



## Research Article

# Use of Single- or Two-dose Pulse Methylprednisolone in the Treatment of Acute Immune Thrombocytopenic Purpura

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### Abstract

**Objectives:** In immune thrombocytopenic purpura (ITP) treatment, the main goal is achieving the platelet level most rapidly for hemostasis. Pulse steroid therapy is common due to the rapid increase in the platelet count within the first 48 hours. Intravenous (IV) pulse steroid therapy is usually administered as a single methylprednisolone dose in the morning. Oral methylprednisolone is generally used as two divided doses due to its half-life, but there is no efficacy study for the use of pulse methylprednisolone therapy in two doses. In this study, we aimed to investigate whether the administration of single or double doses of pulse steroid treatment, which is the cheapest and most economical way to treat patients, differ in terms of platelet count increase rate.

**Methods:** The diagnosis of acute ITP was made based on the appropriate clinical, laboratory, and bone marrow findings and platelet count  $<100.000/\text{mm}^3$ . All the patients were diagnosed with bone marrow aspiration, and they were admitted to the hospital. All patients with platelet counts below  $20000/\text{mm}^3$  and those who had wet purpura or active bleeding were treated. Patients in need of treatment were randomly divided into two treatment groups with closed envelope method. The first group was given IV pulse methylprednisolone (30 mg/kg/day for three days and 20 mg/kg/day for four days) in the early morning hours. The second group received the same daily dosages in two divided doses. Hemoglobin, white blood cell, and platelet counts were evaluated before and on the first, second, third, fifth, and seventh days of treatment. To evaluate the rate of treatment response, platelet counts over  $20.000/\text{mm}^3$ ,  $50.000/\text{mm}^3$ , and  $100.000/\text{mm}^3$  obtained on the first, second, third, and seventh days of treatment were compared.

**Results:** Sixty patients with acute ITP diagnosis receiving pulse steroid therapy were included in the study. Platelet counts of the patients in group 2, who received pulse steroids in two doses, reached  $\geq 20.000/\text{mm}^3$  on the second day [median, (2–3) days],  $\geq 50.000/\text{mm}^3$  on the third day [median, (2.7–3.5) days],  $\geq 100.000/\text{mm}^3$  on the fifth day [median, (3–5) days], which were significantly lower than the platelet counts of the patients in the first group on the third day [median, (2–5) days], fifth day [median, (4–7) days], and seventh day [median, (4–7) days], respectively ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.004$ ).

**Conclusion:** This study shows that administration of IV pulse steroid therapy in two doses is more effective in increasing the platelet count in early period in patients with acute ITP, especially whose platelet count is less than  $20.000/\text{mm}^3$ , and when we prefer to increase the platelet counts rapidly due to risk of intracranial hemorrhage.

**Keywords:** Child; Immune thrombocytopenic purpura; steroid.

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Acute immune (idiopathic) thrombocytopenic purpura (ITP) is the most frequently seen, self-confining cause of acquired thrombocytopenia with a benign course char-

acterized by increased destruction of platelets in reticuloendothelial system.<sup>[1]</sup>

Although the sure cause of ITP is unknown, anti-platelet

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antibodies found in 50%–80% of children are held responsible. These antibodies have mostly an IgG structure, and produced by plasma cells derived from B lymphocytes against glycoprotein IIb/IIIa and Ib/IX, which are the major membrane antigens of platelets. Platelet–antibody complexes are rapidly removed from the circulation by macrophages in the spleen and liver. However, cellular immunity has also a role in the pathogenesis of thrombocytopenia except for anti-platelet antibodies.<sup>[2–5]</sup>

In most patients, acute ITP improves spontaneously without treatment. Although there is insufficient evidence to suggest that the medical treatment changes the natural course of the disease, many clinicians tend to give treatment, and there is still a debate about which treatment regimen should be chosen.<sup>[6–8]</sup> The main aim of the treatment is to prevent intracranial hemorrhage (ICH) seen in about 1% of the cases. The risk of developing ICH is higher within the first days of thrombocytopenia, but it can be seen at any time. Since the platelet counts are usually below 20.000/mm<sup>3</sup>, treatment is recommended for such patients. Corticosteroid, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin are usually used in the treatment.<sup>[9–11]</sup>

Pulse steroid or high-dose steroids are used in the form of short-term infusions, and different glucocorticoid derivatives can be used in this treatment. However, generally, glucocorticoid derivatives with higher anti-inflammatory and immunosuppressive effects, in addition to hypothalamic-pituitary adrenal axis suppression properties, minimal mineralocorticoid effects, rapid clearance, and shorter half-life are being used. Methylprednisolone is preferred for a “pulse steroid” due an elimination half-life of 3 h and its dose-independent stable pharmacokinetic properties.<sup>[12]</sup> Methylprednisolone is usually taken twice daily oral doses.<sup>[13, 14]</sup> This treatment, called “pulse methylprednisolone” treatment or high-dose IV steroid therapy, has been used since 1965. It has become popular in the treatment of different disease groups, including childhood diseases. In the treatment of ITP, corticosteroids act by inhibiting antibody production and antibody-antigen binding, as well as by reducing phagocytosis and vascular permeability.<sup>[1, 9, 10]</sup>

The biosynthesis rate of the cortisol and the basal secretion rate dependent on it together with its plasma levels show episodic changes. This condition is because the basal secretions of CRH and ACTH demonstrate a circadian rhythm, and they are released 7–15 times a day. After each episode, the level of cortisol increases to suppress the secretion of ACTH, it then begins to fall, suppression after a certain point is eliminated, and ACTH secretion is stimulated again. In the early morning rhythm, the rate of cortisol secretion and plasma levels peak in early morning. The level of ACTH

in plasma is parallel to that of cortisol. The degree of negative feedback inhibitory effects of endogenous and exogenous glucocorticoids on ACTH secretion also demonstrates a circadian rhythm.<sup>[15–17]</sup> It is recommended that two-thirds of the daily dose be given in morning, and the remaining dose should be given in the afternoon or evening. There are two reasons for this application. The first one is that ACTH is rapidly released during the early morning, and therefore the extent of the undesirable reduction in ACTH secretion is lower. The second reason is related to the production of the drug plasma profile mimicking the natural circadian rhythm of the plasma glucocorticoid level.

In the treatment of ITP, increasing the platelet count as fast as possible is the main target; and to this end, it is common to use IV pulse steroids because of the rapid increase in platelet counts within the first 48 hours. Pulse steroid therapy is commonly used as a single dose of methylprednisolone in the morning. There is no efficacy study for the use of two doses of methylprednisolone in pulse therapy, which is generally used in two doses because of its shorter half-life.

In this study, we aimed to investigate whether administration of pulse steroid, which is the most effective and economical treatment method, in single or double doses is different in terms of rate of increasing platelet count.

## Methods

The study population consisted of 60 inpatients who were diagnosed as acute ITP and those who received IV pulse steroid therapy given by Eskişehir Osmangazi University Faculty of Medicine, Department of Pediatric Hematology-Oncology. Consent was obtained from Eskişehir Osmangazi University local ethics committee for the study. The diagnosis of acute ITP was determined based on clinical, laboratory, and bone marrow findings and the platelet count of <100.000/mm<sup>3</sup>. Other causes of thrombocytopenia (disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, connective tissue disease, or hypersplenism) were excluded. Each patient included in the study was questioned about his/her complaints, history of infection prior to admission (1–4 weeks before expulsion of URTI, AGE, eruptive disease), drug use, and vaccination. Detailed systemic physical examinations of all patients were performed, and any evidence of bleeding, organomegaly, lymphadenopathy, presence of bone pain, and infection focus were investigated. All patients were diagnosed with bone marrow aspiration, and they were followed up in the hospital. Any complications developed during steroid treatment were recorded. None of the patients had any symptoms of viral infection at the time of di-

**Table 1.** Comparison of clinical and laboratory features of the patients

	Patients receiving once daily doses Group I (n=30)	Patients receiving twice daily doses Group II (n=30)	p
Age (year), median (25%–75%)	6 (3–11)	8 (4.8–11.3)	0.436
Gender, Male (n%)	13 (43.3)	15 (50)	0.605
Medication history (n%)	1 (3.3)	2 (6.7)	0.554
Vaccination history [(Within last 2–8 weeks), (n%)]	1 (3.3)	1 (3.3)	1.0
Platelet counts (/mm <sup>3</sup> )	3000	3000	0.526
Median (25%–75%)	(2000–4000)	(2000–5000)	
Hemoglobin (g/dl), mean±SD, (min.–max.)	11.9±1.3 (9.6–14.6)	12.2±1.3 (9.1–14.2)	0.368
White blood cell count (/mm <sup>3</sup> ),	7750	8600	0.455
Median (25%–75%)	(6400–10425)	(6575–11375)	

agnosis. Written informed consent was obtained from the parents before the study.

All patients with platelet counts below 20000/mm<sup>3</sup> who had wet purpura or active bleeding complaints (nosebleed, gingival bleeding, hematuria, melena, hematemesis, subconjunctival hemorrhage) were treated. The treated patients were randomly divided into two treatment groups. In group 1, intravenous pulse methylprednisolone (30 mg/kg/day for three days, and then 20 mg/kg/day for four days) was given as a single dose in the early morning. In group 2, the same total dose was divided into two doses to be given every 12 hours namely in the morning and in the evening. Follow-up of vital signs (blood pressure, pulse rate, blood glucose, and electrolyte levels) were performed during the treatment period. Hemoglobin, white blood cell, and platelet counts were examined before and 1, 2, 3, 5, and 7 days after steroid therapy. To determine the response rates of both groups, the treatment times elapsed for the platelet counts to exceed 20.000/mm<sup>3</sup>, 50.000/mm<sup>3</sup>, and 100.000/mm<sup>3</sup> on the first, second, third, fifth, and seventh days of the treatment were compared. To achieve standardization in the treatment protocol, treatment was given for 7 days in both groups regardless of the increase in platelet counts.

Data analysis was performed using the SPSS Windows 18 (Statistical Package for Social Sciences: SPSS Inc. Chicago, IL, USA) package program. In the descriptive statistical analysis, the mean±standard deviation (minimum-maximum) values were compared with the one-way Anova test for the variables with normal distribution, while the median (25%–75%) values were given for the non-normally distributed variables. The results were compared using the Mann–Whitney U test. Chi-square (x<sup>2</sup>) test or Fisher's exact test was used to compare categorical data, and Student's t-test was used to compare continuous data. p≤0.05 was accepted as the significance level for all analyses.

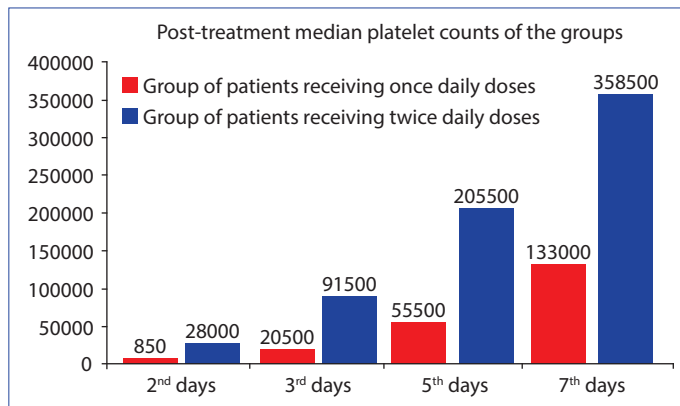
## Results

Sixty patients who received a single dose (group 1, n=30) or two doses (group 2, n=30) of pulse steroid treatment were included in the study. The median ages of the patients receiving single or two doses were 6 (3–11) years, and 8 (4.8–11.3) years respectively, without any statistically significant intergroup difference (p=0.436). Male patients consisted of 43.3% (n=13), and 50% (n=15) of the patient population in groups 1 and 2, respectively, without any intergroup difference (p=0.605, Table 1).

In both groups, three patients received antibiotherapy due to a history of upper respiratory tract infection. There were two patients with a history of immunization within 2–8 weeks prior to diagnosis. All the patients included in this study were hospitalized by considering their platelet counts and clinical findings. None of the patients included in the study had significant hepatomegaly, splenomegaly, and lymphadenopathy. Intracranial bleeding or other serious bleeding complications were not observed in any patient. The median platelet, mean hemoglobin, and median leukocyte counts were statistically similar when the patients were compared in terms of the exact blood count values at the time of diagnosis (Table 1).

The median platelet count of the patients in the second group who received two doses of pulse steroid was found to be statistically significantly higher than the patients in the first group who received single-dose pulse steroids on the second, third, fifth, and seventh days of treatment (p<0.001, p<0.001, p<0.001, p<0.001, respectively Figure 1). There was no statistically significant difference within the first 24 hours of treatment.

To determine the response rate of the treatment, the time to achieve platelet counts above 20.000/mm<sup>3</sup>, 50.000/mm<sup>3</sup>, and 100.000/mm<sup>3</sup> was compared between the two groups on the days 1, 3, 5, and 7 of the treatment. In group



**Figure 1.** Intergroup comparisons of post-treatment median platelet counts.

2 patients who received two doses of pulse steroids, the median time intervals elapsed to attain platelet levels were  $\geq 20.000/\text{mm}^3$  [median 2 (2–3) days],  $\geq 50.000/\text{mm}^3$  [median 3 (2.7–3.5) days], and  $100.000/\text{mm}^3$  [median 5 (3–5) days], while in group 1 receiving single doses median time intervals were significantly shorter [median 3 (2–5), 5 (4–7), and 7 (4–7) days, respectively] ( $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.004$ , respectively) (Figure 2).

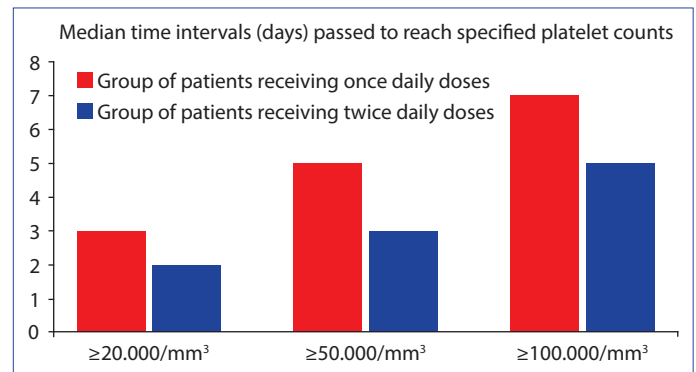
On the seventh day of the treatment, platelet count was higher than  $100.000/\text{mm}^3$  in all patients who received steroid therapy in divided doses. However, only 11 patients (36.7%) in group 1 receiving single-dose therapy could not increase the number of platelets above  $100.000/\text{mm}^3$  ( $p < 0.001$ ).

In group 1, the number of patients with a platelet count above  $20.000/\text{mm}^3$  at 24 h (0%), 48 h ( $n = 7$ ; 23.3%), and 72 h ( $n = 16$ ; 53.3%) after initiation of treatment were indicated as shown in parentheses, while the corresponding number of patients in group 2 who received pulse steroid in two divided doses were 1 (3.3%), 23 (76.7%), and 29 (96.7%), respectively. The intergroup difference between the 48<sup>th</sup> and 72<sup>th</sup> hour estimates was statistically significant ( $p < 0.001$  and  $p < 0.001$ , respectively).

When the patients were evaluated in terms of treatment complications, none of the patients had hypertension and electrolyte disorder. Two (6.7%) patients in the single, and five (16.7) patients in the two-dose group developed hyperglycemia, without a statistically significant difference between groups ( $p = 0.228$ ). Patients with fasting blood sugar levels without ketonemia improved with dietary therapy, and hyperglycemia did not persist during control visits.

## Discussion

This study showed that the administration of the short-term IV pulse methylprednisolone for the treatment of acute ITP



**Figure 2.** Evaluation of the time intervals estimated to reach platelet counts of  $\geq 20.000/\text{mm}^3$ ,  $\geq 50.000/\text{mm}^3$ , and  $\geq 100.000/\text{mm}^3$  in both groups.

in two divided doses instead of single dose affected the rate and amount of increase in platelet counts.

Since medical treatment in ITP does not resolve the underlying pathology and provide full recovery together with side effects of the medications, medical treatment of acute ITP is usually questioned. The current treatment approach is based on the principle of “watchful waiting.”<sup>[18]</sup> Treatment in acute ITP aims to increase the platelet count to a sufficient level to prevent bleeding and to keep the duration of thrombocytopenic state as shorter as possible, rather than as a treatment directed at etiology. Therefore, the goal of the treatment is not to achieve normal platelet count, but to achieve the highest level of platelets to provide hemostasis. The main aim of the treatment is to prevent ICH, which is seen in about 1% of the cases.<sup>[9, 19]</sup>

Since the thrombocyte count is usually below  $20.000/\text{mm}^3$  in patients who developed ICH, medical treatment is generally recommended for such patients.<sup>[1, 10, 11, 20, 21]</sup> Although there is no efficacy study in the divided dose administration of pulse steroid therapy in pediatric patients with ITP, there are studies in the literature comparing steroid therapy with different doses (oral, intravenous), immunoglobulin (IVIG), and anti-D therapies.<sup>[21–26]</sup> Albayrak et al.<sup>[27]</sup> compared IVIG (0.5 g/kg/day for 4 days) and methylprednisolone (30 mg/kg/day or 50 mg/kg/day for 7 days, oral) in the treatment of ITP, and could not find any difference as for increase in platelet counts. Tarantino et al.<sup>[28]</sup> compared IVIG and anti-D treatments, and similarly reported lack of any statistically significant difference. Erduran et al.<sup>[29]</sup> compared oral methylprednisolone (30 mg/kg/day for 3 days, and 20 mg/kg/day for 4 days) with IVIG treatments, and found similar effects of both medications in the acute treatment of ITP. In our study, when the steroid treatment was given as divided doses, the fact that the time to increase the platelet counts above  $20.000/\text{mm}^3$  was found to be shorter supports this route of administration of this treatment.

In patients presenting with ITP, clinically significant bleedings have been shown to occur within the first 48 hours in 62% of the cases.<sup>[30]</sup> Therefore, the therapies that increase the platelet counts maximally as fastest as possible on the second day of treatment carry importance.<sup>[31,32]</sup> Blanchette et al.<sup>[22]</sup> reported that in patients with platelet counts below 20.000/mm<sup>3</sup> with IVIG (1 g/kg, 2 days) and prednisone therapy (4 mg/kg/day, oral), platelet counts reached above 50.000/mm<sup>3</sup> 2 and 4 days after onset of these treatments, respectively. While in untreated patients, this interval was as long as 16 days. In our study, after a median of 3 days, the platelet counts reached above 50.000/mm<sup>3</sup> in patients in whom IV pulse steroid was given in two divided doses. Also, in patients who received steroids in two doses, platelet counts were significantly higher after the first day, especially at 48 and 72 hours. Therefore, it is thought that the treatment method that elevates the platelet counts fastest should be preferred.

Also in our study, the number of patients whose platelet counts were over 20.000/mm<sup>3</sup> beyond 48–72. hours after onset of the treatment differed statistically significant between the groups. The mean percentages of patients with platelet counts greater than 20.000/mm<sup>3</sup> at 48 and 72 hours after treatment in those receiving once daily doses were 23.3% (n=7) and 53.3% (n=16), respectively, while in patients receiving two divided daily doses the corresponding estimates were 76.7% (n=23), and 96.7% (n=29), respectively. Previous studies have compared different treatment protocols. Blanchette et al. compared the patients whose platelet counts were above 20.000/mm<sup>3</sup> at 72 hours, and found that the number of patients who received IVIG treatment had been found to be significantly lower than those receiving anti-D.<sup>[21]</sup>

The side effects associated with steroid use are closely related to the dose and dosage schedule.<sup>[1,9,10,12]</sup> Side effects of steroids such as increased appetite, weight gain, insomnia, increased blood pressure, and hyperglycemia are not expected in short-term treatments such as in our study. Steroid side effects were not statistically different in our patients.

Although steroid treatment delivered in two divided doses, and platelet count increase earlier, as is seen in our study, since duration of treatment is 7 days in both groups, there will be no difference in the cost-effectiveness when hospital stay is taken into consideration. The fact that treatment is given in two doses instead of a single dose increases the nurse workload and application of cortisol not in accordance of the rhythmic physiological release of the cortisol in the body are among the handicaps of the study.

These results suggest that the delivery of IV pulse steroid therapy in two doses, similar to oral dosage schedule, as

early as possible in consideration its shorter half-life in the treatment of acute thrombocytopenia in patients with acute ITP whose platelet counts are lower than 20.000/mm<sup>3</sup> because of the risk of intracranial bleeding is effective in providing faster increase in platelet counts within a short term.

#### Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship contributions:** Concept – A.B.T., Ö.B.; Design – A.B.T., Ö.B.; Supervision – A.B.T., Ö.B.; Materials – A.B.T., Z.C.Ö.; Data collection &/or processing – A.B.T., Z.C.Ö.; Analysis and/or interpretation – A.B.T., Z.C.Ö., Ö.B.; Literature search – A.B.T.; Writing – A.B.T., Z.C.Ö., Ö.B.; Critical review – A.B.T., Ö.B.

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