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Can mean platelet volume have predictive value in premature retinopathy?

Prematüre retinopatisinde mean platelet volüm'un prediktif değeri olabilir mi?

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Abstract

Aim: Retinopathy of prematurity, a proliferative vitreoretinopathy resulting from the vascular disorder of the retina, is the most frequent cause of blindness in childhood. In the pathogenesis of the disease, in particular, there are stages developing diametrically opposite to each other (the first phase vasoobliteration, the second phase neovascularization) helped our thoughts of the disease to form. Premature retinopathy is quite an important problem in newborn units not only as far as its consequences but also its follow-up and management. Our controlled clinical study aims to present a simple method that will facilitate the follow-up of the disease while guiding clinicians in predicting the prognosis of the disease.

Material and Methods: In our case-controlled study we have assessed 64 preterm cases at the risk of premature retinopathy, considering both the 46 preterm cases having been realized at the follow-up to need laser photocoagulation, and the first and second stage of the disease, in terms of thrombocytes, which play an important part in the transport and storage of vascular endothelial growth factor.

Results: No statistically significant difference was found between the control and laser groups in terms of the thrombocyte count and mean platelet volume values during the first stage of the disease ($p>0.05$). During the second stage of the disease, while no difference was detected between the control and laser groups in terms of the thrombocytes count, ($p=0.98$, $p>0.05$), Significant differences were found in mean platelet volume values ($p=0.001$, $p<0.05$).

Conclusion: In our study we have obtained data to facilitate clinicians' treatment and follow-up of the cases at the risk of mean platelet volume values reflecting the elevated vascular endothelial growth factor levels in the stage of neovascularization, which constitutes the basis of our study.

Keywords: Premature Retinopathy; Platelet; Mean Platelet Volume.

Öz

Amaç: Prematüre retinopatisi retinanın damarsal bozukluğu sonucu oluşan proliferatif vitreoretinopati olup çocuklardaki körlüklerin sık nedenlerindendir. Özellikle hastalık patogenezinde, birbirinin zıttı olarak gerçekleşen fazların (birinci faz-vasoobliteration, ikinci faz-neovascularization) olduğunun bulunması prematüre retinopatisi hakkındaki düşüncelerin şekillenmesine yardımcı olmuştur. Prematüre retinopatisi yenidoğan ünitelerinde sonuçları açısından olduğu kadar takibi ve tedavisi açısından da oldukça önemli bir problemdir. Biz kontrollü klinik çalışmamızda, hem hastalığın takibinde kolaylık sağlayacak hem de hastalığın prognozunun tahmin edilmesinde klinisyenlere yol gösterecek basit bir yöntemi gündeme getirmek istedik.

Gereç ve Yöntemler: Biz vaka kontrollü çalışmamızda, ROP riski altındaki 64 preterm olguyu, takipleri sonucu lazer fotokoagülasyon ihtiyacı duyulmuş 46 preterm olgu ile hastalığın birinci ve ikinci fazlarını göz önünde bulundurarak, bu fazlarda önemli rol oynayan vasküler endotelyal growth faktörün taşınması ve depolanmasında rol oynayan trombositler açısından değerlendirdik.

Bulgular: Hastalığın birinci fazında, trombosit sayıları ve ortalama trombosit hacmi değerleri açısından kontrol ve lazer grupları arasında istatistiksel bir fark bulunmadı ($p>0.05$). Hastalığın İkinci fazında da kontrol ve lazer grupları arasında trombosit sayıları açısından istatsitiksel bir fark bulunmazken ($p=0.98$, $p>0.05$), aynı fazdaki ortalama trombosit hacmi değerleri açısından ise anlamlı fark bulundu ($p=0.001$, $p<0.05$).

Sonuç: Çalışmamızda, hastalığın temelini oluşturan neovaskülarizasyon fazında (faz-2), artmış vasküler endotelyal büyüme faktör düzeylerini yansıtan ortalama trombosit volüm değerleri açısından risk altındaki olguların tedavi ve takibinde hekimlere kolaylık sağlayabilecek veriler elde edildi.

Anahtar Kelimeler: Prematüre Retinopatisi; Trombosit; Ortalama Trombosit Hacmi.

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INTRODUCTION

Premature retinopathy (ROP) is a disease of retinal vascular development, and one of the leading causes of blindness in pediatric period worldwide (1). The commonly held view in our time as to its pathogenesis is that it consists of vaso-obliteration, resulting from the reduction in blood level in response to hyperoxy in the first phase, caused by mediators acting on vascular development such as vascular endothelial growth factor (VEGF) and insulinlike growth factor-1 (IGF-1), and of vascular proliferative phase characterized by the elevated level of such mediators as VEGF, IGF-1 in the second phase in reaction to the first phase (2-4).

Thrombocytes store, transport, and release various factors -including VEGF, crucial to ROP pathogenesis- which regulate angiogenesis. Accordingly, their importance in the pathogenesis of the disease has been the research topic of some studies (3-7).

In 2010, Vinekar et al., (6) found considerable differences in the platelet counts of 21 control cases and 10 cases of aggressive-posterior ROP (AP-ROP) to prognosticate laser therapy, and propounded the existence of a possible relationship between AP-ROP and thrombocytopenia. Jensen et al., (7) also found a direct relationship between laser therapy and thrombocytopenia in their study in 2011. However, these studies had been done without considering the biphasic theory, which was first introduced by Aston and Simith (8,9), and is of critical importance to understanding the pathophysiology of ROP. We have realized our study in view of biphasic theory on thrombocytes, responsible for the transport and release of VEGF, which, in turn, is important in ROP development (3,10-15). We have researched into the differences that might arise during the first and second phase of ROP in thorombocyte counts and in mean platelet volume (MPV) in cases subjected to laser therapy and those unsubjected to it.

Our hypothesis is that thrombocytes may be more active in the second phase of ROP than in the first, and therefore, increase neovascularization in the second phase. Detection of such a difference between the phases in thrombocytes, which reflects VEGF levels, will offer advantages, such as cautious follow-up and more precise timing of laser therapy in infants at risk of ROP.

MATERIALS and METHODS

We included in our study 64 preterm cases at risk of ROP monitored in our hospital between August 2012 and May 2014. In our region, birth weights below 2000 gm and births at a gestational age below 34 weeks qualify as newborns at risk of ROP, and such cases were included in our control group. As for the photocoagulation group, it consisted of 46 cases exposed to laser therapy according to Early Treatment of ROP (ET-ROP) criteria.

The thrombocyte counts at post-natal day 7 of the cases in the control and laser coagulation groups were recorded in their study lists. The thrombocyte levels at this week were considered to reflect the first phase of ROP.

In the control group, phase-2 was determined according to post-menstrual age. No thrombocyte counts taken earlier than post-menstrual week 31 were recorded for this ROP period. In cases with gestational week below 27, in those born at gestational week 27-29, and in those born at gestational week 30 or later, thrombocyte counts were taken at post-menstrual week 32, 33, and 34, respectively, at the earliest, and recorded in their study lists as the thrombocyte values reflecting the second phase of the control group.

In laser coagulation group, the thrombocyte counts taken in the week prior to laser therapy were recorded in their study lists, and this data were considered to be thrombocyte values reflecting the second phase of ROP in the laser group. The cases without thrombolytic records for the period in question were excluded from the study. Siemens Advia 2120 was used for determining thrombocyte counts, and MPV values were calculated as (fl).

One hour before the infants were examined, their pupillae were dilated with tripocamide of 1% and phenilephrine of administered twice, in 3 drops each time, at an interval of 15 minutes. Topical anesthesia was instituted with proparacain of 0.5% before examination. After attaching cover speculum, first the front segment and then the fundus were examined with binocular indirect ophthalmoscope and lenses of 20 and 28 diopters. The patients were assessed simultaneously by two opthalmologists and it was decided to treat and monitor them. Vital changes observed during the examination were also recorded and monitored.

Use was made of international scoring system for scoring bronchopulmonary dysplasia (BPD). BPD records were obtained even when the patients' BPD was slight. The cases with necrotizing enterocolitis (NEC) and those with sepsis were recorded and included in the same category. The cases who had received surfactant within the first 24 post-natal hour were assumed to have respiratory distress syndrome (RDS) and recorded as such. The gestational ages, birth weights, sexes, and the duration of mechanical ventilation in minute of the cases were recorded.

The retina was divided into 3 zones for an objective follow-up of ROP to be achieved .Zone 1 is the circle with a radius twice as long as the distance from the optic disc to the central macula, and with the optic disc in its center. Zone 2 is the circle with a radius from the optic disc to the nasal ora serrata and with an optic disc in its center. Zone 3 is the one shaped like half moon seen outside the zone 2 in the retina. Pre-Threshold disease was defined as plus disease, or ROP in stage-3 in zone 1, as plus disease accompanied by ROP in stage-2/3. The cases with prethreshold ROP detected at follow-up underwent laser photocoagulation therapy. Premature retinopathy was scored with international scoring system.

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The program used for statistical analyses was SPSS 21.0 (SPSS Inc. Chicago, Illionis). Data distribution was studied with Shapiro-Wilk Normality test. Normal and abnormal distributions between the groups were compared by means of independent sample t and Mann-Whitney U test, respectively. For the analyses of rational data, chi-square test was used. P=0.05 was taken as the point of statistical significance. Any P value below 0.5 was considered significant.

RESULTS

The study group and laser coagulation group consisted of 64 and 46 cases, respectively. The diseases that may affect ROP, interventions, and the demographic distributions of the cases according to the study groups have been presented in table 1. The most important factors to affect ROP are gestational age and birth weight. Accordingly, the differences in the data obtained from the relevant cases were studied in terms of gestational age and birth weight. There was no statistically significant difference of gestational age between the control group (28.2±1.29) and laser photocoagulation group (27.1±1.37) (p=0.07, p>0,05). In terms of birth weight, there was not any statistically significant difference between the control group (995.0±222.0) and the laser photocoagulation group (980.0±276.5) (p=0.09, p>0,05). The study groups did not differ significantly in sex, either (p=1.0, P>0,05) (Table-1).

Table1. The distribution of the diseases that may affect ROP, and of the interventions.

	Study Groups		p value
	Control Group (n:64) (med±SD)	Laser Photocoagulation Group (n:46) (med±SD)	
Gestational age (week)	28.2±1.29	27.1±1.37	0.07
Gestational weight (gr)	995.0±222.0	980.0±276.5	0.09
Gender (female/male)	35(54.7%)/29(45.3%)	26(56.5%)/20(43.5%)	1.00
Sepsis-NEC (38.2%)	25 (39.1%)	17 (37.0%)	0.84
BPD (28.1%)	15 (23.4%)	16 (34.8%)	0.20
RDS (67.9%)	38 (60.3%)	36 (78.3%)	0.06
Mechanical ventilation time (hour)	576.9±360.0	712.1±606.7	**0.01**
Oxygen using time (day)	24.00±28.01	34.00±19.41	**0.01**

Since the most important neonatal disease to affect ROP, as mentioned in the literature, are Sepsis-NEC, BPD, and RDS, the study groups were researched for these diseases (Table-1). Sepsis and NEC were assessed together (n:42, 38.2%). When looked from the perspective of the study groups, sepsis-NEC was detected in 25 (39.1%) patients in the control group, and in 17 (37.0%) patients in the laser photocoagulation group. These data were not statistically significant (p=0.84, p>0,05). BPD, (n:31, 28,1%), was detected in 15 (23,4%) patients in the control group, in 16 (34,8%) patients in the laser photocoagulation group (p=0.2, p>0.05). RDS (n:74, 67.9%), however, was detected in 38 (60.3%) cases in the control group, and in 36 (78.3%) cases in the laser photocoagulation group. There was no statistically significant difference of RDS between the study groups (p=0.06, P>0.05) (Table-1).

The duration of the time spent in ventilation, one of the most important factors to affect ROP in terms of external interventions, was recorded in hour. When looked from the perspective of the time spent in ventilation in the control (360.0±576.9) and laser photocoagulation (712.1±606.7) group, statistically significant differences were found between the groups (p=0.01, p<0.05) (Table-1). This, however, is a feature pointed out in all ROP studies, and therefore, it was not a coincidence that it occurred in our study, also. The values regarding the usage of oxygen in the study groups were recorded in hour. There was a statistically significant difference between the control group (24.00±28.01) and laser group (34.00±19.41) (p=0.01, p<0.05) (Table-1).

There was no statistically significant difference in thrombocyte counts (219.5±114.5, 222.0±88.1) (324.0±204.1, 307.0±128.7) in the first and second phase in the study groups between the control group and laser photocoagulation group (p=0.81/0.98, p>0.05) (Table-2) (Figure-1,3).

Table2. The distribution of platelet counts in the 1st and 2nd phase of ROP.

	Study Groups		p value
	Control Group (n:64) (med±SD)	Laser Photocoagulation Group (n:46) (med±SD)	
Platelet count in Phase-1 (mm^3)	219.5±114.5	222.0±88.1	0.81
Faz-1 MPV (fl)	10.0±1.32	10.0±1.56	0.43
Platelet count in Phase-2 (mm^3)	324.0±204.1	307.0±128.7	0.98
Faz-2 MPV (fl)	9.9±1.34	11.6±1.06	**0.001**

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Figure1. The distribution of platelet counts in the 1st phase in the study groups.

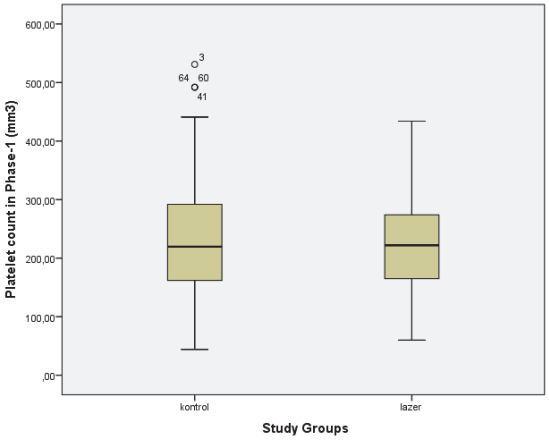


Figure 2. The distribution of MPV in the 1st phase in the study groups.

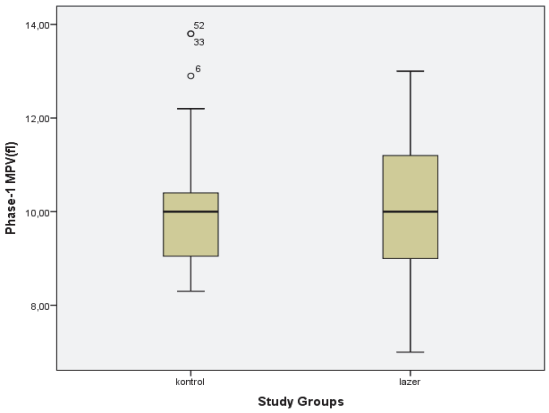
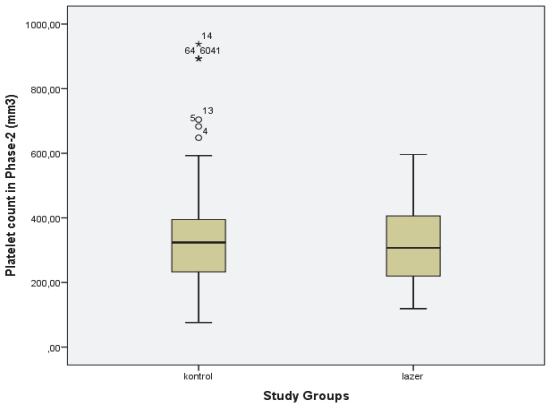


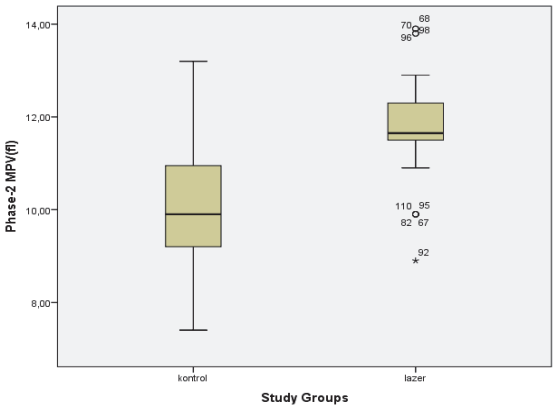
Figure 3. The distribution of platelet counts in the 2nd phase in the study groups



There was no significant difference of MPV in the first phase between the control (10.0±1.32) and the laser photocoagulation (10.0±1.56) groups (p=0.43, p>0.05) (Table-2) (Figurel-2).

When looked from the MPV viewpoint, the study groups in the second phase of ROP differed significantly. The difference between the control group (9.9±1.34) and laser photocoagulationgroup (11.6±1.06) was pronounced (p=0.001, p<0.05) (Table-2) (Figure-4).

Figure 4. The distribution of MPV in the 2nd phase in the study groups.



DISCUSSIONS

Considering the phases of ROP in our study, we have researched into the thrombocyte counts in cases, exposed to laser therapy for ROP in advanced stage, and in the control group consisting of preterm infants at risk of ROP. While no difference of thrombocyte count was found in the study groups in the first phase of the disease, MPV values of the study group in the same phase differed significantly.

The difference in the mean thrombocyte volume was ascribed to the increase in VEGF in the second phase of ROP cases (16). If it is considered that the high VEGF levels may be pronounced in the second phase of ROP in advanced stage -which requires laser photocoagulation therapy in particular- The elevation of MPV levels in these cases acquire a special importance. This is because neovascularization in the second phase of the disease giving rise to laser photocoagulation is predicated on elevated VEGF levels observed again in this phase, and our study demonstrates that elevated MPV levels in the second phase might give us foresight as to high VEGF levels (4,17-20).

In the study, the thrombocyte counts in the first (vasoobliteration) and the second (vasoproliferation) phase of ROP were studied separately as the disease consits of these diametrically opposed phases (4,9,21). A large number of researcher have reported that while there occurs in the first phase of ROP a reduction in the number of mediators which affects vascular development, there occurs an increase in the number of the same mediators during the second phase. This differentiation constitutes the basic pathology of the disease (4,9,21). Accordingly, the study of the mediators known to affect ROP, such as VEFG, should not be conducted without considering ROP phases in question.

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Low gestational age and low birth weight are risk factors in ROP. These two factors are associated with the profundity of retinal vascular and neural development maturity at birth (22,23). The incidence of the disease being higher in blacks than in whites and in males than in females has borne the necessity of dwelling upon genetic factors (24). There was no statistically significant difference of gestational age, weight, and gender between our study groups, which made the case distribution homogenous.

In a study on 1544 infants with birth weights below 1000 gm, a group of infants with target SpO2 over 95% was compared with another having target SpO2 below 95%. The study revealed that the rate of ROP was reduced from 29 to 10%, the rate of retinal surgical intervention from 12 to 4%, chronic pulmonary disease from 53 to 27%, and the rate of mortality from 24 to 17% (25).

It was researched in some studies that in the second phase of ROP, oxygen, could, in theory, suppress the high levels of the oxygen-dependent factor which, like VEGF, causes vascular proliferation. In one study 358 infants with gestational ages below 30 weeks were checked, and the effects of different oxygen targets in the second phase of ROP were investigated. Researchers comparing SpO2 targets of 91-94% and 95-98% reported that the severity of the disease differed while there was no change in the number of infants and in their development in 12 months. In that study, it was demonstrated that the high oxygen saturation in phase-2 was of no use. Chen et al., (26), however, have reported that low oxygen saturation (70-96%) in the first several postnatal weeks and high oxygen saturation (%94-99) at post-menstrual day 32 or later reduce the grave risk of ROP progression. The importance of oxygen in ROP has been proven in many other comprehensive studies (27,28).

The study by Chen (26), in particular, investigating the effect of oxygen on ROB is one done by considering the phases of the disease, and was consistent with the basic philosophy of our study. We have studied in our cases, not the usage of oxygen, but the thrombocyte counts, which reflect VEGF levels in terms of the phase of the disease and their predictive value. In our study group, as was expected, oxygen usage was, significantly great in the laser photocoagulation group, which was in agreement with the findings from the previous studies done on the etiology of ROP and accepted widely in our time.

Premature retinopathy affects primarily the infants who had a history of severe disease (sepsis, NEC, BPD) or prolonged oxygen therapy (29,30). In addition, prenatal infection and inflammation have been thought to trigger the recently defined phase called pre-phase (31). A large number of researcher report that RDS increases patients' oxygen consumption, thereby increasing the incidence of ROP. Consequently, RDS causes the growth factor which enables vascular development to be suppressed, triggering the second phase, which is primarily responsible for the development of ROP (32-34).

In our study we did not investigate the effects of sepsis, NEC, RDS, and BPD, on ROP. There are studies demonstrating that these diseases are important in ROP etiology. However, there is not enough concensus among researchers about all except BPD. In our study there was not any difference between the study groups in terms of these diseases.

The primary contribution of the other factors to the impairment of the regulation of the coroidal blood flow and retinal blood flow is hypercarbia in mechanical ventilation and preterm pulmonary damage (35). The decrease in antioxidant defence and the increase in the pressure of secondary oxygen in mechanical ventilation, particularly in preterm infants, increase the pathology (36). We did not dwell on the duration of mechanical ventilation as it was not the main topic of our study. However, we have seen that when we look at the study groups from this perspective, the pronounced difference between the control group and laser photocoagulation group is in favor of the laser group, which is consistent with previous studies. The similarity between the characteristics of these data obtained from the demographic records in our study and of generally accepted factors in ROP etiology, such as the duration of mechanical ventilation, has led us to suggest that the conclusions drawn from our study are healthy, and therefore, reliable.

The most important of the mediators to function in premature retinopathy VEGF. Its levels in the first phase of ROP are low, but they are expected to be high in the second phase (4,17-21). In addition to storing and transporting these mediators thrombocytes stimulate endothelial cells in in vitro medium, contributznt to neovascularization. When looked from this perspective, high MPV in the second phase of the disease may reflect the VEGF levels which have been elevated in this phase. The data obtained from our study corroborate this view (3,37,38).

The absence of any difference in MPV between the study groups in the first phase of the disease, when vasoobliteration occurs, is due to low VEGF levels in both study groups in this phase. However, the significant difference in MPV in the second phase of the disease, when vasoproliferation arises, stems from VEGF levels' being low in the group which does not require laser therapy, while being high in the group which requires laser therapy. The striking difference between MPV levels, which reflects the high VEGF level in the second phases of the cases, may help clinicians, by facilitating ideal follow-up, to make decisions as to the treatment and prognosis of the disease.

CONCLUSIONS

Despite the progressively increasing importance of premature retinopathy in our time, the degree of the increase in the progress achieved in its diagnosis is not

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at desirable level. The follow-up of the patients at risk, in particular, is rather difficult for both patients and clinicians, owing to the burden involved. Studies intended to overcome these difficulties, however, are few in number.

Accordingly, we planned to do our study on this topic, with a more non-invasive method, considering the two phases, which constitute the pathophysiology of the disease. We have obtained results that may help the clinician and the patient in treating and monitoring the disease, with the aid of MPV values reflecting elevated VEGF levels in neovascularization phase (phase-2), which is the root of the disease.

The data obtained from this study may enable ophtalmologists to more precisely monitor the disease in infants at risk of ROP, and to have foresight as to the course of the disease.

REFERENCES

1. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008;84(2):77–82.
2. Smith LE. Pathogenesis of retinopathy of prematurity. Growth Horm IGF Res 2004;14:140–44.
3. Italiano JE Jr, Richardson JL, Patel-Hett S, Battinelli E, Zaslavsky A, Short S. Angiogenesis is regulated by a novel mechanism: pro-and antiangiogenic proteins are organized into separate platelet alpha granules and differentially released. Blood 2008;111(3):1227-33.
4. Sapieha P, Joyal JS, Rivera JC, Kermorvant-Duchemin E, Sennlaub F, Hardy P. Retinopathy of prematurity: understanding ischemic retinal vasculopathies at an extreme of life. J Clin Invest 2010;120(9):3022-32.
5. Folkman J. Angiogenesis: an organizing principle for drug discovery? Nat Rev Drug Discov 2007;6(4):273-86.
6. Vinekar A, Hegde K, Gilbert C, Braganza S, Pradeep M, Shetty R. Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina 2010;30(4):S20–3.
7. Jensen AK, Ying GS, Huang J, Karp K, Quinn GE, Binenbaum G. Thrombocytopenia and retinopathy of prematurity. J AAPOS 2011;15(1):e3–e4.
8. Ashton N. Retinal angiogenesis in the human embryo. Br. Med Bull 1970;26(2):103-6.
9. Smith LE. Pathogenesis of retinopathy of prematurity. Semin Neonatol 2003;8(6)469-73.
10. Browder T, Folkman J, Pirie-Shepherd S. The hemostatic system as a regulator of angiogenesis. J Biol Chem 2000;21;275(3):1521-4.
11. Pinedo HM, Verheul HM, D'Amato RJ, Folkman J. Involvement of platelets in tumour angiogenesis? Lancet 1998;28;352(9142):1775-7.
12. Wartiovaara U, Salven P, Mikkola H, Lassila R, Kaukonen J, Joukov V. Peripheral blood platelets express VEGF-C and VEGF which are released during platelet activation. Thromb Haemost 1998;80(1):171-5.
13. Kaplan DR, Chao FC, Stiles CD, Antoniades HN, Scher CD. Platelet alpha granules contain a growth factor for fibroblasts. Blood 1979;53(6):1043-52.
14. Ben-Ezra J, Sheibani K, Hwang DL, Lev-Ran A. Megakaryocyte synthesis is the source of epidermal growth factor in human platelets. Am J Pathol 1990;137(4):755-9.
15. Hla T. Physiological and pathological actions of sphingosine 1 phosphate. Semin Cell Dev Biol 2004;15(5):513-20.
16. Brian W. Fleck and neil mcIntosh. retinopathy of prematurity: recent developments. Neo Reviews 2009;10:20-30.
17. Sapieha P, Sirinyan M, Hamel D, Zaniolo K, Joyal JS, Cho JH. The succinate receptor GPR91 in neurons has a major role in retinal angiogenesis. Nat Med 2008;14(10):1067-76.
18. Alon T, Hemol, Itin A, Pe'er J, Stone J, Keshet E. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat Med 1995;1(10):1024-8.
19. Kermorvant-Duchemin E, Sapieha P, Sirinyan M, Beauchamp M, Checchin D, Hardy P. Understanding ischemic retinopathies: emerging concepts from oxygen-induced retinopathy. Doc Ophthalmol 2010;120(1):51-60.
20. Smith LE. Through the eyes of a child: understanding retinopathy through ROP the Friedenwald lecture. Invest Ophthalmol Vis Sci 2008;49(12):5177-82.
21. Dorrell MI, Aguilar E, Friedlander M. Retinal vascular development is mediated by endothelial filopodia, a preexisting astrocytic template and specific R-cadherin adhesion. Invest Ophthalmol Vis Sci 2002;43:3500-10.
22. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics 2005;115(4):990-6.
23. Roth AM. Retinal vascular development in premature infants. Am J Ophthalmol 1977;84(5):636–40.
24. Husain SM, Sinha AK, Bunce C, Arora P, Lopez W, Mun KS. Relationships between maternal ethnicity, gestational age, birth weight, weight gain, and severe retinopathy of prematurity. J Pediatr 2013;163(1):67-72.
25. Sun SC. Relation of target SpO2 levels and clinical outcome in ELBW infants on supplemental oxygen. Pediatr Res 2002;51:350.
26. Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity. Pediatrics 2010;125(6):e1483-92.
27. Askie LM, Henderson-Smart DJ, Irwig L, Simpson JM. Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;4;349:(10) 959-67.
28. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremly preterm infants. N Engl J Med 2010;362:1959-69.
29. Leviton A, Dammann O, Engelke S, Allred E, Kuban KC, O'Shea TM. The clustering of disorders in infants born before the 28th week of gestation. Acta Paediatr 2010;99(12):1795–800.
30. Brennan R, Gnanaraj L, Cottrell DG. Retinopathy of prematurity in practice. I. Screening for threshold disease. Eye (Lond) 2003;17(2):183-8.
31. Lee J, Dammann O. Perinatal infection, infl ammation, and retinopathy of prematurity. Semin Fetal Neonatal Med 2012;17(1):26–9.
32. Chen J, Connor KM, Aderman CM, Willett KL, Aspegren OP, Smith LE. Suppression of retinal neovascularization by erythropoietin siRNA in a mouse model of proliferative retinopathy. Invest Ophthalmol Vis Sci 2009;50(3):1329–35.
33. Pierce EA, Avery RL, Foley ED, Aiello LP, Smith LE. Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal

2016;23(2):185-91
DOI:10.5455/jtomc.2016.01.016

neovascularization. Proc Natl Acad Sci USA 1995;31;92(3):905–09.
34. Pierce EA, Foley ED, Smith LE. Regulation of vascular endothelial growth factor by oxygen in a model of retinopathy of prematurity. Arch Ophthalmol 1996;114(10):1219–28.
35. Checchin D, Hou X, Hardy P, Abran D, Najarian T, Beauchamp MH. PGE(2)-mediated eNOS induction in prolonged hypercapnia. Invest Ophthalmol Vis Sci 2002;43(5):1558-66.
36. Chemtob S, Hardy P, Abran D, Li DY, Peri K, Cuzzani O. Peroxide-cyclooxygenase interactions in postasphyxial changes in retinal and choroidal hemodynamics. J Appl Physiol (1985) 1995;78(6):2039-46.
37. D'Amore P, Shepro D. Stimulation of growth and calcium influx in cultured, bovine, aortic endothelial cells by platelets and vasoactive substances. J Cell Physiol 1977;92(2):177-83.
38. Pipili-Synetos E, Papadimitriou E, Maragoudakis ME. Evidence that platelets promote tube formation by endothelial cells on matrigel. Br J Pharmacol 1998;125(6):1252-7.