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Platelet transfusion as a risk factor for development retinopathy of prematurity

Prematüre retinopatisi gelişimi için bir risk faktörü olarak trombosit transfüzyonu

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ABSTRACT

Aim: The aim of this study was to determine the potential association between platelet transfusions and the development of retinopathy of prematurity.

Materials and Methods: This was a retrospective, cross-sectional, case-control study. Premature infants with gestational age <32 weeks were divided into two groups: those who developed severe retinopathy of prematurity (ROP) (Stage >2) and those who did not. Demographic data, short- and medium-term morbidities, presence of transfusion and number of transfusions were recorded from the hospital data system and patient files. Conditional logistic regression analysis was performed to adjust for matching.

Results: A total of 130 premature infants were included in the study between January 2017 and January 2021. Severe ROP was detected in 80 (61.5%) of the patients. Birth weights in the groups with and without severe ROP were 1201±256 g and 1035±341 g (p=0.03), and gestational ages were 28.6±2 weeks and 27.5±2 weeks (p=0.06), respectively. Twenty-one patients received platelet transfusion. The number of platelet transfusions was higher in the severe ROP group (p<0.01). There was a significant correlation between the number of platelet transfusions and the need for ROP treatment (-0.21, p=0.016).

Conclusion: There was a significant correlation between the number of platelet transfusions and the development of retinopathy requiring treatment. Further prospective randomised controlled trials are needed to establish a link between platelet transfusions and the development of severe retinopathy of prematurity.

Keywords: Platelet transfusion, prematurity, retinopathy

ÖZ

Amaç: Bu çalışmanın amacı trombosit transfüzyonları ile prematüre retinopati gelişimi arasındaki potansiyel ilişkiyi belirlemektir.

Gereç ve Yöntemler: Bu retrospektif, kesitsel, vaka-kontrol çalışmasıdır. Gebelik yaşı <32 hafta olan prematüre bebekler, ciddi prematüre retinopatisi (ROP) gelişen (Evre >2) ve gelişmeyenler olarak iki gruba ayrılmıştır. Demografik veriler, kısa ve orta vadeli morbiditeler, transfüzyon varlığı ve transfüzyon sayıları hastane veri sisteminden ve hasta dosyalarından kaydedildi. Eşleştirmeyi ayarlamak için koşullu lojistik regresyon analizi yapıldı.

Bulgular: Ocak 2017 ve Ocak 2021 tarihleri arasında toplam 130 prematüre bebek çalışmaya dahil edildi. Hastaların 80'inde (%61,5) ciddi ROP saptandı. Ciddi ROP olan ve olmayan gruplarda doğum ağırlıkları sırasıyla 1201±256 g ve 1035±341 g (p=0.03), gebelik yaşları 28.6±2 hafta ve 27.5±2 hafta (p=0.06) idi. Yirmi bir hastaya trombosit transfüzyonu yapıldı. Trombosit transfüzyonu sayısı ciddi ROP grubunda daha fazlaydı (p<0.01). Trombosit transfüzyonu sayısı ile ROP tedavi ihtiyacı arasında anlamlı bir korelasyon vardı (-0.21, p=0.016).

Sonuç: Trombosit transfüzyonu sayısı ile tedavi gerektiren retinopati gelişimi arasında anlamlı bir ilişki bulunmuştur. Ciddi prematüre retinopatisi gelişimi ile trombosit transfüzyonları arasında bir bağlantı kurmak için daha fazla prospektif randomize kontrollü çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Trombosit transfüzyonu, prematürite, retinopati

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INTRODUCTION

Retinopathy of prematurity (ROP) is the leading cause of ocular morbidity in premature infants and is also the most common preventable cause of visual impairment in childhood (2). The prevalence of ROP varies worldwide, with approximately 60% observed in extremely low birth weight infants (1). However, studies have reported higher ROP rates in both extremely low birth weight infants and infants weighing over 1500 grams and born at 28 weeks or more, particularly in underdeveloped and developing countries (2).

Retinopathy is closely associated with low birth weight, gestational age, and hyperoxia (3). Premature infants often require blood product transfusions during their stay in the neonatal intensive care unit. Blood transfusions can have adverse effects on infants. While allergic and hematological side effects are frequently discussed, recent years have seen an understanding that blood product transfusions increase the release of vascular endothelial growth factor (VEGF), other cytokines, and inflammatory modulators, possibly leading to an inflamed state. Considering the pathophysiology of retinopathy, this inflammatory process, particularly the potential of increased VEGF release in the developing retina, may trigger the development of new blood vessels and consequently contribute to the development of ROP (1,2). There is evidence in the literature suggesting that erythrocyte transfusions can increase the risk of ROP, as transfusion of adult erythrocytes to premature infants leads to decreased fetal hemoglobin levels. Elevated oxygen affinity of adult hemoglobin in the retina can increase hyperoxic conditions, potentially triggering the development of severe ROP (2,5). Platelet transfusions in premature infants are also controversial due to their pro-inflammatory and anti-angiogenic properties (4).

While ROP remains a significant concern, identifying associated factors and improving outcomes are crucial. The objective of this study is to investigate the relationship between platelet transfusion and the development of ROP.

MATERIALS AND METHODS

This retrospective study included 130 premature infants with a gestational age of less than 32 weeks who were born in the third-level neonatal intensive care unit (NICU) between January 2017 and January 2021. Ethical approval of the study was obtained from the local ethics committee (26.05.2023/419). All premature babies born in our centre with a gestational age less than 32 weeks and followed up for retinopathy of prematurity were included in the study. Infants with major congenital anomalies, asphyxia, intrauterine infections, missing data in hospital records and those who were lost before their first retinopathy examination were excluded. Patients were divided into two groups as severe ROP and ROP not requiring treatment according to the 'Turkey Retinopathy of Prematurity Guideline 2021 update' of Turkish Neonatology Society and Turkish Ophthalmological Society. Severe ROP was defined as Type 1 ROP ('plus' disease at any stage in Zone I, stage 3 ROP in Zone I, stage 2 or stage 3 ROP and 'plus' disease in Zone II) and Aggressive-ROP was defined as severe ROP requiring treatment (6). Both groups were compared in terms of demographic data. The incidence of respiratory distress syndrome (RDS), haemodynamically significant patent ductus arteriosus (hsPDA), stage 2-3 according to modified Bell staging necrotizing enterocolitis (NEC), Stage 3 intraventricular haemorrhage (IVH)/periventricular haemorrhagic infact according to Volpe staging and severe bronchopulmonary dysplasia (BPD) was evaluated. In our clinic, platelet transfusions are performed according to the threshold values recommended by the Turkish Neonatology Society: Platelet count <25.000/μL; all infants, neonatal alloimmune thrombocytopenia, 25.000/-49.000/μL; birth weight <1000 grams, coagulopathy, severe morbidity, invasive intervention, minor bleeding, 50.000-100.000/μL; active or major bleeding, disseminated intravascular coagulopathy, perioperative, >100.000/μL; major surgery (7). Erythrocyte trasfusions are also performed in accordance with the recommendations of the same guideline Erythrocyte transfusion was performed on premature infants based on their post-conceptional age and respiratory support status, targeting hemoglobin values according to age or providing 15-20 ml/kg of erythrocyte suspension in cases of tachycardia, increased oxygen support, or poor weight gain. (7). The numbers of erythrocyte and platelet transfusions were recorded retrospectively from hospital records. Erythrocyte and platelet transfusions were performed according to the transfusion recommendations of the guidelines and administered to infants at a dose of 10-15 ml/kg (7).

Statistical Analysis

Statistical analyses were conducted using the SPSS statistical software for Windows, V.21.0 (SPSS, Chicago, Illinois, USA). The Shapiro–Wilk test was used to test for the normality of data. Chi-square or Fisher's exact test was used for comparison of categorical variables as appropriate. Differences between the groups concerning continuous variables were compared by Student's t test and Wilcoxon test where appropriate. A p value of <0.05 was considered statistically significant. Conditional logistic regression analysis was conducted to determine the relationship between transfusions and severe ROP development and to assess all potential risk factors.

RESULTS

A total of 130 premature infants were included in the study between 1 May 2023 and 1 June 2023. Eighty (61.5%) infants were followed up with the diagnosis of severe ROP and 50 (38.5%) infants were followed up with the diagnosis of ROP not requiring treatment. Birth weights were 1035±341 and 1201±256 g (p=0.03) and gestational ages were 27.5±2 and 28.6±2 weeks (p=0.06) in the severe ROP and treatment-naive ROP groups, respectively. There was a significant difference in terms of mechanical ventilation and length of hospital stay between the severe ROP and treatment-free ROP groups (p<0.05). The incidence of respiratory distress syndrome, patent ductus arteriosus, intracranial haemorrhage, necrotising enterocolitis and other short-term morbidities were similar in both groups (p>0.05). Total oxygen duration was significantly associated with the development of severe ROP group (p<0.05). No significant difference was observed between the two groups in terms of early and late neonatal sepsis (p=0.41) (Table 1). Red cell transfusion was performed in 76 patients. Red cell transfusion was performed in 54% of patients with severe ROP and 22% of patients with ROP not requiring treatment, and this rate was higher in patients with severe ROP (Table 2). A total of 21 patients received platelet transfusions. The number of platelet transfusions was higher in the severe ROP group (p<0.01). There was a positive correlation between the number of platelet transfusions and the need for ROP treatment. The transfusion volume in the severe ROP group was 28±8 mg/kg, which was higher than the ROP group that did not require treatment (p=0.042) (Table 2). Linear regression analysis of some parameters associated with the development of ROP showed that platelet transfusion was associated with the development of severe ROP (Table 3).

Table 1. Clinical findings and releated complications of the patients

	Low stage ROP (N=50)	Severe ROP (N=80)	p
Gestational age,week*	28,6±2	27.5±2	**0.06**
Birthweight, g*	1201±256	1035±341	**0.03**
Male/female, n	25/26	42/38	0,49
Sepsis, n (%)	23 (46)	42 (52)	0,41
Severe IVH, n (%)	6 (12)	14 (17.5)	0,26
NEC, n (%)	1 (2)	8 (16)	0,076
RDS, n (%)	41 (82)	73 (91)	0,064
Severe BPD, n (%)	11 (22)	30 (37.5)	**0,041**
hsPDA, n (%)	33 (66)	44 (55)	0,179
Surfactant, n (%)	37 (74)	61 (76.3)	0,39
Phototherapy, n (%)	43 (85)	35 (43.8)	0,36
Apgar, 5. minute**	7 (1-10)	6 (2-9)	**<0,01**
Duration of hospitalisation (day)*	46±23	75±44	**<0,01**
Duration of invasive mechanic ventilation (day)**	13±2,8	38±4,7	**<0,01**
Duration of total oxygen therapy (day)*	30 ±3,6	62 ±5,1	**0,04**

* Mean±Standart deviation **Median (minimum-maximum)

Table 2. Comparison of transfusions in severe ROP and ROP not requiring treatment groups

	Low stage ROP (N:50)	Severe ROP (N:80)	P value
Platelet transfusion, n (%)	2 (4)	21 (26)	**<0,01**
Red blood cell transfusion, n (%)	22 (44)	54 (67.5)	**<0,005**
Platelet transfusion volume, mL/kg *	15±5	28±8	**0.042**

*Mean±Standart deviation

Table 3. Logistic regression analysis of the variables

	B	S.E.	Sig.	Exp(B)
Platelet transfusion	-1,781	,855	,034	,169
Red blood cell transfusion	-,615	,606	,310	,541
Birthweight, g	-,568	,001	,050	1,000
Gestational age,week	-,500	,109	,017	,931

DISCUSSION

Partial oxygen pressures are higher in the postnatal period compared to the intrauterine period. Hyperoxia suppresses VEGF, thus retinal vascularisation is delayed. The metabolically active retina gradually becomes more and more hypoxic and abnormal

vascularisation is caused by an increase in VEGF and other pro-angiogenic factors. the most known risk factors are low birth weight and gestational age (8). Hyperoxia (8) and sepsis (9) are also reported to be serious risk factors. Studies have shown that erythrocyte and platelet transfusions have some side effects, such as the release of proinflammatory and immunomodulatory mediators such as VEGF (10).

In this study, we found a significant relationship between platelet transfusion and the development of ROP.

Infants requiring transfusion are not only premature but also critically ill. These patients are at higher risk of neonatal complications due to maternal diseases, prolonged mechanical ventilation due to respiratory distress, and delayed initiation of breastfeeding, all of which can increase the incidence of sepsis. While the presence of sepsis, a known risk factor for ROP, was similar in our patient groups, especially late neonatal sepsis is one of the common causes of neonatal thrombocytopenia in hospitalized premature infants (11). Thrombocytopenia itself increases mortality and morbidity in these patients. The relationship between thrombocytopenia and retinopathy is another area of investigation. Some studies have shown an association between thrombocytopenia and the development of ROP (12-15).

Blood product transfusions come with certain side effects. Considering the pathophysiology of retinopathy, it is known that platelets induce pro-inflammatory and anti-angiogenic reactions (4). Platelet transfusion releases cytokines, VEGF, and other immunomodulatory mediators, supporting inflammatory and proliferative processes (2,12,16). Consistent with the literature, our study also found an increased incidence of severe retinopathy in infants who received platelet transfusions. Therefore, careful consideration should be given to pre-transfusion decisions, particularly in premature infants with inadequate anti-inflammatory and antioxidant responses. Adherence to recommended indications for platelet transfusion in guidelines is essential. Hengartner et al (17) reported that patients who received 1 or more platelet transfusions had a higher risk of developing ROP (39% vs. 18%, $p < 0.001$, $r = 0.23$), but there was no difference between the groups in terms of the number of transfusions per infant, transfusion volumes and timing of transfusions. However, in our study, high platelet volume was also associated with the development of severe ROP, probably because the number of platelet transfusions was low in the untreated ROP group.

The relationship between erythrocyte transfusions and the development of ROP can be better understood when compared to platelet transfusions. The presence of adult hemoglobin leads to hyperoxic conditions in the retina, negatively impacting retinal neovascularization and thus increasing the risk of ROP (14). In our study, a significant association was found between the number of erythrocyte transfusions and the development of severe retinopathy. However, since anaemia frequently develops in premature infants, erythrocyte transfusions were frequently performed in both groups and no association was found with the development of severe ROP in logistic regression analysis.

Although the study includes patients from a single center, ensuring standardized transfusion quantities, there are limitations. It is important to note that our study is observational, so we can not definitively establish a causal relationship between platelet transfusion and ROP. More randomized controlled trials, are needed to confirm these findings. Other limitation is days of initial transfusion were not recorded. The postnatal days requiring platelet transfusion in relation to the stages of retinopathy could also influence the severity of retinopathy.

In conclusion, we identified a significant relationship between platelet transfusion and the development of severe retinopathy. However, more randomized controlled trials are necessary to definitively establish platelet transfusion as a risk factor in the etiology of premature retinopathy.

Disclosure statement:
The authors report there are no competing interests to declare.

İnformed consent:
Verbal consent was obteined from the families of patients included in the study.

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We declare that we have no conflicts of interest

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