

A randomized and comparative study of intravenous immunoglobulin and mega dose methylprednisolone treatments in children with acute idiopathic thrombocytopenic purpura

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The most common cause of mortality in childhood acute idiopathic thrombocytopenic purpura (ITP) is intracranial hemorrhage (ICH), which occurs in about 0.1% of children with platelet counts below 20,000/ μ l.

Forty-two children (1-13 years) with ITP and platelet counts \leq 20,000/ μ l were randomly divided into two groups. Twenty patients received mega-dose methylprednisolone (MDMP) in a dosage of 30 mg/kg/d for three days and 20 mg/kg/d for four days. Twenty-two patients received intravenous immunoglobulin (IVIG) in a dosage of 1 g/kg/d two days. Platelet counts of the patients were determined at diagnosis, at 2, 4, 7, 14, 30, 60, 90, 120, 150, and 180 days and at three-month intervals after the 6th month. The mean platelet counts of both groups gradually increased and peaked on the 7th day ($p>0.05$). There were no significant differences between the mean platelet counts of patients, in the two groups on treatment days 0, 2, 4, 7, and 14. The mean time for achievement of platelet counts above 20,000/ μ l in the MDMP group and the IVIG group was 4.1 and 2.9 days ($p<0.05$) and above 50,000/ μ l was 5.0 and 5.2 days ($p>0.05$), respectively. The percentages of patients with platelet counts above 20,000/ μ l at the 2nd day of the treatment were 50% in the MDMP group, and 86% in the IVIG group ($p<0.05$). No significant differences were observed in the mean platelet counts of the two groups treatment days 30, 60, 90, 120 and 180 ($p>0.05$). Chronic ITP developed in five patients (25%) in the MDMP group, and in four patients (18%) in the IVIG group ($p>0.05$).

Intravenous immunoglobulin (IVIG) (1 g/kg/d for 2 days) and MDMP treatments (30 mg/kg/d for 3 days, 20 mg/kg/d for 4 days, orally) are equally effective in the treatment of acute ITP. Because of its nonbiologic source, lower cost, fewer side effects and oral use, we prefer oral preparations of MDMP in the treatment of childhood ITP.

Key words: intravenous immunoglobulin, mega-dose methylprednisolone, idiopathic thrombocytopenic purpura.

Childhood acute idiopathic thrombocytopenic purpura (ITP) is generally a self-limited disorder with an excellent prognosis^{1,2}. Sixty percent of affected children have a history of an infectious illness within 21 days before onset of purpura^{3,4}. In over 80% of children with acute ITP, permanent and complete recovery occurs, irrespective of treatment⁵.

The major concern in children with ITP is the risk of intracranial hemorrhage (ICH). This complication occurs in approximately 0.1% of

children with ITP and platelet counts below 20,000/ μ l⁶. The risk of ICH is highest within the first 48 hours after diagnosis of ITP⁷. Fear of this complication prompts many physicians to recommend treatment for children with such counts.

Numerous pharmacological and surgical treatments have been employed for the treatment of ITP, but for initial therapy in children with acute ITP, either corticosteroids or intravenously administered immunoglobulin (IVIG) have been

shown to be effective in increasing platelet count rapidly⁸⁻¹². In a comparative study of IVIG (0.5 g/kg per day for 5 days) and very high oral doses of methylprednisolone therapy (30 mg/kg per day for 7 days and 50 mg/kg per day for 7 days), these treatment protocols were reported to be equally effective in children with ITP¹³. However, the effectiveness of these two therapies remains to be investigated in children in a randomized fashion. We therefore studied the rate of platelet response to available treatments. The purpose of this study was to further define treatment options in a comparison of platelet responses to IVIG (1 gm/kg/d for 2 days) and orally administered mega-dose methylprednisolone (MDMP) (30 mg/kg/d for 3 days and 20 mg/kg/d for 4 days) in children with ITP. The doses in this study have not been compared previously in the literature.

Material and Methods

Forty-six children aged between 1-13 years with ITP and platelet counts $\leq 20,000/\mu\text{l}$ were included in the study. The patients were randomly separated into two groups according to their treatments. Three patients in the MDMP treatment group and one patient in the IVIG treatment group were excluded from the study because of their irregular attendance in the follow-up period. Twenty patients (11 girls, 9 boys) aged between 1-13 years received oral doses of MDMP treatment (Prednol-L^R) in a dosage of 30 mg/kg/d for three days and 20 mg/kg/d for four days before 9 a.m. after breakfast as described by Özsoylu et al¹⁰. Salt intake was not restricted and administration of MDMP was abruptly discontinued after seven days. Twenty-two patients (13 girls, 9 boys) aged between 1-12 years received IVIG (Octagam^R) in a dosage of 1 g/kg/d for two days.

We chose other dosage regimens of MDMP and IVIG in this study because these dosages had not been standardized in the treatment of children with ITP to date^{4,5,7-21}. The criteria for the diagnosis of acute ITP were as follows:

- Isolated thrombocytopenia ($\leq 20,000/\mu\text{l}$)
- Negative throat culture, LE cell, anti-double stranded DNA (ds-DNA), anti-nuclear antibody (ANA), direct Coombs' test.
- Negative septicemia, disseminated intravascular coagulation, Evans' syndrome and active infection.

- Negative history of blood transfusion and of drug intake causing thrombocytopenia, splenectomy, and chronic ITP.
- Normal or increased megakaryocytes in bone marrow.
- Physical signs such as petechial, purpuric, and ecchymotic skin eruptions.
- Absence of familial thrombocytopenia.

The patients were hospitalized until their platelet counts increased above $20,000/\mu\text{l}$. Platelet counts were obtained at diagnosis, at days 2, 4, 7, 14, 30, 60, 90, 120, 150, and 180 and at three-month intervals after the 6th month. Platelet counts were determined by Coulter STKS machine. Ig A, Ig G, Ig M, and C³ and C⁴ levels were established in recurrent patients.

The results were assessed as early and late periods according to the responses of patients to the treatment. The first 14 days after beginning of the treatment was considered as the early period, and a follow-up period of at least six months after the 14th day was considered as the late period. Persistent platelet counts lower than $100,000/\mu\text{l}$ for more than six months were considered as chronic ITP.

If the platelet counts decreased below $20,000/\mu\text{l}$ during the follow-up period, the treatment model was switched to another one.

Statistical Analyses

The probabilities of significant differences between the platelet counts on the same days for independent groups were assessed by Mann-Whitney U test. Wilcoxon matched pairs signed-ranks test was used for determination of the differences between platelet counts on the different days for dependent groups. Fisher's exact chi-square test was used to compare the rates of remission and the rates of patients with platelet counts $< 20,000/\mu\text{l}$, $< 50,000/\mu\text{l}$ and $< 100,000/\mu\text{l}$ on the same days for both groups.

Results were calculated as arithmetic means and standard deviation ($\bar{x} \pm \text{SD}$).

Results

The physical examination findings and baseline laboratory data for patients were typical for childhood ITP. Average platelet counts of the patients at diagnosis were $7,409/\mu\text{l}$ (1,000-20,000/ μl) in the MDMP group and $6,850/\mu\text{l}$

(1,000-18,000/ μ l) in the IVIG group ($p > 0.05$). No patient had positive ANA, anti-DNA, direct Coombs' test, LE cell or throat swab culture.

Results of Patients in the Early Period

The platelet counts of the patients at diagnosis and on treatment days 2, 7 and 14 in both groups are shown in Figure 1. The mean platelet counts of patients in both groups gradually increased and peaked at the 7th day. There were no significant differences between the mean platelet counts of the two groups at days 2, 4, 7 and 14 ($p > 0.05$). The mean platelet counts of both groups days 2, 4, 7 and 14 were significantly higher than the counts at diagnosis ($p < 0.001$).

The mean times until platelet counts increased above 20,000/ μ l in the MDMP and IVIG groups were 4.1 and 2.9 days ($p < 0.05$), and above 50,000/ μ l were 5.0 and 5.2 days ($p > 0.05$), respectively.

The percentages of the patients with platelet counts above 20,000/ μ l at the 2nd day of the treatment were 86% (19 patients) in the IVIG group and 50% (10 patients) in the MDMP group ($p < 0.05$) (Table I). However, there were no significant differences between the percentages of the patients with platelet counts above 20,000/ μ l, 50,000/ μ l and 100,000/ μ l in the MDMP and the IVIG groups at treatment days 4, 7 and 14, reciprocally ($p > 0.05$).

Table I. Percentages of the Cases with Platelet Counts Above 20,000/ μ l Over Time

Days	IVIG group n (%)	MDMP group n (%)	p
2	19 (86)	10 (50)	<0.05
4	21 (95)	19 (95)	>0.05
7	21 (95)	19 (95)	>0.05
14	20 (91)	19 (95)	>0.05

IVIG: intravenous immunoglobulin; MDMP: mega-dose methylprednisolone.

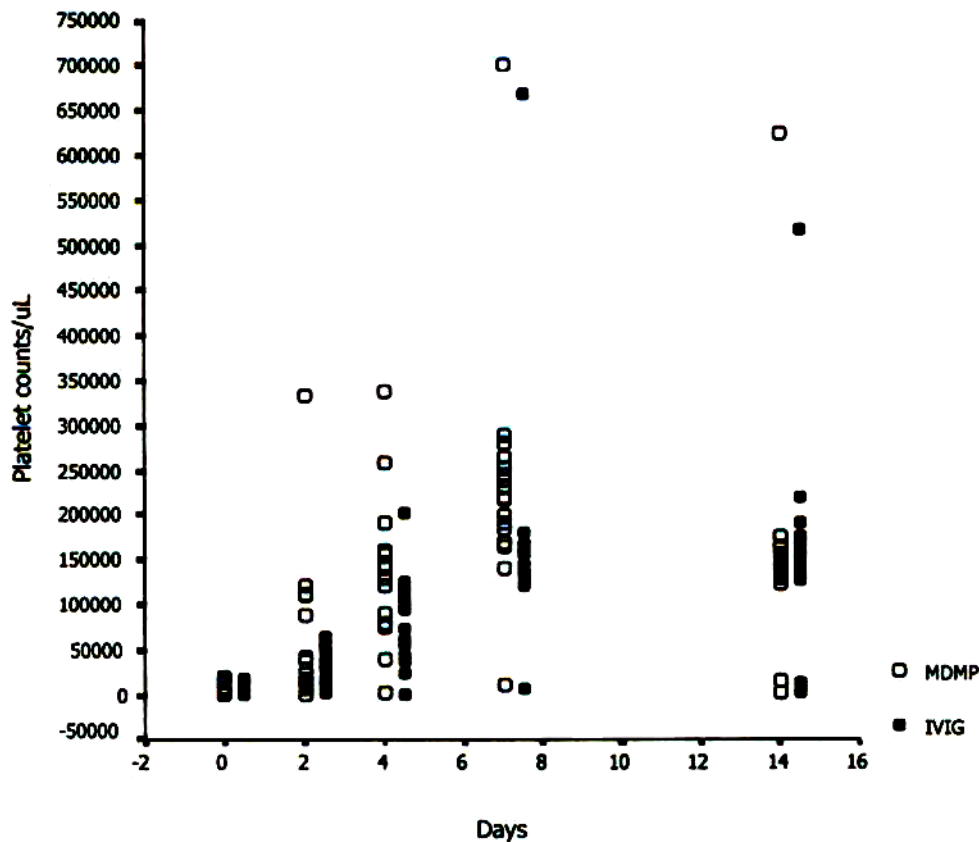


Fig. 1. Platelet counts of patients in megadose methylprednisolone (MDMP) and intravenous immunoglobulin (IVIG) groups at diagnosis, and at day 5 2, 4, 7, and 14.

Platelet counts of six patients (30%) in the MDMP group were higher than 100,000/ μ l, while platelet counts of none of the patients in the IVIG group were higher than 100,000/ μ l at the 2nd day of the treatment ($p < 0.05$).

Two patients in the MDMP group and three patients in the IVIG group, in whom platelet counts were lower than 20,000/ μ l, received IVIG and MDMP, respectively, as the second-line treatment.

None of the patients developed ICH.

Results of Patients in the Late Period

The mean platelet counts of cases in both groups at days 30, 60, 90, 120 and 180, excluding second-line treatment patients, are shown in Table II. There were no significant differences between the mean platelet counts at days 30, 60, 90, 120 and 180 ($p > 0.05$).

normal level without medical intervention. Behavioral disturbance appeared in three patients. No child had hyperglycemia.

Five patients had fever (temperature, 37.6-39°C), headache and vomiting after infusion of IVIG. Lumbar puncture was not done because physical examination failed to show evidence for meningeal irritation. These complaints improved with paracetamol. One patient had macular eruption which disappeared spontaneously within three days. No hemolysis or anaphylaxis developed in the patients.

Discussion

The aim of therapy for ITP is the assumption that a rapid reversal of thrombocytopenia will minimize the risk of ICH^{4,22}. Although children with acute ITP and platelet counts below 20,000/ μ l are at risk of life-threatening

Table II. Mean Platelet Counts of Both Groups Excluding the Second-line Treatment Patients

Days	Platelet counts (μ l)		p
	IVIG (x+SD) (n=22)	MDMP (x+SD) (n=20)	
30	209.133 (102.000-478.000)	257.500 (38.000-640.000)	>0.05
60	253.866 (33.000-610.000)	299.071 (112.000-448.000)	>0.05
90	281.400 (119.000-621.000)	217.429 (123.000-388.000)	>0.05
120	265.867 (62.000-436.000)	262.357 (104.000-327.000)	>0.05
150	275.733 (126.000-406.000)	265.643 (55.000-473.000)	>0.05
180	281.933 (118.000-415.000)	256.143 (101.000-464.000)	>0.05

IVIG: intravenous immunoglobulin; MDMP: mega-dose methylprednisolone.

During the follow-up in the late period, six patients in the MDMP group and seven patients in the IVIG group received the second-line treatment. Chronic ITP developed in five patients (25%) in the MDMP group (in one, spontaneous remission was observed after 16 months) and in four patients (18%) in the IVIG group ($p > 0.05$). One patient in the MDMP group and three patients in the IVIG group went into remission in the late period.

Adverse Effects

In Group I, two patients complained of gastric discomfort, which responded to antacid therapy. Increase of appetite, weight gain and mild cushingoid appearance with malar erythema appeared in all patients. Two had a transient increase of blood pressure which returned to

hemorrhage^{5,14}, Lelleyman⁶ claimed that ICH in childhood ITP may have a precipitating cause and is not necessarily fatal, and that ICH can occur at any time during the course of the illness when the platelet count is less than 10-15,000/ μ l.

Since the 1940s, corticosteroids have been used in the treatment of adult and childhood ITP. Various effects of prednisone have been observed on the platelet counts of patients with ITP. In several studies, prednisone (2-4 mg/kg/d) in divided doses three times daily was shown to increase the platelet counts in some patients^{3,4,15,23}, while in other studies no differences were found between the responses of patients who were treated with prednisone and those untreated^{16,24}. Özsoylu et al.⁸ stated that prednisone treatment (2 mg/kg/dose) delays spontaneous remission in children with ITP.

Today, new treatment regimens such as IVIG and high/mega-dose methylprednisolone have been used in the treatment of patients with ITP because prednisone is not a satisfactory and effective treatment. Otherwise, there are a number of studies such as the one by Blanchette et al.⁵ that support the use of oral corticosteroids (4 mg/kg/d) as therapy for children with ITP. Although adverse effects after MDMP were not reported by some investigators⁹, others observed glycosuria, weight gain and behavioral changes in patients who received prednisone at doses greater than 3-4 mg/kg/d^{17,18}. It was suggested that potential toxicity of very high-dose parenterally administered corticosteroids (over 4 mg/kg/d of oral prednisone) did not appear warranted^{5,17,18}. We did not observe glycosuria; weight gain and increase of appetite appeared in all patients, and behavioral disturbance appeared in three patients treated with MDMP. Intravenous immunoglobulin (IVIG) use in the treatment of ITP was begun after it was shown to be effective by Imbach et al.¹¹ IVIG was first used in a dosage of 0.4 mg/kg/d for five days¹¹. It was suggested that IVIG in a dosage of 1 g/kg/d for two days caused a greater increase in the platelet counts of patients with ITP^{14,25}. It was reported that single dose IVIG (0.8 g/kg) had a similar effect as IVIG therapy in a dosage of 1 g/kg/d for two days in increasing the platelet counts of patients with ITP^{5,26}. Side effects of IVIG such as fever (>38.5°), nausea, vomiting, headache and meningism may be seen, and symptoms were more frequent for the higher dose (1 g/kg/d for 2 days). In general symptoms disappeared within 24 hours and were controlled with paracetamol⁵. These side effects of IVIG occurred in our five patients (22.7%) and disappeared with oral paracetamol. MDMP was first used in the treatment of children with ITP by Özsoylu et al.^{8,9,19} and it was suggested that MDMP should be used in the treatment of childhood ITP as the first-line therapy.

Various results have been observed in ITP patients treated with IVIG or MDMP to increase platelet counts and to obtain safer platelet levels in a short time^{10,13,14}. Özsoylu et al.¹⁰ suggested that IVIG (0.4 g/kg/d for 5 days) and MDMP (30 mg/kg/d for three days, 20 mg/kg/d for 4 days, perorally) treatments had similar effects in increasing the platelet counts above 150,000 μ l, but proposed MDMP as the first-line therapy in the treatment of children with ITP because it is

cheaper than IVIG. In addition, no statistically significant differences were found between IVIG (0.4 g/kg/d for 5 days), MDMP (30 mg/kg/d for 7 days) and MDMP (50 mg/kg/d for 7 days) treatments in increasing platelet counts in children with ITP, and the use of MDMP treatment (30 mg/kg/d) was proposed¹³. IVIG preparations are expensive. At the time of preparation of this report, relative costs in Turkey (per kg) for IVIG therapy was 90 times the cost of oral MDMP. IVIG treatment is not seen as cost effective in comparison to MDMP treatment.

We compared the effects of orally administered MDMP (30 mg/kg/d for 3 days, 20 mg/kg/d for 4 days) and IVIG (1 g/kg/d for 2 days) treatments in children with acute ITP with platelet count $\leq 20,000/\mu$ l. IVIG caused a greater increase in the percentage of patients with platelet counts above 20,000/ μ l at the 2nd day of treatment than MDMP treatment, while platelet counts higher than 100,000/ μ l were determined in six patients in the MDMP group and in none of the patients in the IVIG group at the 2nd day of the treatment. MDMP treatment caused a greater increase in the platelet counts in a small number of patients than IVIG treatment. In addition, platelet counts of patients treated with IVIG increased above 20,000/ μ l significantly earlier than patients treated with MDMP. Although MDMP and IVIG treatments showed similar effects on the rates of developing chronic disease and recurrence in long-term follow-up in children with ITP, the number of children was too small to allow a definitive conclusion to be drawn.

In this study, MDMP and IVIG showed similar effects for increasing platelet counts in the early period and on the platelet counts at the long-term follow-up period in children with acute ITP. IVIG is an expensive biologic product and causes fever (38.5 °C), meningism and injection reaction in patients. MDMP is a nonbiologic product and cheaper than IVIG. Because of the lower cost, oral route, nonbiologic source and fewer side effects, we propose use of oral MDMP in the treatment of ITP, if the patients do not have the acute infectious disease.

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