Pre-treatment and post-treatment changes in platelet indices in patients with immune thrombocytopenia

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ABSTRACT

الأهداف: دراسة فيما إن كان هنالك ارتباط بين معدل حجم الصفائح قبل وبعد العلاج وتوزيع الصفائح الدورية وقيمة الصفائح، ودراسة فيما إن كان بإمكاننا دراسة المؤشرات المخبرية لتقدير انتكاس الصفائح المناعية للمرضى.

الطريقة: اشتملت هذه الدراسة على مرضى مصابين بانتكاس المناعية في عيادة أمراض الدم، كلية الطب، سيفاس، تركيا خلال الفترة من يناير 2005م وديسمبر 2011م عن طريق مراجعة استباقية لسجلات المرضى. تم جمع 81 مريض مصاب بانتكاس الصفائح المناعية للمرضى. حدثت النكسة الأولى في فترة التنويم قبل فترة العلاج الثانية، بينما النكسة الثانية حدثت قبل العلاج البديل. قمنا بتوفير المعلومات التالية للمرضى المصابين بانتكاسات الصفائح الدموية في التشخيص، قبل وبعد الأنتكاسة، الأعراض الظاهرة، عدد وحجم وتوزيع الصفائح، وقيم الصفيحة الحرجة.

النتائج: أظهرت الدراسات اختلافات إحصائية بين قيم حجم الصفائح الدموية بعد العلاج الأولي وقبل خطة العلاج الثاني (النكسة الأولى) p=0.005، واختلافات إحصائية بين قيمة حجم الصفائح بعد استئصال البنكرياس وقبل التثبيط المناعي أو علاج تعديل المناعة (النكسة الثانية) p=0.028 وكذلك بين قيم الصفيحة الحرجة بعد استئصال البنكرياس وقبل النكسة الثانية p=0.043.

خاتمة: ارتفع حجم معدل الصفائح قبل النكسة الأولى والثانية وحصلنا على النتائج الطبيعية بعد الحصول على العلاج المناسب. أن معدل الصفائح الدموية مؤشر مفيد لحدوث النكسة.

Objectives: To investigate if there is a correlation between pre- and post-treatment mean platelet volume (MPV), platelet size deviation width (PDW), and platecrit (PCT) values and to investigate whether we can use them as laboratory parameters to estimate the relapses of immune thrombocytopenia (ITP) patients.

Methods: Patients with ITP diagnosed at the Hematology Clinic, School of Medicine, Cumhuriyet University, Sivas, Turkey between January 2005 and December 2011 were evaluated by a retrospective review of our patients' records. Eighty-one patients with ITP were collected. The first relapse was termed as the hospitalization day before second-line therapy, and the second relapse was termed as the hospitalization day before alternate second-line therapy. We provided the following data of ITP patients at diagnosis, before and after first relapses, and before and after second relapses: presenting symptoms, platelet count, MPV, PDW, and PCT values.

Results: We obtained significant statistical differences between MPV values after initial treatment and before second-line therapy (first relapse) (p=0.005), between MPV values after splenectomy and before immunosuppressive or immune modulator therapy (second relapse) (p=0.028), and also, between PCT values after splenectomy and before second relapse (p=0.043).

Conclusion: Mean platelet volume is gradually increasing before first and second relapses, and again normal values are being obtained after appropriate therapies. We conclude that MPV is a useful parameter as a predictor of relapses.

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Immune thrombocytopenia (ITP) is an autoimmune disease characterized by isolated thrombocytopenia (platelet count <100x10^9/L) resulting from accelerated clearance and destruction of antibody-coated platelets by tissue macrophages, predominantly in the spleen.[1]

Antiplatelet antibodies also target antigens on megakaryocytes and suppress platelet production.[2,3] Because of accelerated clearance via megakaryocytes and platelets, plasma thrombopoietin (TPO) is generally normal or minimally elevated.[4] Infection with hepatitis B, hepatitis C, human immunodeficiency virus (HIV), *Helicobacter pylori*, and coexistence of systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), or common variable immunodeficiency (CVID) are potential underlying etiology giving rise to secondary ITP, and these are identified in approximately 20% of patients with ITP.[5] To demonsrate an underlying cause is important, because it may impact the efficacy and safety of treatment approaches. Splenectomy remains the most effective treatment in cases that are refractory to first-line therapy. As the availability of alternate medical therapy such as Rituximab, and the associated risk of infection and surgery related complications, its use has declined. Among the blood cell parameters, platelet indices, such as mean platelet volume (MPV), and platelet size deviation width (PDW) provide some important information in routine clinical use.[6] Several investigators have used a series of platelet indices such as MPV and PDW, which are easily measured by hematology analyzers, given the fact that platelet activation causes morphologic changes of platelets.[7] The MPV is probably the most extensively studied platelet indice.[7-9] Platelets with increased or decreased number and size of pseudopodia differ in size, and consequently affects PDW. The ratio of the volume occupied by thrombocytes to the volume of the whole blood is called platecrit (PCT). As it known, relapses are encountered in patients with ITP, especially in the first 2 years after surgery, but 60% of patients remain in clinical remission throughout 5-10 years after splenectomy. And complete remissions generally persist at least one year in patients with ITP who are treated only with Rituximab; those with partial remissions usually relapse within 6 months.[10] But, there is no known parameter to predict relapses in this patient population. To our knowledge, this is the first study demonstrating a relationship between MPV and relapses of ITP. We conducted this study to investigate whether platelet indices are useful markers to estimate the relapses of ITP beforehand.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Methods. Records of patients with ITP diagnosed at the Hematology Clinic, School of Medicine, Cumhuriyet University, Sivas, Turkey between January 2005 and December 2011 were retrospectively reviewed. Eighty-one patients with ITP were collected. The first relaps was termed as the hospitalization day before second-line therapy, and the second relaps was termed as the hospitalization day before alternate second-line therapy. We provided the following data of ITP patients at diagnosis, before and after first relapses, and before and after second relapses: presenting symptoms, platelet count, MPV, PDW, and PCT values. The only exclusion criteria was age and patients aged under 18 were not included to the study. The diagnosis of ITP was made according to the British Society for Haematology,[11] and was confirmed by the evaluation of subsequent retrospective data analysis. The study was approved by the local Ethics Committees and was in accordance with the Declaration of Helsinki.

Bone marrow examination was performed in patients older than 60 years of age at the time of diagnosis and in patients whom splenectomy is considered. The causes of secondary ITP as drug-induced, hepatitis B virus, hepatitis C virus, a *Helicobacter pylori* infection, a lymphoproliferative disorder, or SLE were all recorded. Today, primary ITP is classified according to its duration as follows: newly diagnosed (<3 months), persistent (3-12 months), and chronic (>12 months). Immune thrombocytopenia tends to be chronic in adults, and presents with a more indolent course than in childhood. Primary goals of management are to achieve a safe platelet count to prevent serious bleeding with minimum treatment-related complications. Adults with platelet counts of less than $30x10^9$/L were usually treated. According to the response: a complete response was defined as platelet counts >$100x10^9$/L; a response was defined as platelet counts 30-$100x10^9$/L and platelet counts have to reach at least 2 folds of the beginning; no response was defined as platelet counts <$30x10^9$/L and platelet counts have not reached at least 2 folds of the beginning. Refractory ITP was defined as, first splenectomy should be performed, second clinical conditions as bleeding symptoms or treatment requirement should be in postsplenectomy thrombocytopenic patient. The diagnosis of chronic refractory ITP was made by the occurrence of clinical relapses due to inadequate control of the disease.

Platelet indices. All blood samples have been collected in tubes with potassium ethylenediaminetetraacetate (EDTA). The following hematological parameters have been studied in all blood samples in a matter of hours after the sampling: platelet count, MPV, PDW and PCT. Platelet counts have been also confirmed by

the examination of peripheral blood smear by optical microscopy. Impedance resistance has been used for the measurement of platelet indices in all blood samples. All samples have been processed in the same laboratory with the analyzers Mindray BC-6800 and Siemens Advia 2120i. Before and after the treatment modalities, the values of platelet counts and platelet indices (MPV, PDW, and PCT) were recorded.

Statistical analysis. All statistical analyses were performed using SPSS version 14.0.1 program (SPSS, Chicago, IL). Descriptive statistics were calculated for each of the variables. Paired sample t test was used to evaluate the normally distributed varables. Wilcoxon Signed Ranks test was used to compare medians of numerical variables which were not normally distributed. All results for non-parametric analysis were expressed as median and range. A *P*-value of <0.05 was considered statistically significant.

Results. A total of 81 patients (32 [39.5%] male, 49 [60.5%] female) were treated for ITP during the 5-years period. The median age of the patients was 42 years (range; 18-82). Echymosis was the most seen presenting sign (87.6%). We did not encounter with intracranial or gastrointestinal bleeding. None of the patients had hepatomegaly and/or splenomegaly on physical examination or performed abdominal ultrasonography. Bone marrow examination was performed in patients older than 60 years of age at the time of diagnosis and in patients whom splenectomy is considered, and showing normal or active megakaryopoeisis as being consistent with ITP. The general patients' clinical and laboratory characteristics at initial presentation are given in **Table 1**.

Primary ITP comprised of 91.4% (74/81) patients and secondary ITP comprised of 8.6% (7/81) patients. Pregnancy in 3 (42.9%) patients, systemic lupus erythematosus in 3 (42.9%), and *Helicobacter pylori* infection in 1 (14.2%) were the problems underlying secondary ITP.

The glucucorticoids were used in 77 (95.1%) of the patient population, namely glucucorticoids were the principle treatment as a first-line treatment option and in 4 (4.9%) patients, IVIG was used as a primary therapy. Relapses were occurred in 14 and 4 for whom glucucorticoids failed, namely 22.2% (18/81) of patients, underwent splenectomy as a second-line treatment. One of the patients failed to respond splenectomy. After post-splenectomy period, we obtained relapses in 5 (6.2%) patients. In totaly, 6 (7.4%) of the patients used immunosuppressive or immune modulator drugs after splenectomy. Of the 6 patients, one used rituximab and 5 used azathioprine. We did not encounter with any relapsed patients in post-splenectomy period. Our median follow up period was 48 months (range 21-76 months). Treatment outcomes were summarized in **Table 2**.

We obtained that MPV was higher in patients diagnosed with ITP, and after first-line treatment MPV was normalized. In first relapse, we saw that MPV was increased, and again it was normalized after second-line treatment (splenectomy). In second relapse, MPV was again higher, and it was normalized after immunosuppressive or immune modulator treatments. We obtained significant statistical differences between MPV values after initial treatment and before second-line therapy (first relaps) (splenectomy) [8.75 (5.3) versus 9.55 (1.9); p=0.005] (**Table 3**). And also, there was significant statistical differences between MPV values after splenectomy and before immunosuppressive or immune modulator therapy (second relaps) (8.10 [2.1] versus 11.5 [5.8]; p=0.028) (**Table 3**).

We could not obtain significant statistical differences between PDW values after initial treatment and before second-line therapy (splenectomy) [17.25 (72.1) versus 18.35 (55.2); p=0.088] (**Table 3**). There was no statistical differences between PDW values after splenectomy and before immunosuppressive or

Table 1 - General patients' initial clinical and laboratory characteristics.

Patient's characteristics	n (%)
Median age (range)	42 (18-82)
Female/male	49/32
Echymosis	71 (87.6)
Oral/gum bleeding	5 (6.2)
Epistaxis	2 (2.5)
Genital tract bleeding	2 (2.5)
Hematuria	1 (1.2)
Primary ITP/secondary ITP	74/7
Platelet count (x10^9/L) (mean±SD)	17.0±7.0
MPV (fL) (median and range)*	11.35 (3.4)
PDW (%) (median and range)*	17.4 (67.9)
PCT (%) (median and range)*	0.025 (0.037)

MPV - mean platelet volume, PDW - platelet size deviation width, PCT - platecrit, *normal values, MPV (fl) (6.85-11), PDW (%) (15-17), PCT (%) (0.12-0.36), ITP - Immune thrombocytopenia

Table 2 - Treatment outcomes of the patients.

Responses	First-line treatment n=81	Second-line treatment n=18	Alternate second-line treatment n=6
Complete response	64 (79.0)	14 (77.8)	5 (83.3)
Response	13 (16.1)	3 (16.6)	1 (16.7)
No response	4 (4.9)	1 (5.6)	0 (0.0)
Total	**81 (100.0)**	**18 (100.0)**	**6 (100.0)**

Data were expressed as number and percentage (%)

Table 3 - The changes in platelet indices after initial treatment and before second-line therapy (first relaps); the changes in platelet indices after second-line therapy and before alternate.

Platelet indices	After initial treatment n=18	Before second-line therapy (first relaps) n=18	*P*-value	After second-line therapy n= 6	Before alternate second-line therapy (second relaps) n=6	*P*-value
MPV (fL)	8.75 (5.3)	9.55 (1.9)	0.005	8.10 (2.1)	11.5 (5.8)	0.028
PDW (%)	17.25 (72.1)	18.35 (55.2)	0.088	36.85 (49.8)	64.65 (85.9)	0.345
PCT (%)	0.06 (0.18)	0.0125 (0.030)	0.326	0.19 (0.258)	0.0145 (0.050)	0.043

Second-line therapy (second relaps), (median and range). MPV - mean platelet volume, PDW - platelet size deviation width, PCT - platecrit

Table 4 - Pre-treatment and post-treatment values of platelet indices (median and range).

Platelet indices	At diagnosis n=81	After initial treatment n=81	*P*-value	Before second-line therapy n=18	After second-line therapy n=18	Results	Before alternate second-line therapy n=6	After alternate second-line therapy n=6	*P*-value
MPV(fL)	11.35 (3.4)	8.75 (5.3)	0.001	9.65 (6.5)	8.10 (2.1)	0.001	11.5 (5.8)	8.55 (3.3)	0.075
PDW (%)	17.4 (67.9)	17.25 (72.1)	0.115	19.05 (56.9)	36.85 (49.8)	0.469	64.65 (84.9)	48.7 (53.2)	0.345
PCT (%)	0.025 (0.037)	0.06 (0.180)	0.001	0.023 (0.23)	0.19 (0.36)	0.001	0.19 (0.361)	0.225 (0.30)	0.022

MPV - mean platelet volume, PDW - platelet size deviation width, PCT - platecrit

immune modulator therapy [36.85 (49.8) versus 64.65 (85.9); p=0.345] (**Table 3**). Although, there was not significant statistical differences between PCT values after initial treatment and before second-line therapy (splenectomy) [0.06 (0.18) 0.0125 (0.030); p=0.326], but we obtained statistical differences between PCT values after splenectomy and before immunosuppressive or immune modulator therapy [0.19 (0.258) 0.0145 (0.050); p=0.043] (**Table 3**). A summary of all the pre-treatment and post-treatment values of platelet indices are displayed in **Table 4**.

Discussion. Immune thrombocytopenia is an acquired immuno-mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100x10^9/L, and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia.[12] There is no "gold standard" test that can reliably establish the diagnosis. Therefore, the diagnosis of primary ITP is one of exclusion and is based principally on patient history, physical examination, complete blood count, and review of the peripheral blood smear.[12] Recent epidemiologic data suggest that the incidence in adults is approximately equal for the sexes except in the mid-adults (3rd-6th decades), when the disease is more prevalent in women[13,14] and the female-to-male ratio ranges from 1.2-1.9.15 In our study, 60.5% of the patients were females and female to male ratio was 1.5. Immune thrombocytopenia typically has an insidious onset in adults and it normally follows a chronic course.[16] It can be characterized as primary (idiopathic) or secondary to several associated disorders such as infection with hepatitis B, hepatitis C, HIV, *Helicobacter pylori*, and coexistence of SLE, APS, or CVID.[12] Approximately 20% of ITP cases are secondary to other disorders in the United States.[5] In our study, primary ITP comprised of 91.4% of the patients and secondary ITP comprised of 8.6% of the patients. The incidence and etiology of secondary ITP may vary greatly worldwide. In our study group, both pregnancy and SLE were the most common causes in secondary ITP.

Signs and symptoms may vary widely. Mucocutaneous bleeding, including petechiae, purpura, epistaxis, and gum bleeding, is the most common initial manifestation of ITP.[13] In our study group, echymosis was the most presenting sign (87.6%).

Physical examination should be normal aside from bleeding manifestations. Mild splenomegaly may be found in younger patients, but moderate or massive splenomegaly suggests an alternative cause. And also, constitutional symptoms, such as fever and weight loss, hepatomegaly and/or lymphadenopathy may indicate underlying disorder. None of our patients had hepatomegaly and/or splenomegaly on physical examination or performed abdominal ultrasonography. ITP is characterized by isolated thrombocytopenia and bone marrow examination may be informative in patients older than 60 years of age, especially in those with systemic symptoms or in some cases in which

splenectomy is considered.[11,17] We performed bone marrow examination in patients older than 60 years of age and in patients whom splenectomy is considered and found normal findings.

Several factors, including bleeding risk, toxicities of specific therapies, patient age and comorbidities, and patient preference and lifestyle, must be considered before treatment is initiated in adults with primary ITP.[16] The aim of the therapy should be to increase the platelet count to a safe level and/or to prevent further bleeding with minimal toxicities. Treatment should be considered when the platelet count is 20-30x10^9/L, and maintenance of a platelet count 30x10^9/L is an appropriate goal. In our study group, of all the patients' platelet counts were below 30x10^9/L.

The underlying disease should be treated preferably for secondary ITP. In primary ITP, corticosteroids are the standard initial therapeutic agents.[16] Prednisone is the most frequently used drug, and it is given orally at a dose of 0.5-2 mg/kg daily. When corticosteroids used alone, 65-70% of patients respond.[16] The glucucorticoids were used in 77 (95.1%) of the patients population as a first-line treatment option and IVIG was used as a primary therapy in 4 (4.9%) patients. When complete response (79%) and response (16.1%) were evaluated together, a higher resonse rate (95.1%) were obtained with initial therapy.

The management of patients who fail corticosteroids is challenging. The International Consensus report lists more than 10 second-line therapeutic options, such as splenectomy.[16] Splenectomy has a potential of cure in ITP by removing both the primary site of platelet destruction and an important site of antiplatelet antibody production in a large proportion of patients.[18] Platelet counts rise rapidly in 85% of patients. And 60%-65% of patients remain in clinical remission throughout 5-10 years after splenectomy.[19] So, we performed splenectomy in all first relapsing patients (18 of 81 patients, 22.2%). We obtained a higher response rate (complete response+response) with splenectomy as a value of 94.4%. But, after a period of time we encountered with second relapses in 6 patients. In patients whom failed to splenectomy, requires further immunosuppressive therapy including azathioprine, cyclosporine A, cyclophosphamide, vinca alkaloids or immunomodulator drugs as rituximab or thrombopoietin receptor agonists as romiplostim and eltrombopag. Rituximab was used in one patient and a response was achieved. Azathioprine was administered in 5 patients and a response was achieved again. All these 6 patients are alive and 5 of them are still under oral azathioprine therapy.

Mean platelet volume and PDW are increased in ITP was recognized already since 1983.[20] Ntaios et al[20] concludes that increased MPV and PDW may provide a reliable positive diagnosis of ITP in case of thrombocytopenic patients. Kaito et al[21] suggests that MPV and PDW were significantly higher in ITP than in aplastic anemia, and the sensitivity and specificity of platelet indices were sufficient to enable a diagnosis of ITP. In our study, MPV and PDW values were significantly higher than the upper limits and PCT were significantly lower than the inferior limits as expected in ITP patients. We obtained significant statistical differences between MPV values after initial treatment and first relaps (p=0.005), and also between MPV values after splenectomy and before second relaps (p=0.028).

The limitations of our study were as follows: a) the small sample size of study population, b) the minority of first and second relapsing patients, c) borderline P values of platelet indices in first and second relapsing patients, especially due to small sample size, and d) PDW did not significantly change, which may be also due to small sample size. We recommend that larger studies are needed in the future targeting ITP patients to externally cross-validate our findings in a larger cohort of ITP patients.

In summary, primary ITP is an autoimmune disease characterized by isolated thrombocytopenia, and the diagnosis is one of exclusion. Platelet indices provide a lot of clinical information about the underlying conditions of thrombocytopenia. As can be seen apparently, among these parameters, MPV is gradually increasing before first and second relapses, and again normal values are being obtained after appropriate therapies. If, MPV can be followed regularly after both clinical and hematologic remissions, one would be able to pick up early relapses. So, more attention should be paid to MPV for estimating relapses beforehand. Finally, the present results would suggest further studies to encourage the use of platelet indices, especially MPV, as a marker for estimating relapses.

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