Can Propranolol Affect Platelet Indices in Infantile Hemangioma?

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Introduction: Propranolol, a nonselective beta-blocker used in the medical treatment of infantile Hemangioma (IH), has been shown to decrease the levels of vascular endothelial growth factor and reduce angiogenesis with its antiproliferative and antiangiogenetic effects.

Materials and Methods: It has been reported that the storage, transport, and secretion of vascular endothelial growth factor (VEGF) are associated with platelet volume indices (PVI). We aimed to investigate the effect of propranolol on PVI in IH patients. Propranolol treatment was started on 22 IH patients. Platelets, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit values in the follow-ups at months 0, 1, and 2 were compared between 22 patients who received treatment and 25 patients who did not.

Results: While a statistically significant difference between months 0, 1, and 2 in PDW and MPV values was detected in the treated group, it was not detected in the untreated group. Taking into consideration that VEGF levels were higher at the beginning of the treatment in the pathophysiology of the disease, it was thought that the decrease in VEGF levels by propranolol may have led to a decrease in MPV and PDW levels in the treatment group.

Conclusion: Consequently, in IH cases, propranolol response follow-up can be evaluated with PVIs, especially MPV and PDW, and it may facilitate clinicians' monitoring of the disease after propranolol administration.

Key Words: infantile hemangioma, platelet indices, propranolol

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Infantile Hemangioma (IH) is the most common benign vascular tumor in infancy. The incidence of IH is between 3% and 12% in newborns.[1–4] It usually occurs within a few days after birth, and the natural cycle of it consists of 3 phases: proliferation, plateauing, and involution. The proliferative phase is characterized by the proliferation of endothelial cells (EHs). During the plateau phase, the lesions gradually transform into fatty and fibrous tissue, and EH proliferation and fatty fibrous infiltration coexist in IH lesions.[5] In the involution phase, irregular vascular channels consisting of flat EH and pericytes undergo apoptosis and are replaced by connective tissue and fatty tissue over time.

Most IHs are small lesions that are not life-threatening but can affect the child's health and cause disfigurement.[6] While most IH lesions spontaneously regress, a small proportion require clinical intervention. Treatments for infantile hemangioma are β-blockers, corticosteroids, interferon α, vincristine, imiquimod, bleomycin, laser therapy, ACE inhibitor, and surgical excision.[7] However, these treatments are only partially effective, have side effects, and cannot prevent the recurrence of hemangiomas. Thus, studies regarding the pathogenesis of IHs may provide new therapeutic strategies.

Multiple irregular vascular structures are supported by EHs and pericytes in infantile hemangiomas. Angiogenesis increases with the proliferation of EHs.[8] Vascular endothelial growth factor receptor 2 (VEGFR2) is positive in endothelial cells as well as interstitial and perivascular cells. Some studies have demonstrated that VEGF, microRNA (miRNA), long non-coding RNAs, and various other molecules are abnormally expressed in IH.[9–12] During angiogenesis, endothelial cells are activated; they proliferate and migrate with the VEGF gradient, aggregate, and form new vascular structures.[13,14]

Platelets have been shown to cause endothelial cell proliferation and vascularization.[15] VEGF, fibroblast growth factor, epidermal growth factor (EGF), platelet-derived growth factor, and matrix metalloproteinases are stored, transported, and released by platelets.[15] Many experimental data and clinical studies suggest that platelets are the main regulators of angiogenesis. Platelet volume indices (PVI) are a group of parameters obtained from inexpensive and routine blood counts. Mean platelet volume (MPV) and PDW (platelet distribution width) are frequently used in clinical settings for research since they are the most validated and prominent indices.[16,17] It has been reported that the storage, transport, and secretion of VEGF are associated with PVI.[18]

Propranolol, a nonselective beta-blocker used in the medical treatment of IHs, has been shown to decrease levels of VEGF and reduce angiogenesis with its antiproliferative and antiangiogenetic effects.[19] For this reason, in our study, we aimed to investigate whether the efficacy of propranolol treatment in IH patients is associated with PVI that is inexpensive and easy to access.

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MATERIAL AND METHOD

Measurement and Definition of Platelet Volume Indices

Platelet volume indices such as platelet count, MPV, PDW, and plateletcrit (PCT) were measured routinely in an automated hematology analyzer named the Sysmex xn2000 device using the electrical impedance or optical fluorescence method. MPV, PDW, PCT, and platelet counts were recorded from routine hemograms of the patients.

Forty-seven pediatric patients (< 1 y old) with IH who were admitted to Afyonkarahisar Health Sciences University, Faculty of Medicine, Pediatric Hematology and Oncology Outpatient Clinic between April 2021 and December 2022 were included in the study. A consent form was obtained from all patients, and the approval numbered 2021/213 dated April 2, 2021 was obtained from the ethics committee of Afyonkarahisar Health Sciences University, Faculty of Medicine. Propranolol treatment at a dose of 2 mg/kg/day was initiated to 22 patients for rapidly growing and very large lesions (> 2 cm) that caused loss of function and complications such as bleeding and/or infection. Treatment was not initiated in 25 patients with infantile hemangiomas smaller than 2 cm in facial, periorbital, anogenital, oral, and tongue regions without ulcer, bleeding, scarring and/or infection. Before the treatment was started, patients were evaluated with abdominal ultrasonography and echocardiography. Platelet, MPV, PDW, PCT values at 0-, 1- and 2-months follow-up of 22 treated patients and 25 untreated patients were compared.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 18.0, Chicago). In descriptive statistics, categorical data are shown as percentage frequencies, and continuous variables that do not conform to normal distribution are shown as median, minimum, and maximum. The conformity of the continuous data to the normal distribution was evaluated with the Shapiro-Wilk test and observed that it did not fit the normal distribution. The Friedman test was used to compare dependent groups. In every instance, a P value <0.05 was considered significant.

TABLE 1. Demographic Data of the Patients

	Group 1 (n:27)	Group 2 (n:20)	P
Sex			
Female	21 (44)	18 (38)	—
Male	6 (12)	2 (0.04)	—
Age (mo)	6.82 ± 3.34	6.92 ± 2.81	0.1
Treatment start age (mo)	2.56 ± 2.29	—	—
Number of lesions	1.63 ± 1.32	1.68 ± 1.46	—
Lesion diameter	2.25 ± 0.97	1.23 ± 0.74	—

RESULTS

While the mean age was 6.82 ± 3.34 months in the treated group, it was 6.92 ± 2.81 months in the untreated group ($P = 0.10$). While 78.7% of the patients were female, 21.3% were male. The mean age at starting the treatment was 2.56 ± 2.29 months (Table 1). The mean number of lesions in the treated and untreated groups was 1.63 ± 1.32 and 1.68 ± 1.46, while the mean lesion diameter was 2.25 ± 0.97 and 1.23 ± 0.74. There was no difference between the months 0, 1, and 2 in platelet values in both treated and untreated groups ($P = 0.26$, $P = 0.60$). While a statistically significant difference was detected between the MPV values at months 0, 1, and 2 in the treated group, it was not detected in the untreated group ($P < 0.001$, $P = 0.17$) (Fig. 1 a,b). While a statistically significant difference was detected between months 0, 1, and 2 in PDW values in the treated group, it was not detected in the untreated group ($P = 0.01$, $P = 0.06$, respectively) (Fig. 2 A,B). There was no statistically significant difference between the PCT(%) values at months 0, 1, and 2 in both groups ($P = 0.62$, $p = 0.11$) (Table 2).

DISCUSSION

Platelets can modulate angiogenesis by releasing promoters such as VEGF, fibroblast growth factor, EGF, platelet-derived growth factor, and matrix metalloproteinase.[20]

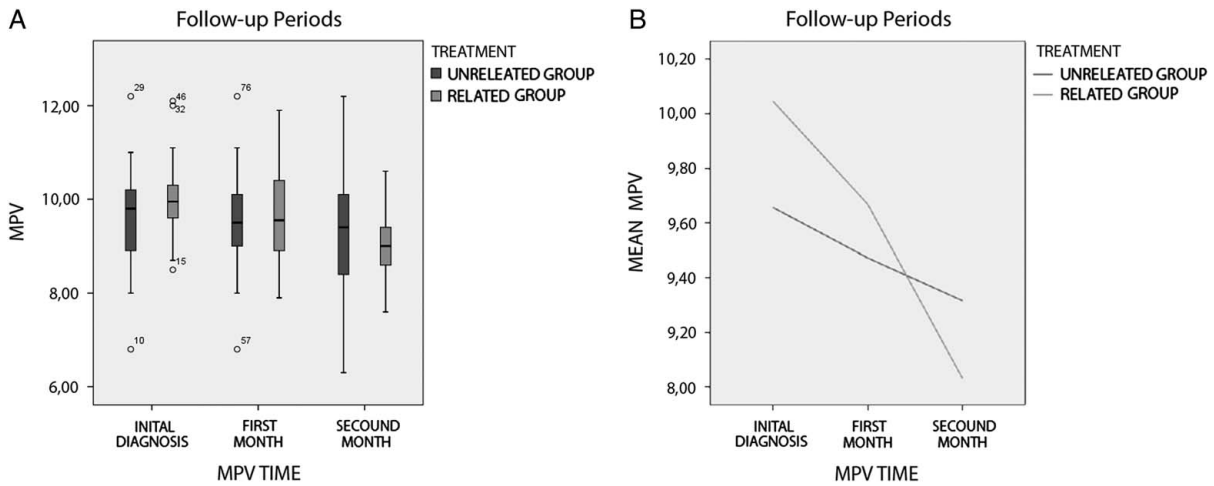

FIGURE 1. A and B, Serial MPV levels in infantile hemangioma cases who were treated untreated with propranolol and had serial measurements. MPV indicates mean platelet volume.

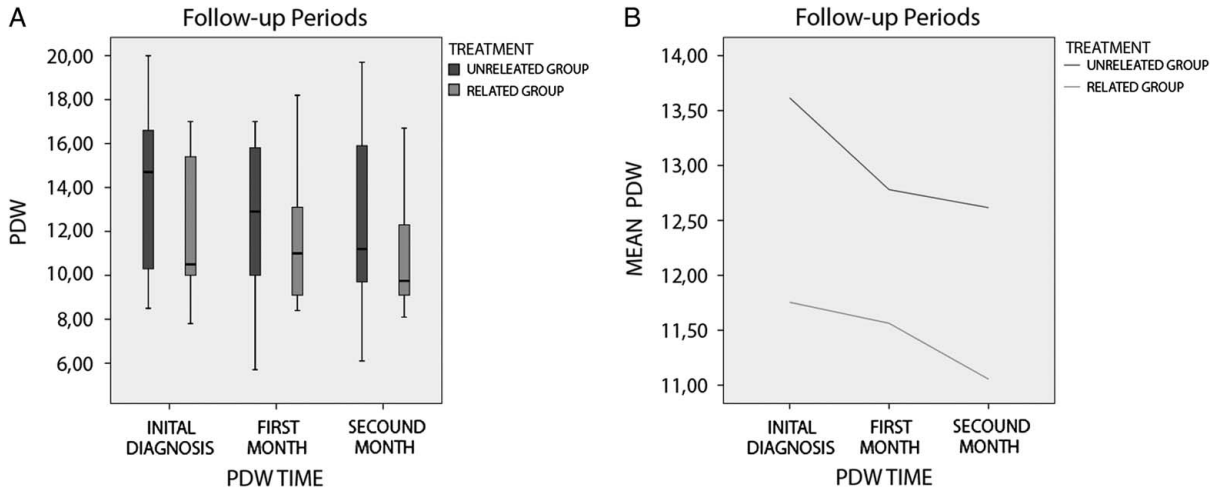

FIGURE 2. A and B, Serial PDW levels in infantile hemangioma cases who were treated untreated with propranolol and had serial measurements. PDW indicates platelet distribution width.

VEGF are important proangiogenic growth factors that can stimulate both endothelial cell proliferation and differentiation and promote vasculogenesis.[21]

Overexpression of VEGF in IH tissue has been confirmed in several studies to increase the proliferative phase of hemangiomas.[22–26] In a study conducted by Şen et al[20] on IH patients, it was observed that 91% of the patients were younger than 1 year, and almost all of them were in the proliferation phase. Serum VEGF levels of the patients were observed to be significantly higher at the first admission when compared with the control group, which supports the hypothesis of increased activity of these cytokines. The results of high serum VEGF levels detected in this study are in line with many similar studies.[22–27]

Currently, oral propranolol is the first-line therapy of choice for IH, and response rates to treatment with propranolol are high, ranging from 80% to 100%. Based on case reports and case series, oral propranolol appears to have a good safety profile in children.[28–30] Şen et al[20] demonstrated that plasma VEGF levels were significantly decreased in patients with hemangioma in the months after propranolol was started. Similar studies investigating the effects of propranolol on serum cytokines also show that VEGF levels decrease with treatment.[24–26,31,32] While in some studies, reduction in serum VEGF levels was much more significant after 12 weeks of propranolol treatment, Chen et al[25] reported that very high serum VEGF levels were significantly reduced after 1 month, compared with 3 months of treatment with propranolol.

As platelets play a role in VEGF transport, storage, and release, it is considered that platelet index values may increase in parallel with the increase in VEGF in the infantile hemangioma proliferation phase.[32–34] In addition, some studies have reported that platelets contribute to vascularization by stimulating endothelial cells due to their effects on VEGF.[1,35] When considered from this perspective, platelet indices in the proliferation phase appear to be correlated with the increase in VEGF in the same phase. The mechanism of action of propranolol in IH remains unclear. It has been suggested that the early effects of propranolol are vasoconstriction; its intermediate effects include inhibition of angiogenesis resulting from blocking proangiogenic cytokines such as VEGF; and its prolonged effects are characterized by the induction of apoptosis in IH endothelial cells, resulting in tumor regression. Leaute-Labreze et al[36] also suggested that propranolol may reduce VEGF expression. Thus, in our study, we aimed to investigate whether the efficacy of propranolol treatment in IH patients is associated with platelet indices. While there was a statistically significant difference between the PDW values at months 0, 1, and 2 in the group that received propranolol treatment, it was not detected in the group that did not receive treatment ($p = 0.01$, $p = 0.06$, respectively). While there was a statistically significant difference between the MPV values at months 0, 1, and 2 in the treated group, it was not detected in the untreated group ($p: < 0.001$, $p = 0.17$). In our study, with propranolol treatment in the proliferation phase of IH patients, it was determined that

TABLE 2. Platelet Volume Indices and Platelet Counts According to the Treatment Months of the Patients

	Group 1 (n:27)				Group 2 (n:20)			
	Initial diagnosis	First month	Second month	*P*	Initial diagnosis	First month	Second month	*P*
Platelet (×103/μL)	317 ± 103	355 ± 903	390 ± 121	0.26	393 ± 128	411 ± 132	389 ± 117	0.60
Mean platelet volume: MPV (fL)	10 ± 0.92	9.66 ± 0.96	9.03 ± 0.81	0.00	9.6 ± 1.12	9.47 ± 1.14	9.31 ± 1.21	0.17
Platelet distribution width: PDW(%)	11.7 ± 3	11.5 ± 2.9	11 ± 2.8	0.01	13.6 ± 3.6	12.7 ± 3.1	12.6 ± 3.4	0.06
Plateletcrit: PCT (%)	0.32 ± 0.07	0.34 ± 0.87	0.36 ± 0.10	0.62	0.39 ± 0.16	0.36 ± 0.11	0.36 ± 0.11	0.11

there was a significant decrease in MPV and PDW values, which are platelet indices, due to the suppression of angiogenesis and VEGF.

Our results showed that propranolol treatment in IH patients reduced VEGF-related platelet indices, which are effective in angiogenesis with treatment, considering the reduction mechanism of VEGF. Our study is the first in the literature. But there is no statistical difference between the 3 PCT values and platelet counts in both the treated and untreated group. There are different studies with PVI in cardiovascular diseases, obesity, immune thrombocytopenic purpura, atherosclerosis, and myocardial infarction,[37] but our study is the first study conducted with platelet volume indices in infantile hemangioma patients.

This study has some limitations. We studied only a small group of patients. In addition, objective evaluation is also limiting, since there are limited measurement values in the study. These findings require further studies and larger patient groups.

Consequently, considering that VEGF levels were higher at the beginning of treatment in the pathophysiology of infantile hemangiomas, it was thought that the decrease in VEGF levels by propranolol might have led to a decrease in MPV and PDW levels in the treatment group. In infantile hemangiomas, platelet indices may be an indirect indicator of changes in growth factors and platelet activity during propranolol treatment. MPV and PDW, which are evaluated in routine hemogram evaluation, and may facilitate clinicians' monitoring of the disease after propranolol administration.

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