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# Platelet indices: a new tool for monitoring infantile hemangioma treatment

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## ABSTRACT

**Aims:** Infantile hemangioma (IH) is the most common benign vascular tumor in childhood. Diagnosis, treatment decision-making, and monitoring of the treatment are challenging. This study aims to investigate the utilization of platelet (PLT) indices as a marker in the follow-up of IH treatment.

**Methods:** The patients who were admitted and followed up in the outpatient clinic of Erciyes University Department of Pediatric Hematology and Oncology were enrolled in the study. The demographical data, treatment results, and PLT indices of the patients at certain time points were analyzed retrospectively. PLT, mean platelet volume (MPV), and platelet distribution width (PDW) were measured at various time points: upon admission, after the first and second months of treatment, at treatment completion, and during rebound episodes in affected patients.

**Results:** A general decrease in PLT, PDW, and MPV values was noted when comparing admission levels to the first month of treatment. The mean PLT count was 452.680/mm3 at admission, it decreased to 405.900/mm3 at the 1st month, 376.600/mm3 at the 2nd month and 359.900/mm3 at the end of treatment (p: 0,002). Besides MPV was evaluated, it was observed that while the mean was 10.43 fl at the time of admission, it decreased to 9.51 fl in the following months and the decline was statistically significant with a p value of 0,031. Lastly, regarding the mean PDW values, a decline was detected once again from 11.34 % to 10.2 % between the admission time and termination of the treatment with a statistically significant p value of <0.001.

**Conclusion:** Up to 15% of IH patients may require treatment due to complications. This study highlights that PLT, PDW, and MPV values can serve as valuable biomarkers for assessing treatment response and guiding clinical decision-making.

**Keywords:** Infantile hemangioma, platelet indices, propranolol treatment

## INTRODUCTION

Hemangiomas are vascular tumors, which can be divided into two subgroups: infantile and congenital. Infantile hemangioma (IH) is the most common benign tumor in childhood, with a frequency of 5-12%.[1] Typically IH are not present at birth but arise in the first weeks of life exhibiting three unique evolutionary phases. On the other hand, congenital hemangiomas are rare and present at birth.

Some risk factors are determined according to the literature such as; prematurity, low birth weight, female gender, and multiple pregnancies.[2,3] The course of IHs is predictable, with three phases consisting of; proliferative, plateau, and involution. The proliferative phase can last until the age of 12 months followed by a plateau. The duration of the last phase may vary between 5- 12 years of age.[4] Only 5-10% of IF left scars, ulcers, or hyperpigmentation in the regression phase.[5]

Owing to the heterogeneous nature of the IH course, the necessity of treatment should be assessed carefully. The clinicians and family should be aware of the natural course and determine a risk/ benefit ratio. High-risk lesions should be evaluated and treatment options should be considered in terms of treatment results, prognosis, and impairment caused by the lesion. The most common choice of medical treatment is oral propranolol since discovered in 2008.[6,7] However, still, the timing of the termination of propranolol and tools that can be helpful for follow-up is still unclear. The main purpose of the current study is to investigate the use of platelet indices as a traceable, innovative, and non-invasive biomarker when evaluating the efficacy of propranolol in the treatment of IHs.

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## METHODS

The study was conducted with the permission of Erciyes University Health Sciences Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025/54). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the current retrospective cohort study, medical records of the patients who were admitted to Erciyes University Pediatric Hematology and Oncology outpatient clinic between January 2021 and December 2024 and diagnosed with IH were evaluated. Of these 142 patients; topical treatment was initiated for 18 of them and these patients were excluded. The remaining 124 patients who received systemic propranolol treatment were enrolled. Age, gender, complaints on admission, location of the lesion, and platelet indices at certain time points of treatment were assessed. Platelet count (PLT), mean platelet volume (MPV), and platelet distribution width (PDW) were determined at admission, in the first month of treatment, in the second month, at the end of treatment, and at the time of rebound in patients with rebound. The changes in mean and median values of platelet indices between these time points were interpreted.

### Statistical Analysis

In the present study, clinical results were evaluated using descriptive statistical methods. The quantitative characteristics of the patients are shown with numbers (n) and frequencies (%) in the text and tables. Descriptive statistics; number and percentage for categorical variables; For numerical variables, data that provided normal distribution parameters were given as mean±standard deviation, and for data that did not comply with normal distribution, they were given as median (minimum-maximum value). Comparison of data was made with Student's t-test for variables with normal distribution, and with Mann-Whitney U test for those with non-normal distribution. Besides, an ANOVA test was performed to compare the multiple parametric results in dependent groups.

## RESULTS

Of the 124 patients enrolled, 25.8% (n: 32) were male and 74.2% (n:92) female. The mean age on admission was 4.47±2.9 months and the median was 3.75 months (minimum 15 days-maximum 15 months). The mean time of diagnosis by the family doctor or a pediatrician was 1±0.8 months. 25.8% (n: 32) of patients had superficial lesions, 50.8% (n: 63) had mixed lesions, and 23.3% (n:29) had deep IH lesions. Regarding the location of IH lesions; the most common site was the head-neck region with 46.7% (n: 58). Of these patients, 18.9% (n: 11) originated from the periocular area. 38 patients (30.6%) had ulcerated lesions. Of them, 39.4% (n: 15) originated from the head-neck region while the remaining 34.2% (n:13) from the extremity and 26.3% (n:10) from the genital region. Demographical findings are available in Table 1.

**Table 1.** Demographical findings of patients with infantile hemangiomas

| | n (%) |
|---|---|
| **Sex** | |
| Female | n: 92 (74,.2%) |
| Male | n: 32 (25.8%) |
| **Age on admission (months)** | |
| Mean±SD | 4.47±2.9 months |
| Median (min-max) | 3.75 months (min 15 days-max 15 months) |
| **Lesion type** | |
| Superficial lesions | n:32 (25.8%) |
| Deep lesions | n:29 (23.3%) |
| Mixed lesions | n:63 (50.8%) |
| **Location** | |
| Head-neck | n:58 (46.7%) |
| Periocular | n:11 (18.9%) |
| Body | n:20 (16.1%) |
| Extremity | n:33 (26.6%) |
| Genital area | n:13 (10.4%) |
| **Treatment duration time (months)** | |
| Mean±SD | 9.98±4 months |
| Median (min-max) | 10 (min 1-max 21) months |

SD: Standard deviation, Min: Minimum, Max: Maximum

83 patients (66.9%) were initiated peroral propranolol treatment at the age of ≤5 months. The dose of oral propranolol was initiated as 1 mg/kg/day and escalated to 2 mg/kg/day. The mean treatment duration was 9.98±4 months and the median was 10 months (minimum 1- maximum 21 months). The patient who had the treatment for 1 month, developed severe difficulty in breathing during the bronchiolitis period, and owing to this the treatment was terminated with the informed consent of the family. On the other hand, the patient who had the treatment for 21 months, had an ulcerated hemangioma originating from the extremity covering a large area. 54 patients (43.5%) are still on treatment. Regarding the side effects, a total of 48 patients (38.7%) had complaints during the propranolol treatment. The most common complaint was restlessness in 26 patients (54.1%), followed by loss of appetite and inability to gain weight in 21 patients (43.7%), and respiratory distress in only 1 patient (0.2%), whose treatment period was terminated early.

Platelet indices (PLT, MPV, PDW) were analyzed in certain time points described previously. Rebound growth of hemangioma was observed in only 21 (16.9%) patients. None of these patients restarted the treatment. Of them, only 7 patients had the PLT indices checked. Owing to the insufficient number, the rebound group was not enrolled in the statistical evaluation. The mean, median, standard deviation, and minimum-maximum values of PLT indices are available in Table 2. In terms of PLT, the mean value was initially 452.680/mm³ upon admission. Over the course of the treatment, this value progressively decreased, reaching 405.900/mm³ by the 1st month, 376.600/mm³ at the 2nd month, and 359.900/mm³ at the end of the treatment. This decline was statistically significant, with a p-value of 0.002, suggesting a notable reduction in PLT throughout the treatment period. Similarly, the mean value for MPV was observed to be 10.43 fl at the time of admission. As the treatment progressed, a consistent decrease was recorded, with the MPV value dropping to 9.51 fl in the subsequent months. The reduction in MPV was also found to be statistically significant, with a p-value of 0.031, indicating that MPV levels declined significantly during the treatment period. Lastly, regarding PDW, the mean value was 11.34% at admission, and it steadily decreased to 10.2% by the end of treatment. This change was highly statistically significant, with a p-value of <0.001, reinforcing the trend of

**Table 2.** Platelet indices on certain time points

| | Admission | 1st month | 2nd month | Termination time | p-value |
|---|---|---|---|---|---|
| PLT (/mm³) | | | | | |
| Mean±SD | 452.680±109.800 | 405.900±96.300 | 376.600±101.200 | 359.900±105.850 | **p1:0.002** |
| Median (min-max) | 441.000 (219.000-959.000) | 394.000 (187.000-636.000) | 373.000 (175.000-701.000) | 336.000 (207.000-767.000) | **p2:0.045** |
| MPV (fl) | | | | | |
| Mean±SD | 10.43±0.99 | 10.02±0.86 | 9.67±0.75 | 9.51±0.74 | **p1: 0.031** |
| Median (min-max) | 10.4 (7.8-12.8) | 9.9 (8.4-12.8) | 9.5 (8.3-11.8) | 9.3 (8.3-11.4) | p2: 0.093 |
| PDW (%) | | | | | |
| Mean±SD | 11.34±2.21 | 10.94±1.7 | 10.55±1.63 | 10.2±1.51 | **p1: <0.001** |
| Median (min-max) | 11.4 (10.8-19.2) | 10.8 (7.8-17.4) | 10.3 (7.8-15.7) | 9.8 (7.8-14.2) | **p2: <0.001** |

SD: Standard deviation

a reduction in PDW throughout the treatment process. The difference for all the indices was statistically significant, with p values available in Table 2.

## DISCUSSION

The present study evaluates the demographic characteristics, treatment responses, and side effects of oral propranolol in IHs. The significant decline observed in platelet indices during the first months of treatment suggests a potential hematological impact that warrants further investigation. These findings contribute to a better understanding of propranolol's effects and may guide future clinical management strategies.

IHs arise 2-5 times more frequently in girls than in boys.[1,2] In the present retrospective cohort, female patients were the majority which is in line with the literature. Regarding other demographic characteristics, the mean age on admission was 4.47 months which is important owing to the fact that the first 5 months is the upper limit of the opportunity window for initiating systemic treatment with propranolol, because IH lesions are in the proliferative period in this time period, full-filling the 80% of their growth.[8-10] On the other hand, the maximum age for admission was 15 months in our retrospective study. This patient has initiated treatment due to an ulcerated lesion and benefited. Based on this, it can be considered that the treatment decision should be evaluated individually and decided according to the area and condition of the lesion.

Regarding the evaluation of treatment necessity, the lesions should be classified as low-risk and high-risk. High-risk criteria consist of; the presence of life-threatening complications, functional loss, ulcers, PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac anomalies, eye anomalies), and permanent deformity.[5,6,11] Although there were no life-threatening events, the remaining criteria were judged at the onset of treatment in our study.

Propranolol is the gold standard in the treatment of IHs. The dosing is determined as beginning with 1 mg/kg/day and escalation to 2-3 mg/kg/day is recommended in the guidelines.[6,7,12] However, the recommended duration of the treatment can range between 6-12 months.[12,13] The mean treatment duration was 9.98±4 months in the present study which is similar to the literature. However, the range is between a minimum of 1 month to a maximum of 21 months. As mentioned earlier, the patient with the 1 month of treatment discontinued the drug owing to a life-threatening side effect. On the other hand, the patient who had the treatment for 21 months had an ulcerated lesion located in a large area on the extremity. Regarding these patients, it should be underlined that exceptions always exist and the treatment should be tailored to the needs of the lesion and the patient. Evaluating the treatment results and rebound rate, the present study had a rebound rate of 16.9 % (n:21), which seems to be less than the literature as reported before as 25%.[6,12,13] Also, 38.7% of our patients had reported a side effect. However, evaluating a complaint as a side effect is a challenging process in IH treatment, owing to some side effects being subjective, i.e. restlessness. The rate of side effects reported in the literature varies between 17% to 96%, which can be attributed to the same evaluation problem.[13,14]

The follow-up period of treatment, the escalation rate of the dosing, and the duration are still matters of debate. Clinicians need an objective and easily applicable tool to manage the treatment process. The pathogenesis of proliferation mainly depends on increased vascular endothelial growth factor (VEGF) release resulting in excessive angiogenesis, especially in the proliferative period.[15,16] Platelets also have a role in angiogenesis and interact with VEGF. Therefore, with sufficient treatment, the VEGF levels are expected to decline, leading to a decline in PLT indices, as described by Eroglu et al before in their study consisting of 22 patients.[17] As expected, a decline was observed in our study, between the admission and termination of the treatment in all of the PLT indices which are available in Table 2. Also, a statistically significant decrease was demonstrated in PDW and MPV values between the admission and termination times. These results can be attributed to the successful treatment and dosing.

The significant decrease observed in PLT, MPV, and PDW during the course of propranolol treatment in IHs suggests the hematological effect of the drug. The decline in PLT from 452.680/mm³ at admission to 359.900/mm³ at the end of treatment (p: 0.002) aligns with previous studies that have reported a reduction in platelet levels following propranolol administration in patients with hemangiomas. This phenomenon may be associated with the drug's vasoconstrictive properties, which could lead to a reduction in blood flow and, consequently, a decrease in platelet production or activity.[17-19] In addition, the statistically significant decrease in MPV from 10.43 fl to 9.51 fl (p: 0.031) supports the hypothesis that propranolol not only affects PLT but may also influence platelet size, indicating changes in platelet function. Previous literature has suggested that MPV can serve as an indicator of platelet activation, and a decrease

in MPV may reflect a reduction in platelet activation or an alteration in platelet production pathways.[17-20] Therefore, the reduction in MPV observed in our study may point to an overall change in platelet activity under the influence of propranolol. Furthermore, the decline in PDW from 11.34% to 10.2% ($p<0.001$) is another noteworthy finding. PDW is an indicator of platelet heterogeneity, and a reduction in this value has been linked to a decreased platelet response to injury or altered platelet function. The observed decrease in PDW may suggest that propranolol affects platelet maturation or their ability to respond to vascular damage, further supporting the drug's systemic effects.[17-21] These hematological changes underscore the importance of monitoring platelet indices during propranolol treatment, particularly in patients with IHs. While these findings are consistent with prior studies, the clinical significance of the changes in platelet indices remains unclear and warrants further investigation. Future studies should aim to elucidate the long-term impact of propranolol on platelet function and its potential implications for patient management.

### Limitations

The major limitation of our study is its retrospective nature. Owing to this, the data about prematurity, and maternal and familial features could not be accessed. In addition to this, VEGF levels, which could have revealed the exact mechanism, were not measured. Besides, only the patients on systemic treatment were enrolled in the study. On account of this, the decline in the PLT indices can not be solely ascribed to the treatment success, because no other data in different groups were evaluated and compared. Lastly, to make these results more useful for clinicians, larger-scale studies should be performed with the aim of determining a cut-off point for PLT indices, enabling their use in daily clinical practice.

## CONCLUSION

IHs generally undergo spontaneous regression. Nevertheless, up to 15% of the patients with IHs can develop complications leading need for treatment. In order to prevent unnecessary treatment and side effects, determining the lesions which actually need treatment and utilizing the appropriate treatment method is vital. Besides, monitoring the treatment results and deciding on timing are important issues for clinicians dealing with IHs. The present study disclosed that PLT, PDW, and MPV values can guide clinicians in evaluating treatment response.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was conducted with the permission of Erciyes University Health Sciences Researches Ethics Committee (Date: 05.02.2025, Decision No: 2025/54).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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