment of ROP

Screening programmes for the early detection of ROP began in 1988 after the publication of a multicentre study of cryotherapy for ROP (Cryotherapy for Retinopathy of Prematurity Cooperative Group, 1988). This study defined the presence of one or more of the following as an unfavourable structural outcome: retinal fold involving the macula, retinal detachment affecting zone I in the posterior pole or retrolental tissue or mass. The aim of these programmes was to identify preterm infants who needed treatment for ROP or to facilitate short- and long-term follow-up (Ferrer Novella et al., 2013; Palmer, 1990). It has been suggested that the initial examination should be based on the child's postmenstrual age, since the onset of ROP correlates better with this parameter than with GA. Accordingly, the Ophthalmology Service and the Neonatal Unit at the San Cecilio University Hospital (Granada, Spain) jointly prepared a schedule to begin examining premature infants weighing ≤1500 g at birth or with GA ≤30 weeks. Infants weighing 1500–2000 g or with GA >30 weeks were also screened if they presented an unstable clinical course (including those needing cardiorespiratory support) or who, according to paediatric criteria, were considered at high risk of developing ROP (Chaves-Samaniego et al., 2020). A weekly examination was recommended if any of the following were observed: the presence of immature vascularization in zone I, the absence of vascularization in the retina, the vessels only reaching central zone II or zone I, stage 1 or 2 ROP in zone I, stage 3 ROP in zone II or the suspicion or presence of aggressive posterior ROP. Finally, examinations were performed every 2–3 weeks if stage 1 or 2 or signs of ROP regression were observed in zone III (Lad et al., 2009; International Committee for the Classification of Retinopathy of Prematurity, 2005). We define severe ROP as the existence of stage 3–5 and/or Plus disease in zone I or II.

2.2 | Blood product transfusions

For the present study, the timing and number of blood transfusions performed were obtained from the Granada Provincial Blood Bank database. This information is also documented in the clinical history of each newborn. In all cases, blood product transfusion was performed with prior informed consent. We define 'early red cell transfusion' such as that carried out with adult donor red blood cells in the first 7 postnatal days and 'late red cell transfusion' such as the one carried out after 7 days of postnatal life. In our analysis, the control group was composed of the newborns with no ROP.

According to the transfusion protocol applied by the Neonatal Unit, the transfusion of packed red blood cells during the neonatal period is indicated when Hb values are <10 g/dl, prior to major surgery, on observing

TABLE 1 Pregnancy, neonatal and nutritional characteristics in very low birth weight neonates with and without ROP

Characteristics	No ROP *n* = 375	ROP *n* = 97	*p*
Maternal			
IVF (*n*, %)	65 (17.3)	16 (16.5)	NS
PIH (*n*, %)	46 (12.2)	9 (9.2)	NS
Chorioamnionitis (*n*, %)	53 (14.1)	21 (21.6)	<0.05
Antibiotics (*n*, %)	147 (39.2)	36 (37.1)	NS
Glucocorticoids (*n*, %)	365 (97.3)	90 (92.7)	NS
PPROM (*n*, %)	91 (24.2)	28 (28.8)	NS
Gestation (w)[a]	30 (28, 3)	27 (26, 2)	<0.001
Gestation ≤27 w (*n*, %)	75 (20.0)	61 (62.8)	<0.001
Twin birth (*n*, %)	173 (46.1)	40 (41.23)	NS
Caesarean section	327 (87.2)	81 (83.5)	NS
IUGR	85 (22.6)	20 (20.6)	NS
Neonatal			
Birth weight (g)[a]	1242 (1032, 1455)	932 (758, 1118)	NS
Birth weight (z-score)[a]	−0.51 (−1.15, 0.27)	−0.41 (−1.04, 0.16)	NS
Male gender (*n*, %)	227 (60.5)	53 (54.6)	NS
Apgar<5, 5 min (*n*, %)	45 (12.0)	19 (19.5)	<0.05
CRIB index[a]	2 (1, 5)	4 (1, 8)	<0.01
Milk breastfeeding[b] (*n*, %)	242 (64.5)	46 (47.4)	NS
Probiotics	148 (39.4)	29 (29.9)	NS
Early red blood cell transfusion (*n*, %)	56 (14.9)	12 (12.3)	NS
Late red blood cell transfusión (*n*, %)	121 (32.2)	49 (50.5)	<0.001
Red blood cell transfusion (*n*, %)	184 (49.0)	79 (81.4)	<0.001
Platelet transfusión (*n*, %)	35 (9.3)	27 (27.8)	<0.001
Plasma trnsfusion (*n*, %)	50 (13.3)	22 (22.6)	<0.01
Oxygen[a]	14 (4, 37)	48 (23, 78)	<0.001
Neonatal comorbidities			
BPD	117 (31.2)	72 (74.2)	<0.001
PDA	53 (14.13)	39 (40.2)	<0.001
IVH (Grade I-II)	43 (11.4)	20 (20.6)	<0.01
IVH (Grade III-IV)	25 (6.6)	7 (7.2)	NS
NEC (Grade≥2)	30 (8.0)	19 (19.5)	<0.001
Early sepsis	38 (10.1)	23 (23.7)	<0.001
Late onset sepsis	78 (20.8)	49 (50.5)	<0.001

Abbreviations: BPD, Bbronchopulmonary dysplasia; CRIB, cClinical risk index for babies; IUGR, Iintrauterine growth restriction (decrease in the rate of weight increase that manifests in weight below the 10th percentile for gestational age); IUGR, iIntrauterine growth retardation; IVF, iIn vVitro fFertilization; IVH, iIntraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, pPatent ductus arteriosus; PIH, pPregnancy induced hypertension; PPROM, pPreterm prelabour rupture of membranes; ROP, Retinopathy of prematurity.

[a]Median (IQR).

[b]Supplemented in <25% of the weekly volume with premature formula milk.

moderate cardiopulmonary disease or during the first week of life when clinical disease is observed; when Hb values are <13 g/dl and severe cardiopulmonary disease requires mechanical ventilation and/or supplemental oxygen with $FiO_2 \geq 0.4$; when Hb values are <8 g/dl and there is symptomatic anaemia (apnoea, tachycardia, tachypnoea, poor weight curve, decreased activity); or in the presence of acute bleeding with the loss of ≥25% of blood volume or with persistent clinical symptoms of hypoxia after the correction of blood volume with crystalloids/colloids. The transfusion of packed red blood cells, previously irradiated, is performed at a ratio of 10–15 ml/kg body weight.

Indications for platelet transfusion in newborns include a platelet count <50 000 in the absence of other risk factors for bleeding. The following dosage is applied: 1 platelet concentrate for every 5 kg of body weight (approximately 10 ml/kg).

Fresh-frozen plasma transfusion is considered in newborns whenever there is massive haemorrhage and multifactorial deficit, as is the case in disseminated intravascular coagulation. The dosage used is 10 ml per kg of body weight.

2.3 | Neonatal morbidity

In accordance with the thresholds proposed by the National Institute of Child Health and Human

Development (NIHCD; Doyle et al., 2005) and by Jobe and Bancalari (2001), bronchopulmonary dysplasia (BPD) is defined as a need for supplemental oxygen >21% at 28 days of life and/or a need for supplemental oxygen >21% or for positive airway pressure at 36 weeks' corrected GA, similarly to that reported in previous works (Uberos et al., 2020).

Chorioamnionitis is acute inflammation of the chorion with or without involvement of the amnion and is evidence of a maternal immunological response to infection, with a history of foul-smelling amniotic fluid, fever, increased acute-phase reactants and/or spontaneous onset preterm labour (Hall et al., 2022).

A diagnosis of late-onset sepsis is made when a nosocomial sepsis (NOSEP-1) score >8 is recorded. On this scale, the presence of CRP > 0.014 g/L is assigned five points; that of neutrophils >50%, three points; that of thrombocytopaenia $<150 \times 10^9$/L, five points; and that of fever >38.2°C, five points (Mahieu et al., 2000). Early-onset sepsis is considered when a vertical mother–child transmission mechanism can be demonstrated. (Simonsen et al., 2014).

Persistent ductus arteriosus (PDA) is diagnosed by Doppler ultrasound and treated when clinical repercussions are observed or when the diameter is greater than 2 mm.

The diagnosis of intraventricular haemorrhage (IVH) is based on Papile's classification (Papile et al., 1978). All neonates in this study received a transfontanellar ultrasound examination on the third day of life and every week thereafter.

For the diagnosis of NEC, patients are classified according to Bell's criteria (Caplan & Jilling, 2001). Cases classified as spontaneous intestinal perforations were excluded from this diagnosis.

2.4 | Statistical analysis of the results

The descriptive data are summarized using medians and the interquartile range for the continuous values and the frequency distribution for the categorical variables. The Mann–Whitney *U*-test was used to make univariate comparisons of the continuous variables, and the chi-square test was applied for the categorical ones. Association analysis was performed using multinomial logistic regression. The degree of ROP was considered a dependent variable, since it is a categorical variable, and multinomial analysis was conducted to determine the risk associated with each category. The number of transfusions received and the day on which the first transfusion was performed (early transfusion was defined as that performed during the first 7 days of life) were considered as independent variables. Being transfused for the first time before or after 32 postmenstrual weeks was also considered an independent variable. Oxygen therapy (days) and GA were taken as adjustment variables. All statistical analyses were carried out using the IBM SPSS® 20.0 for Windows package (IBM).

3 | RESULTS

Between January 2008 and December 2021, 565 VLBW newborns with GA <32 weeks or weight at birth <1500 g were treated in our NICU. Of these, 74 died before 36 weeks' corrected GA. In 14 cases, transfusion data were not available, and five infants were not included in the ROP programme (Figure 1). Of the patients who developed ROP, 37 did not receive any red cell transfusion. Forty-nine newborns received their first transfusion with a corrected GA <32 weeks, and 11 newborns

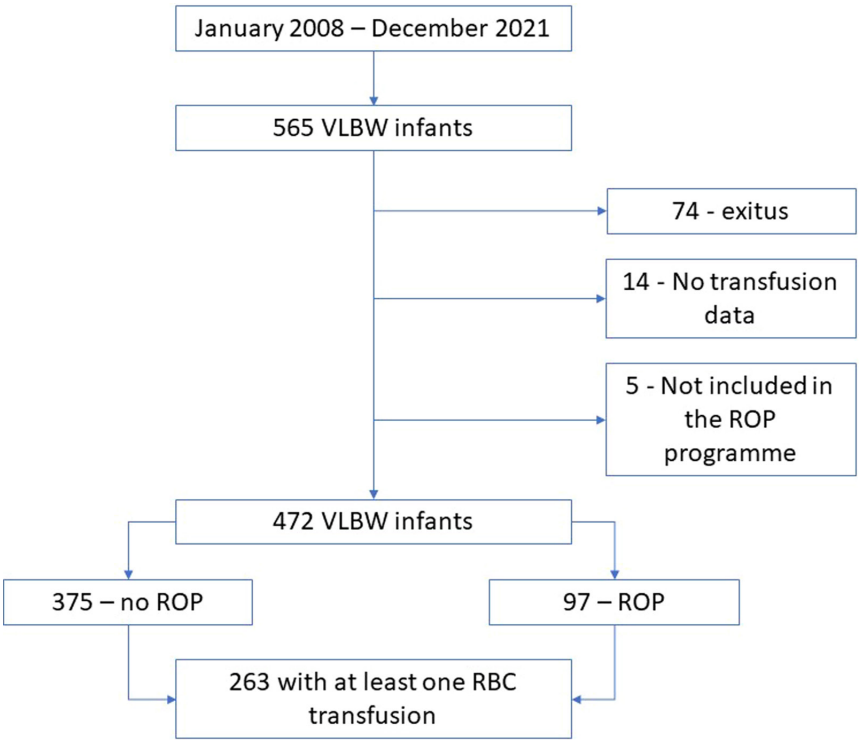

FIGURE 1 Patient flow chart.

received their first red cell transfusion with ≥32 weeks corrected GA. Thirty newborns developed ROP grade 1 and 17 developed ROP grade 2. Fifty newborns developed severe ROP requiring laser treatment. Although only 14.4% received a red blood cell transfusion during the early neonatal period, 55.7% of the study cohort received a red blood cell transfusion before 36 weeks' corrected GA. Moreover, 83.3% of those under 27 weeks' GA received a red blood cell transfusion before 36 weeks' corrected GA. Having received the first red blood cell transfusion before 32 weeks of corrected GA is associated with an increased risk of ROP (OR 2.18; 95% CI 1.09–4.36), while we did not observe a significant association between early red blood cell transfusion and ROP (Table 2). Severe ROP was not significantly associated with early transfusion or receiving the first transfusion before 32 weeks of corrected GA (Table 3).

Overall, 263 of the newborns in our study cohort received a red blood cell transfusion prior to 36 weeks' corrected GA (Figure 1). 26.4% of all red blood cell transfusions were performed between 24 and 26 weeks' corrected GA (Figure 2). This age group accounted for 33.6% of all the cases of ROP detected and had a threefold greater need of oxygen therapy. Table 1 shows the maternal and neonatal characteristics of our study cohort, revealing significant differences with respect to GA at birth and clinical history of chorioamnionitis. As expected, ROP was more prevalent at earlier gestational ages. Regarding the distribution of cases with IUGR, the study cohort presented no significant differences between newborns with or without ROP. The duration of oxygen therapy differed significantly between these groups.

The raw data analysis revealed higher prevalences of red blood cell, platelet and plasma transfusions, together with a greater frequency of other neonatal comorbidities among the patients who developed ROP (Table 1).

TABLE 2 Logistic regression model for ROP risk

	OR (CI 95%) Unadjusted	OR (CI 95%) Adjusted
Early red cell transfusion	3.37 (2.03–5.60)¶¶¶	1.25 (0.68–2.30)
Late red cell transfusion	17.7 (6.82–46.1)¶¶¶	2.05 (0.51–8.21)
Red cell transfusion		
1–2 transfusions	1.66 (0.91–3.02)	0.85 (0.43–1.67)
More than 3	10.8 (6.11–19.1)¶¶¶	2.77 (1.31–5.88)¶¶
First red cell transfusion		
<32 weeks PMA	1.97 (1.19–3.24)¶¶¶	2.18 (1.09–4.36)¶
≥32 weeks PMA	0.90 (0.43–1.92)	1.37 (0.62–3.02)
Platelet transfusion	4.71 (2.64–8.38)¶¶¶	1.86 (0.87–3.98)
Plasma transfusion	2.35 (1.33–4.17)¶¶	0.86 (0.40–1.84)
Chorioamnionitis	1.80 (1.03–3.15)¶	0.83 (0.40–1.73)
Apgar < 5, 5 min	2.00 (1.11–3.63)¶	0.91 (0.41–2.01)
BPD	6.03 (3.66–9.94)¶¶¶	1.18 (0.57–2.44)
PDA	4.33 (2.64–7.08)¶¶¶	1.15 (0.61–2.18)
IVH (Grade I-II)	2.16 (1.20–3.90)¶	0.81 (0.37–1.76)
IVH (Grade III-IV)	1.30 (0.54–3.139	1.08 (0.34–3.39)
NEC (Grade ≥ 2)	3.54 (1.93–6.90)¶¶¶	1.56 (0.70–3.48)
Early sepsis	2.98 (1.68–5.28)¶¶¶	1.66 (0.80–3.44)
Late onset sepsis	4.10 (2.59–6.49)¶¶¶	1.95 (1.13–3.38)¶

Note: Adjusted for gestational age (weeks) and oxygen therapy (days).
Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity.
¶$p<0.05$; ¶¶$p<0.01$; ¶¶¶$p<0.001$.

TABLE 3 Logistic regression model for severe ROP risk

	OR (CI 95%) Unadjusted	OR (CI 95%) Adjusted
Early red cell transfusion	6.86 (2.91–16.1)¶¶¶	1.60 (0.58–4.37)
Late red cell transfusion	4.56 (1.53–13.5)¶¶¶	1.07 (0.27–4.19)
Red cell transfusion		
1–2 transfusions	2.64 (1.00–6.97)¶	1.37 (0.48–3.87)
More than 3	16.9 (7.17–39.8)¶¶¶	3.95 (1.40–11.1)¶¶
First red cell transfusion		
<32 weeks PMA	4.08 (2.17–7.66)¶¶¶	1.39 (0.60–3.19)
≥32 weeks PMA	0.72 (0.23–2.21)	1.22 (0.37–4.04)
Platelet transfusion	6.60 (3.26–13.3)¶¶¶	2.43 (0.98–6.04)
Plasma transfusion	2.02 (0.94–4.37)	0.77 (0.29–2.01)
Chorioamnionitis	2.70 (1.38–5.31)¶¶	1.10 (0.48–2.54)
Apgar <5, 5 min	2.71 (1.32–5-57)¶¶	1.10 (0.75–2.73)
BPD	8.37 (3.96–17.7)¶¶¶	1.36 (0.51–3.61)
PDA	4.83 (2.63–8.87)¶¶¶	1.20 (0.56–2.85)
IVH (Grade I-II)	3.14 (1.54–6.38)¶¶	1.35 (0.56–3.28)
IVH (Grade III-IV)	2.24 (0.80–6.21)	2.22 (0.63–7.76)
NEC (Grade ≥ 2)	4.13 (1.90–8.99)¶¶¶	1.75 (0.68–4.49)
Early sepsis	2.81 (1.37–5.75)¶¶	1.29 (0.55–2.98)
Late onset sepsis	3.34 (1.84–6.06)¶¶¶	1.45 (0.72–2.91)

Note: Adjusted for gestational age (weeks) and oxygen therapy (days).
Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PMA, postmenstrual age; ROP, retinopathy of prematurity.
¶$p<0.05$; ¶¶$p<0.01$; ¶¶¶$p<0.001$.

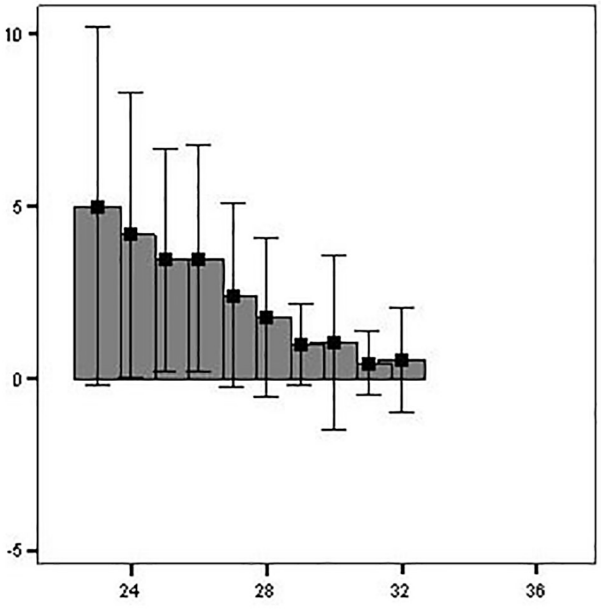

FIGURE 2 Histogram displaying the mean (95% CI) number of transfusions given at each gestational age. Note that most transfusions occurred before 28 weeks of gestational age.

However, the association analysis did not allow us to observe significant associations between ROP or severe ROP and the history of having received platelet transfusions or FFP.

Table 2 shows that having had late-onset sepsis is associated with an increased risk of ROP (OR 1.95; 95% CI 1.13–3.38). However, late-onset sepsis is not significantly associated with severe ROP (Table 3). History of having received more than 3 red blood cell transfusions (OR 2.77; 95% CI 1.31–5.88) was a risk factor for ROP. After adjustment, severe ROP was also found to be associated with a history of having received three or more red blood cell transfusions (OR 3.95; 95% CI 1.40–11.1). In this cohort, all cases of severe ROP were treated with laser.

4 | DISCUSSION

According to the study data obtained, both the number of red blood cell transfusions and having received the first transfusion before 32 weeks corrected gestational age are important factors in determining the risk of ROP in VLBW preterm infants. Having suffered late-onset sepsis is another relevant factor for the risk of ROP.

Red blood cell transfusion during the early neonatal period has been associated with the development of severe Lust et al. (2019) related the use of transfusions during the first 10 days of life with the development of severe ROP. Similarly, Schecter et al. (2021) 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. Our own data show that the number of transfusions received is more significantly related to the risk of ROP and severe ROP than to that of early red blood cell transfusion. However, we observed that the administration of the first red blood cell transfusion during the vaso-obliterative phase of ROP (<32 weeks of corrected GA) is significantly associated with an increased risk of ROP. We did not observe a significant association with the risk of ROP when the first transfusion is performed in the early neonatal period. Bas et al. (2018) reported that transfusions of packed red blood cells were closely related to the development of ROP. In the retina of the premature newborn, vessel growth that would occur in utero slows or ceases after birth and exposure to the relatively hyperoxic environment. As the newborn matures and retinal metabolism increases, local tissue hypoxia causes abnormal vessel growth and the development of retinopathy (Recchia & Capone Jr., 2004). Transfusions of adult red blood cells in the premature newborn increase the concentration of HbA, shifting the oxygen dissociation curve to the right and increasing oxygen delivery to the retinal tissue at a time when it is susceptible to hyperoxia. Moreover, repeated transfusions can lead to an accumulation of free iron, and hydroxyl radicals, which, as revealed by the Fenton reaction, can produce retinal damage (Wardle et al., 2002). Studies have also shown that blood transfusions in very premature newborns may drastically modify HbF levels (De Halleux et al., 2002; Stutchfield et al., 2017).

Bas et al. (2018) suggest 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 (Venancio et al., 2007; Widness et al., 2005).

Platelet alpha granules include IGF-1, IGF-binding protein 3 (the major serum binding protein for IGF-1), VEGF and PDGF. IGF-1 and VEGF levels are critically associated with the development of ROP (Yenice et al., 2013). IGF-1 is necessary for VEGF-induced vessel growth, while low platelet count at an early GA slows vasculogenesis and leads to the development of ROP. In our cohort, the indication for transfusion was always made after confirming platelet values <50 000/μl. In this respect, Sahinoglu Keskek et al. (2020) noted that a low platelet count in the first week of life is an independent risk factor for ROP.

Dani et al. (2014) observed that two or more FFP transfusions in the first week of life reduce the risk of developing any degree of ROP in premature infants with a GA of less than 29 weeks (Dani et al., 2014). We did not observe a significant association between ROP and FFP transfusion, although it is true that the newborns in whom it was indicated were critically ill newborns with consumptive coagulopathy.

Some authors have related neonatal sepsis with the development of ROP possibly acting through the release of cytokines and endotoxins that would directly affect retinal angiogenesis. Neonatal sepsis can increase the duration of NICU care and of oxygen therapy required. Indeed, analysis of our data reveals an association with ROP in our study cohort.

This study presents certain limitations, the most important of which is its retrospective nature. In addition, it is conceivable that the newborns whose condition is most serious are also most likely to require a transfusion. If this were so, the transfusions themselves would be mere confounding factors of another, unevaluated, condition. To address this possibility, we took into account the perinatal factors that are most frequently related to neonatal morbidity. We then considered the existence of an association between ROP and these factors, after adjusting for the variables known to influence the development of ROP, that is GA and oxygen therapy (Chaves-Samaniego et al., 2020; Ng et al., 2020).

5 | CONCLUSIONS

According to our findings, a history of having received more than three red blood cell transfusions or having been transfused before 32 weeks corrected gestational age is associated with an increase in the risk of developing severe ROP, although not with the risk of severe ROP.

AUTHOR CONTRIBUTIONS

J U designed the analysis and data interpretation procedures, co-wrote the article and critically reviewed it for important intellectual content. He approves the present version for publication. He accepts responsibility for all aspects of the work, including the proper investigation

and resolution of questions related to its accuracy and completeness. J L G-S performed the ophthalmological examinations. J L G-S, A C-M, A R-L and E F-M made substantial contributions to the conception and design of the study, co-wrote the article and critically reviewed it for important intellectual content. They approve the present version for publication. They accept responsibility for all aspects of the work, including the proper investigation and resolution of questions related to its accuracy and completeness.

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ETHICAL APPROVAL

The study protocol was approved by the Ethics Committee of the hospital, and all current regulations regarding data confidentiality were respected.

INFORMED CONSENT

The consent of the parents or guardian of the patients was required. Informed consent was requested from all legal guardians.

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