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PERSPECTIVES IN MEDICAL SCIENCES

Megadose Methylprednisolone for Childhood Idiopathic Trombocytopenic Purpura (ITP)

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Abstract: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder. Decreased platelet survival is the main pathogenesis, which is related to platelet antibodies (APA). The levels of these antibodies are correlated with relapse and remission which was shown for the first time by our group. Although APA levels decrease in remission they do not disappear as we have shown. Among the several appraches to ITP treatment, oral megadose methylprednisolone is found to be the cheapest and most effective one. For oral MDMP treatment, admission of the patients is not required and there is some evidence that chronic ITP could be prevented by this approach.

Key Words: Mega dose methylprednisolone, idiopathic trombocytopenic purpura

Introduction

Thrombocytopenias could be primary or secondary (Table 1). Although secondary thrombocytopenias are more common, idiopathic thrombocytopenic purpura (ITP) is the most frequent among the primary thrombcoytopenias.

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder. Therefore, I would like to emphasize that every autoimmune thrombocytopenic purpura is not ITP (1). ITP abbreviation has also been used for infectious thrombocytopenia in addition to immune thrombocytopenia. Since their pathogenesis is similar, idiopathic thrombocytopenic purpura should be diagnosed by exclusion.

The diagnosis of ITP should be based on decreased platelet counts (usually less than 50000/µl) with excessive or normal megakaryocytes in the bone marrow. Hepatosplenomegaly and lymphadenopathy should not be detected and no recent history of drug ingestion including aspirin, platelet or blood transfusions should be present. In the mean time, underlying diseases such as lupus erythemathosus, Coombs positivity (Evans syndrome), hematologic malignancies, anti phospholipid antibodies, thrombotic thrombocytopenic purpura and group A - β hemolytic streptococcus infection should also be excluded (2-4). If it is possible, antiplatelet antibodies (APA) should be shown by Handin-Stossel (4,5) method as modified by us (2).

When the thrombocytopenic period is shorter than 6 months those patients are accepted as acute ITP. If thrombocytopenia persists for longer than 6 months chronic thromocytopenia term is used.

Markedly shortened life-span of platelets in idiopatic thrombocytopenic purpura during the thrombocytopenic phase has repeatedly been demonstrated (6-10). This is related to circulating antibodies first stongly suspected in 1951 and confirmed many times since then (11). However the level of antiplatelet antibodies in relapse and remission was not correlated until our studies (2-4,12).

Decreased platelet survival is essential in the pathogenesis of ITP (6-10) which is improved with remission but not normalized in most, if not all cases (5,10,13), also as shown by us (2) (Table 2). We have also shown the persistence of antiplatelet antibodies in

Table 1. Causes of Thrombocytopenias.

I.Primary		
A.Familial	a)	Hereditary:
		- autosomal dominant : May-Heyglin anomly, Sebastian (SBS), Fechtner (FS), Epstein (EPS), macrothrombocytopenia, nephritis, deafness syndrome
		- autosomal recessive (chronic thrombotic thrombocytopenic purpura (TTP), type II B von Willebrand disease
		- X-linked : Wiscott-Aldrich syndrome
	b)	Non-hereditary: TAR syndrome, amegakaryocyte thromboctopenia, neonatal alloimmune thrombocytopenia, cyclic thrombocytopenia
B) Non-familial: idiopathic thrombocytopenic purpura (ITP)		
II-Secondary: due to	a)	Viral infections
	b)	Sepsis
	c)	Drugs
	d)	DIC
	e)	Toxic (uremic etc)
	f)	Collagene disorders
	h)	Bone –marrow suppression
	g)	Leukemia and malignant disorders
	k)	Cyanotic heart disease
	l)	Alloimmune
	m)	Neonatal (septic. Viremic, etc)

Table 2. mean platelet survival in control subjects and ITP patients in remission: Pagocytosis of donor platelets by autologous leukocytes following sensitization by the own sera indicated.

Age /sex (yr)	Platelet count (µl)	Platelet life-span (days)	Phagocytosis of Platelets (CPM)	Remarks
13 /F		8.0		Normal
9 /F		9.0		Normal
15 /M		9.2		Normal
10 /M		8.9		Normal
15 /F	48000	8.0	1.325	Aplastic anemia
12 /M	52000	8.6	1.289	Aplastic anemia
Adult / M			1.536	Blood donor
Adult / M			1.594	Blood donor
Adult / M			1699	Normal
Adult / M			1682	Normal
Chronic ITP cases in remission				Splenectomized and inremission
15 /F	304000	8.6		2 yr
15 /F	172000	2.8*	2.741	5 yr
12 /M	184000	4.4	2.454	6 yr
	Acute ITP cases in remission			Duration of remission
11 /F	200000	7.4	2.936	6 yr
11 /M	172000	7.8		3 yr
11 /M	204000	2.0	3.212	10 mo
7 /M	1400000	3.0	2.884	> 1 yr
9 /M	172000	5.4		> 2 mos
12/M	396 000	3	2134	> 3 mos
12/M	324000	2.1	2809	> 6 mos
4/M	236000	1.6	2244	> 4 mos
2,5/F	151000		2324	> 4 mos
6/F	368000		1986	> 7 mos

remission for up to 6 years (2) . Platelet counts in relapse and remission were well correlated with antiplatelet antibody levels studied only by us, so far (4,12) (Figure 1-3).

This most likely indicates that normalization of platelet counts in remission depends on compensatory over production of platelets. This latter finding could be important in the explanation of thrombocytopenia of newborns whose mothers had had ITP in their childhood.

As a rule of thumb, treatment modalities should be evaluated following the correct diagnosis and they should be effective, economical, practical, applicable, ethical (and ecological).

For the treatment of ITP, splenectomy, conventional corticosteroid, cytoxan, iv vincristine, plasmaphoresis, vit C, interferon, interleukin, cyclosporine, anti D serum, Fc fragments of gammaglobulin, danazol, iv IgG (IVIG) and megadose methylprednisolone (MDMP) have been used. The presence of many alternatives for the treatment of a disorder usually indicates that the ideal approach has not yet been accepted by all researchers.

The necessity of treatment of acute ITP patients is debatable, since its prognosis is very favorable, especially in patients under 10 years of age. Some authors believe that, with few exceptions, treatment is not required (14,15), since platelet counts generally improve within a few months without treatment (12).

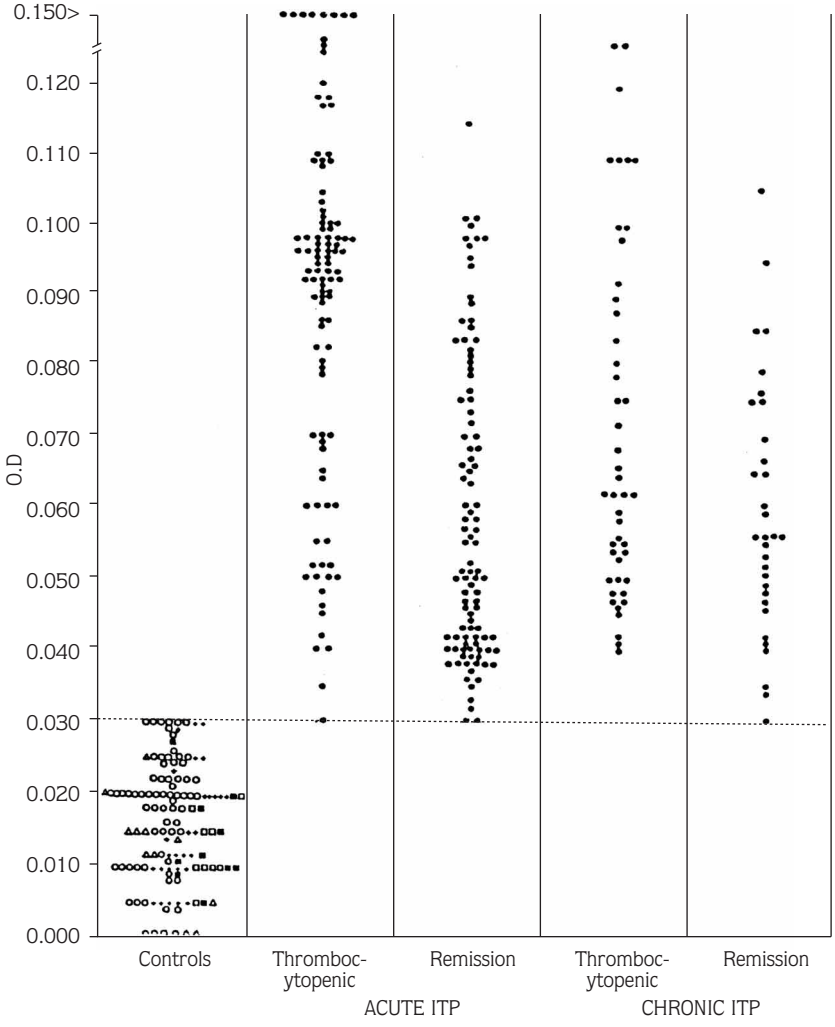

Figure 1. Antiplatelet antibodies (APA) in acute and chronic ITP parients in thrombocytopenic period and in remission.

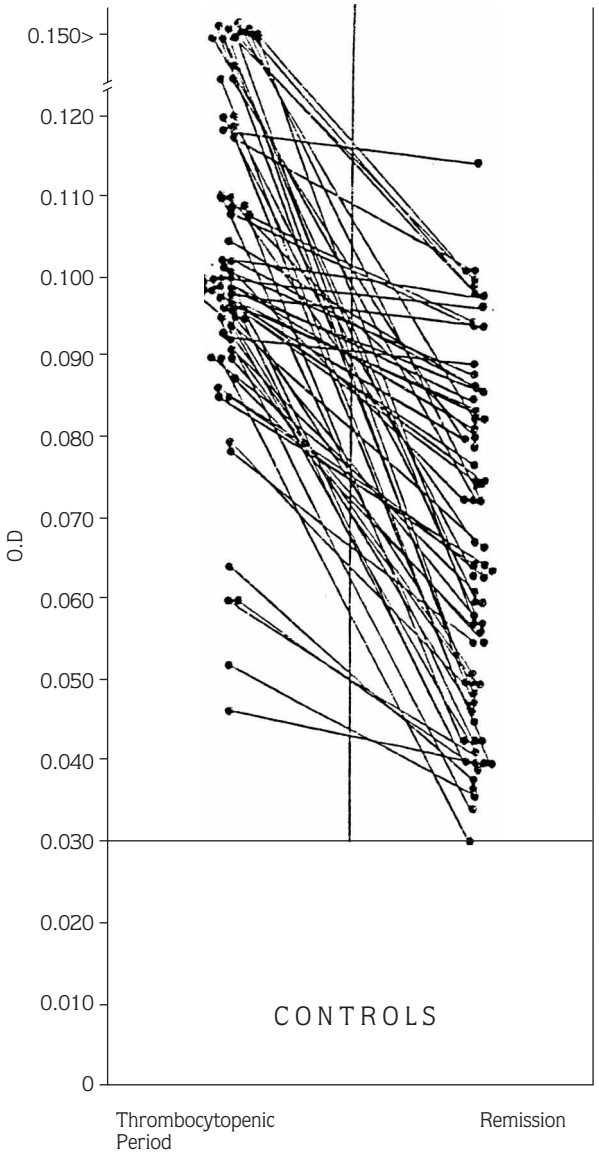

Figure 2. Antiplatelet antibody levels of 67 Children with acute ITP in thromboytopenic Period with corresponding remission.

The main objective of any form of treatment should be to raise the platelet counts rapidly in order to reduce the risk of bleeding, especially intracranial hemorrhage.

Conventional corticosteroid was the drug of choice for the treatment in chronic as well as acute ITP until 1985 when comparative oral corticosteroid, IVIG studies were carried out. Despite similar results obtained in acute childhood ITP treatment, in all rapid responders with both approaches, IVIG has been suggested more often despite its high cost and important side effects (16,17).

We have conducted an original study for the first and so far only time for comparison of conventional oral corticosteroid treatment with (iv) MDMP (13).

Material and Methods

Forty-nine children with acute ITP who did not receive any treatment previously, were the subject of the study. Antiplatelet antibodies (4) (APA) were determined in all patients just prior to treatment and right after platelet counts reached >150000/µl. The diagnosis of acute ITP was made in all 49 children according to the described criteria above and thrombocytopenia was less than a week duration.

The first case was chosen by chance (to the untreated group) and the other patients were allocated to the other groups successively. Platelets were enumerated by phase contrast microscopy (18). Parents and the patients themselves (older children) were comprehensively informed about the disease, its complications and prognosis. The patients were followed closely in the hematology outpatient department.

Oral prednisone (2 mg/kg) was given once a day for 2 weeks, MDMP (iv) was administered in 5 to 10 minutes, once a day (30 mg/kg daily for 3 d, 20 mg/kg for 4 d and subsequently 10,5,2 and 1 mg/kg, for 1 week each) before 9AM. A peripheral smear was obtained every 2nd or 3 rd days. When platelets were seen on the smear, counts were obtained and over 150000/µl was accepted as an indication of success the treatment.

Anemia (Hct<33%) was present in 2,7 and 3 patients and leukocytosis (WBC>11000/µl) was found in 3,5 and 4 patients in the untreated, oral prednisone and MDMP groups, respectively; the lowest Hct (16%) was in the MDMP group and the highest WBC (16900/µl) was in the untreated group.

Findings

In the first 2 weeks of the follow-up period, spontaneous remission was observed in 5 (29.4%) of the 17 untreated children and in 5 (31.2%) of the 16 patients who had been treated with oral prednisone. Platelet counts were above 150000/µl in 11 of 16 patients in the MDMP treatment group on the 3 rd day of administration. In 2 more patients this elevation was observed on the 5 th day and in another 2 on the 14 th day of treatment.

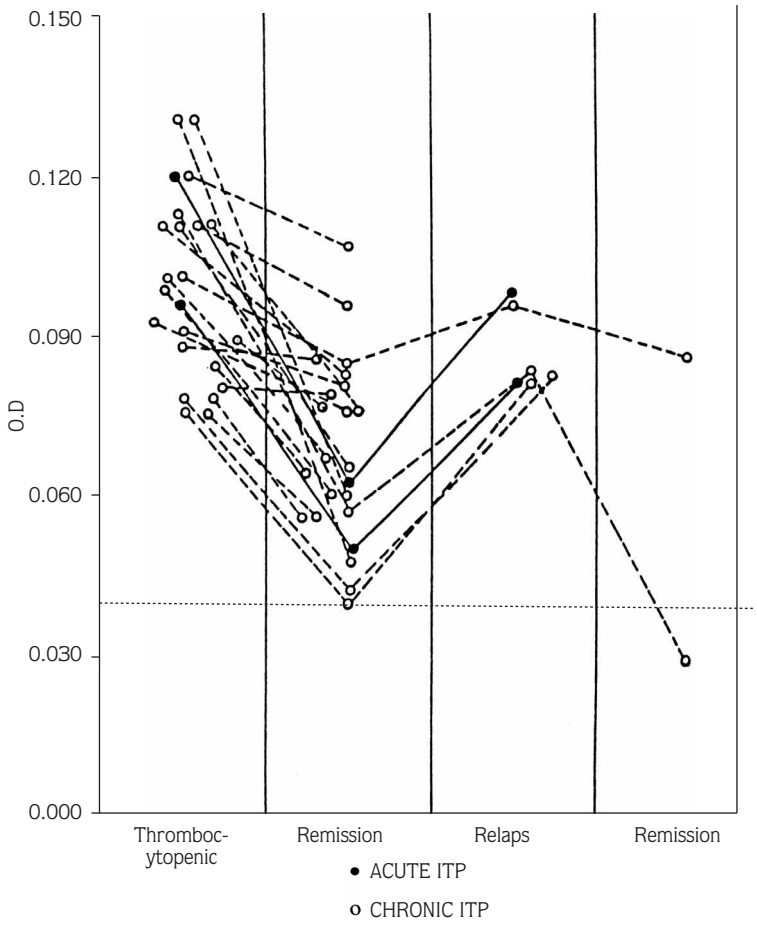

Figure 3. Anteplatelet antibody levels of 21 children with chronic ITP and 2 patients with acute ITP in thrombocytopenic period and in remission are shown. Relas APA values of 4 chronic ITP patinets with their reremission determinations in 2 of them are indicated. Relaps APA values of 2 acute ITP are also included.

In the 4 th week, the platelet count was over 150000/µl in 12 (70.6%) of the 17 untreated patients, in 7 (43.7%) of the 16 patients who had been given oral prednisone for 2 weeks, and in all 16 (100%) of the group treated with MDMP. When the results were evaluated by the chi-square test, significantly better improvement was found only in the MDMP group ($P < 0.01$ for the 1st and 2 nd week and $P < 0.05$ for the 4 th week. No significant differences were observed between the untreated and orally treated groups ($P > 0.05$ at each evaluation) (Table 3).

Initial APAs, indicated as optical density reading over 0.030 at 580 nm, were 0.107 ± 0.044 (X ± S.D., range: 0.46-0.211) in the oral prednisone treated group 0.108±0.038 (range:0:060-0.219) in the untreated group and 0.115±0.035 (range 0.060-0.200) in the MDMP group; there were no significant differences between them. Following normalization of platelet count, the antibodies were decreased but could still be detected in every case (Figure 4). They were found to be below 0.030 in all 126 normal and thrombocytopenic control sera (4).

The early platelet response was also observed in most of the 6 patients unresponsive to oral prednisone who were treated 4 months later with MDMP (Table 3). Decrease of APA, could be determined in 4 of these 6 children in whom platelet counts were normalized as seen in (Figure 4).

Table 3. Age, sex, and time to remission in 3 groups of children with acute ITP treated with MDMP, oral prednisone, or untreated.

	MDMP	oral prednisone (2 mg/kg)	Untreated
No.of patients	16	16	17
Mean age (range) in months	46(3-156)	64.5 (19-132)	77.5 (19-156)
Male: Female	11:5	10:6	7:10
No.of patients in remission*:			
3rd day treatment	11(68.7%)	-	-
1st week treatment	13 (81.2%)	3 (18.7%)	2 (11.7%)
2nd week treatment	15 (93.7%)	5 (31.5%)	5(29.4%)
4th week treatment	16 (100%)	7(43.7%)	12 (70.6%)
Up to 4 months		7+2 (partial)**	14+1 (partial)

* Plt count 150/µl

** Partial remission: 150.000/µl > plt > 100000/µl

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Table 4. Age, sex and days of platelet response to MDMP in children unresponsive to oral prednisone (2mg/kg).

No. of patients	6
Mean age (range) in months	72 (48-84)
Male: Female	4/2
No.of patients in remission:*	
3rd day	3+1 (partial)**
1 week	5 (83.5%)
Unresponsive	1
Number of patients relapsed	2(2 and 6 months later)

and ** as in Table 2

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Discussion

The improvement of platelet counts which occurred within 4 weeks in about 70.6%, and in 88% of these children by the end of 4 months would support the concept that treatment of ITP in children may not be mandatory if bleeding is not a problem; however, such a prediction is not possible.

Our results definitely show that MDMP treatment is much superior to conventional treatment as well as to non treatment. To our surprise, the platelet response of the untreated group seemed better than the conventional treatment group although it was not statistically significant.

Decrease of APA was shown in each case in our study following normalization of platelet counts. The antibodies in 4 of the patients unresponsive to oral prednisone were also found to decrease following normalization of platelet count with MDMP treatment. These determinations could not be performed in 2 patients. One was unresponsive, and posttreatment sera could not be obtained from the other. Although antiplatelet antibodies decreased following remission in all patients; more markedly in MDMP administered group (Figure 4), in they were detectable in each case.

Although remission was observed 70.6% of the untreated and 43.7 % of conventionally treated group at

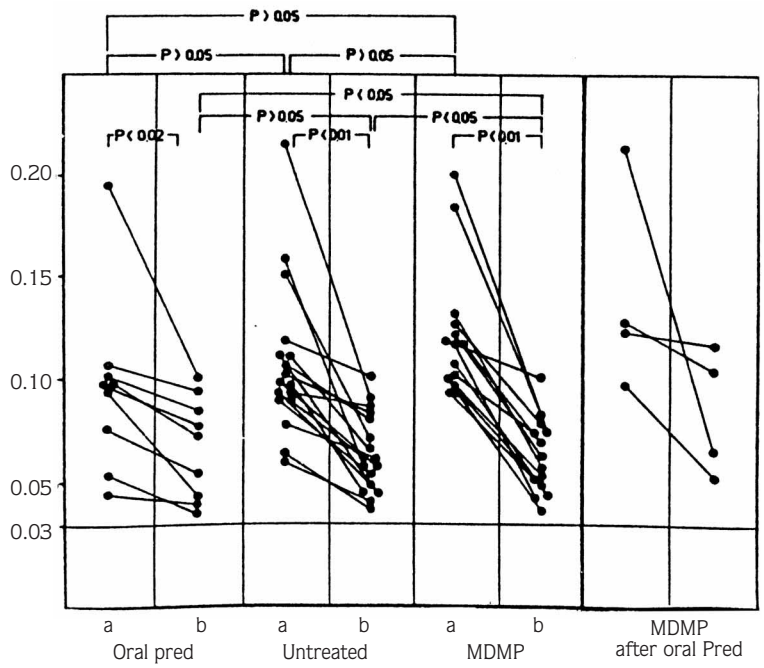

Figure 4. Initial (a) and improvement (b) antiplatelet antibodies of the patients are shown.

4 weeks of follow up period, 68.7% early response at 3 rd day was observed only in patients treated with MDMP. Early elevation of platelet counts, important for families and patients psychologically as well as prevention of bleeding, is expected more in the early days of ITP.

Although response to MDMP treatment was better than conventional corticosteroid treatment, about 35 days of iv administration methylprednisolone period seemed to be too long for a disorder with good prognosis. Since platelet counts were elevated over 150000/µl within a week of the treatment in more than 81% of the patients, we used 7 days (30mg/kg for days then 20 mg/kg for 4 days) treatment. Later these doses were given orally and compared with iv treatment and were found not different from each other (19) (Table 5). Since response to iv MDMP was 68.7% in 3 days, oral MDMP (30 mg/kg) for 3 days treatment, was compared one week (30 mg/kg days then 20 mg/kg for 4 days) MDMP administration. Each oral dose was given at once around 6 AM when blood corticosteroid level was with highest physiologically. Although platelet response (>150000/µl) within a week was comparable, recurrence within 4 weeks were observed in 50% of the cases who were given 3 days treatment but in 12.5% with 7 days administration (Table 6).

Therefore we advise 7 days oral dose regimen for the present, each dose being given around 6 AM. We have also compared IVIG (2 g/kg dose) results with our oral MDMP administration which were found comparable (20) (Table 7).

Chronicity was observed in 4 of 59 (6.8%) patients with acute ITP treated with MDMP and in 13 (12.3%) out of 105 (who could be followed out of 118 patients) treated with conventional corticosteroid ($P < 0.05$). If this is documented in more patients with acute ITP, MDMP administration would have another advantage of prevention of chronic ITP.

We have used iv MDMP in the treatment of chronic ITP cases, earlier than its administration for acute ITP patients (21,22). The same dose of methylprednisolone (30mg/kg for 3 days, then 20 mg/kg for 4 days, followed by 10,5,2 and 1 mg/kg dose for one week, each dose given before 9 AM in 5 to 10 minutes) was given as in treatment of acute ITP cases. The results of 29 patients with chronic ITP were reported in 1984 by us[21]. The results, 14 of more cases with this disorder, were added to initial findings for the evaluation of the responses (22) (Table 8). If platelet response remained under 100 000/µl during 35 days of treatment or after, those cases were accepted as none-responsive. If platelet count

Table 5. Oral versus iv MDMP for acute ITP cases (7 days; 30 mg/kg for 3 days, then 20 mg/kg for 4 days).

	Oral	iv
Patients (n)	15	16
Mean age (range mos)	59.6 (1-132)	64.8(1-166)
Male / female	9/6	6/10
Patients in remission over 2 weeks	13 (86.7%)	12 (75.4%)

Table 6. Three days versus 7 days MDMP treatment.

	3 days (30 mg/kg/dl)	7 days (30mg/kg 3 days; + 20 mg/kg 4 days)
Remission in one week	6/7 (85.7 %)	7/9 (77.8%)
Relaps within 4 weeks	3 (50%)	1 (12.5%)

Table 7. (Age, sex, ahr early response rates to treatment of patients with their 6 months follow-up).

	Oral MDMP 7 days (30 mg/kg 3 days+20 mg/kg 4 days)	IVIG (0.4g/kg for 5 days)
No of patient	10	10
Mean age (range in months)	69.8(2-108)	60.5(2-132)
Male/female	6/4	5/5
No of patients in complete remission (plt count≥150 000/µl	n(%)	n (%)
3rd day treatment	6/10 (60%)	6/10 (60%)
7th day	8/10 (80%)	9/10 (90%)
During follow-up		
4th week	7/10 (70%)	6/10 (60%)
3rd month	7/10 (70(%)	6/8 (75%)
6 th month	9/10 (90%)	6/8 (75%)

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Table 8. MDMP for chronic ITP patient.

	girls (n:18)	boys (n:25)	total (n:43)
Sustained response	3(16.7 %)	13(36%)	16(37.2%)
Non-persistent resp.	11(61.1%)	9(36%)	20(46.5%)
Unresponsive	4(22.2%)	3 (12%)	7 (16.3%)

increased 150 000/µl and remained there sustained response, and if platelet count raised over 100000/µl during treatment but decreased later, nonpersistent response were considered. By this response score only 16.3 % (7 of 43 plt) of the patients were found non responsive, 83.2% responsive; 37.2% (16 pts) were sustained responsive, and 46.5 % (20 pts) were non - persistent responsive (22).

Since response was mostly observed in 2 weeks of treatment, later patients with chronic ITP were treated by oral MDMP (30 mg/kg for 1 week then 20 mg/kg another week). Each dose was given 6 AM at once. In obtaining sustained response, more than one cure of MDMP was required in some cases and 4 cures were necessary for one patient. More than one cure of the treatment were used for those patients who were bleeding with chronic thrombocytopenia, and the response rate was found comparable to iv MDMP.

MDMP treatment has also been used in adult chronic ITP patients with success (23,24).

Because methylprednisolone taste extremely bitter, each daily oral dose (as powder) was put on a tablespoon and was covered by honey so that patients could take it. A glass of milk was given afterwards, as in treatment of acute ITP cases.

Saline nose drops was administered to all patients when MDMP was given, as described by us (25).

The major side effect of the treatment was abdominal disomfort, which was observed in at least half of the patients; was but not severe enough to discontinue MDMP administration in any of them. Mild Cushingoid appearance was observed in more than one tenth of the patients with long term (35 days) administration, but rarely with one or two weeks treatment. Other corticosteroid effects such as hypertension, hyperglycemia, glycosuria and corneal opacities were not seen in patients treated with MDMP for acute or chronic ITP cases as confirmed by others (26). A 13 year old girl with acquired aplastic anemia had developed diabetes due to deltacortril and testosterone treatment, before being referred to us and was then treated with MDMP. Her steroid induced diabetes as well as aplastic anemia was completely cured even though she was insulin dependent prior to MDMP treatment (27).

So far, more than 400 patients with different diagnosis have bean treated with MDMP for much longer period than ITP cases (28-30). Cataract was diagnosed in three of them, two of whom were operated an and one patient with Diamond-Blackfan anemia (congenital pure red cell anemia). Oral moniliasis was observed in 2 patients who used MDMP for a long period of time and was treated by local sodium bicarbonate (1%) administration. All patients used saline nose drops prophylactically at least 3 times a day (25). No serious infections was seen in any of our patients with acute or chronic ITP.

With MDMP administration, erythropoietin (EPO) granuclocyte macrophage colony stimulating factor (GCSF) elevation and some lymphocyte subsetts increase have been shown (31,32). The cost of methylprednisolone is one sixtieth of the IVIG (2 g/kg) price for acute ITP patients. Since oral MDMP is administered at home and hospital admission is advised, for IVIG treatment the cost would be much more than oral MDMP treatment for acute ITP.

From these experiences it could be concluded that:

a. Antiplatelet antibodies which are IgG fraction, are present in all acute and chronc ITP cases,
b. These antibodies could also be shown in all cases during remission, though they are lower,
c. Mean platelet survival is shorter not only in relapse but in remission in most of the cases.
d. Therefore, normal platelet counts in remission should be due to compensatory over production of platelets.
e. If treatment of acute ITP is required, MDMP is the most effective and cheapest approach.
f. With MDMP treatment, APA levels decreased most efficiently, during remission
g. Chronicity of acute ITP would probably be less with MDMP treatment
h. Oral MDMP treatment is more convenient and cheaper than other effective treatments.

Patient admission is not necessary for MDMP administration which makes it more cost effective.

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