CHILDHOOD IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP): OVER 40 YEAR EXPERIENCES

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SUMMARY: Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder. Decreased platelet survival is the main pathogenesis of it, which is related to platelet antibodies (APA). The levels of these antibodies are correlated with relapse and remission which was shown first time by us. Although APA levels decrease in remission but not risappear as studied by us. Among the several approches about ITP treatment, oral megadose methylprednisolone (MDMP) 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 evidences that chronic ITP could be prevented by this approach.

Key words: child, idiopathic thrombocytopenic purpura, thrombocytopenia

INTRODUCTION

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

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 since their pathogenesis is similar, idiopahic thrombocytocytopinec purpura should be diagnosed by exclusion.

Diagnosis

The diagnosis of ITP should be based on decreased platelet counts (usually less than 50000/μl) with the excessive or normal megakaryocytes in the bone marrow. Hepatosplenomegaly and lymphadenopathy should not be detected and recent history of drug ingestion including aspirin quinine, heparin and platelet or blood transfusions should not be present. In the mean time underlying diseases such as lupus erythemathosus, Coombs positivity (Evans syndrome), hematologic malignancies, antiphospholipid antibodies, thrombotic thrombocytopenic purpura, type II, B von Willebrand disease 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 Stosel5 method as modified by us (2).

This method of APA determination depends on opsonization of normal platelets by the patient serum which are phagositized by normal granulocytes. This method of APA determination dose not indicate GPII b/III a or GPIb/IX or other platelet receptor antibody specifically but, most likely includes all of them.

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Table 1: Causes of Thrombocytopenias.

1. Primary	
A. Familial	**a) Hereditary** - *autosomal dominant:* May-Hegglin. Sebastian (SBS), Fechhner, Epstein macrothrombocytopenia nephritis deafness, Thrombocytopenia and radial synotosis, chromosom 10/THC2 syndromes - *autosomal recessive:* Bernard-Soulier, TAR, Amegakaryocytic, Gray platelet syndrome type II B von-Willebrand's disease, Chronic thrombotic thrombocytopenic purpura (TTP) Hereditary hemophagocytic lymphohistiocytosis - *X-linked:* Wiskott-Aldrich, X-Linked thrombocytopenia, GATA-1 mutation
	b) Non hereditary Neonatal alloimmune thrombocytopenia, cyclic thrombocytopenic
B. Non-familial: Idiopathic thrombocytopenic purpura (ITP)	
2. Secondary: viral infections, sepsis, drugs, DIC, Toxic (uremic etc), collagen disorders, Bone-marrow supression, Leukemia and malignant disorders cyanotic heart disease alloimmune; neonatal (septic, virumic etc)	

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

Pathogenesis

Markedly shortened lifespan o platelets in idiopathic thrombocytopenic purpura during the thrombcoytopenic plase has repeatedly been demonstrated (6-10). This is related to circulating antibodies first stongly suggested by Harrington *et al.* in 1951 and confirmed many times since then (11). But the level of antiplatelet antibodies to relaps 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), as also shown by us (2) (Table 2). We have also shown the persistence of antiplatelet antibodies in remission 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) (Figures 1-3).

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

Treatment

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

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

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 generally platelet counts improve within a few months without treatment as was supported by our results (12).

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 till 1985 when comparative oral corticosteroid, IVIG studies were carried out. Despite similar results were obtained in acute childhood ITP treatment, in all rapid responders

Table 2: Mean paleelet survival in control subjects and ITP patients in remission: Pagocytosis of donor platelets by autologous leukocytes following sensitisation 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	5200	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 in remission
15/F	304000	8.6		2 yrs
15/F	172000	2.8*	2.741	5 yrs
12/M	184000	4.4	2.454	6 yrs
	Acute ITP cases in remission			Duration of remission
11/F	200000	7.4	2.936	6 yrs
11/M	172000	7.8		3 yrs
11/M	204000	2.0	3.212	10 mo
7/M	1400000	3.0	2.884	>1 yrs
9/M	172000	5.4		>2 mos
12/M	396000	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

with both approaches, IVIG has been suggested more often despite of its high cost and important side effects (16,17).

We have conducted an original study for the first and so far last time for comparison of conventional oral corticosteroid treatment with (iv) MDMP (12), with untreated group; in all APAs were studied prior to treatment and right after normalization (≥150000/μl) of platelet counts.

Forty-nine children with acute ITP who did not receive any treatment before 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 >150.000/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 choosen by chance (to untreated group) and the other patients were allocated to the other groups successively. Platelets were enumerated by Coulter counter. 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 2 nd or 3 rd days. When paletelets were seen on the smear, counts were obtained and over 150000/μl was accepted as indication of success the treatment.

Anemia (Hct<33%) was present in 2,7 and 3 patients and leukocytosis (WBC>11000/μl) was found 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. In the first 2 weeks of the follow-up period spontaneous remission was observed in 5

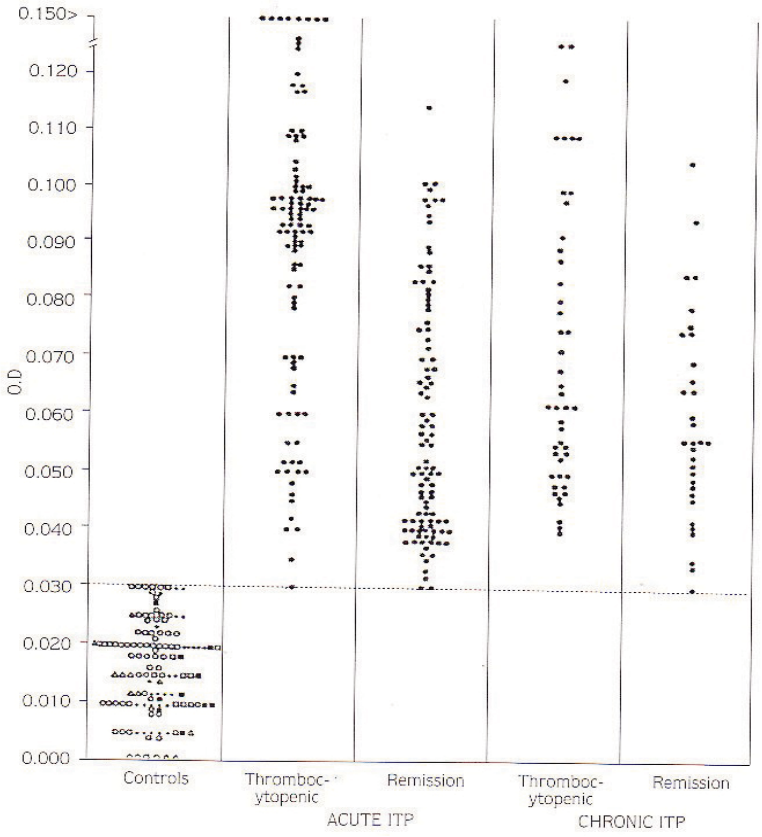

Figure 1: Antiplatelet antibodies (APA) in acute and chronic ITP parents in thrombocytopenic period and in remission.

(29.4%) of the untreated children and in 5 (31.2%) of the 16 patients who had been treated with oral prednisone. Platelet counts were above 150.999/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 the days and in another 2 on the 14 th days of treatment.

In the 4th week, the platelet count was over 150000/μl in 12 (70.6%) of the 17 untreated patient, 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 group with MDMP when the results were evaluated by the chi-spuare test, significantly better improvement was found only the MDMP group ($p<0.01$ for the 1 st and 2 nd week and $p<0.05$ for the 4 the 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 mm, 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 counts the antibodies were decreased but still could be detected in every case (Figure 4). They were found to be below 0.030 in all 126 normal and thrombocytopenic control sera4.

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 4). Decrease of APA, which could be determined 4 of these 6 children in whom platelet counts were normalized as seen in Figure 4.

Comments

Normalisation of platelet counts which occurred within 4 weeks in about 70.6 and in 88% of the children with acute ITP by the end of 4 months without treatment

would support the concept that treatment in acute ITP 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 untreated patients. To our surprise the platelet response of untraeted group seemed better than conventional treatment group though 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 were more marked in MDMP administered group (Figure 4), though they were detectable in each case.

Although remission was observed 70.6% of the untreated and 43.7% of conventionally treated group at 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 which is expected more in early days of ITP.

Although response to MDMP treatment was better than conventional corticosteroid treatment, about 35 days of iv administration methyprednisolone period seemed to be too long for a disorder with good prognosis. Since platelet counts elevated over 150000/μl within a week of the treatment more than 81% of the patients,

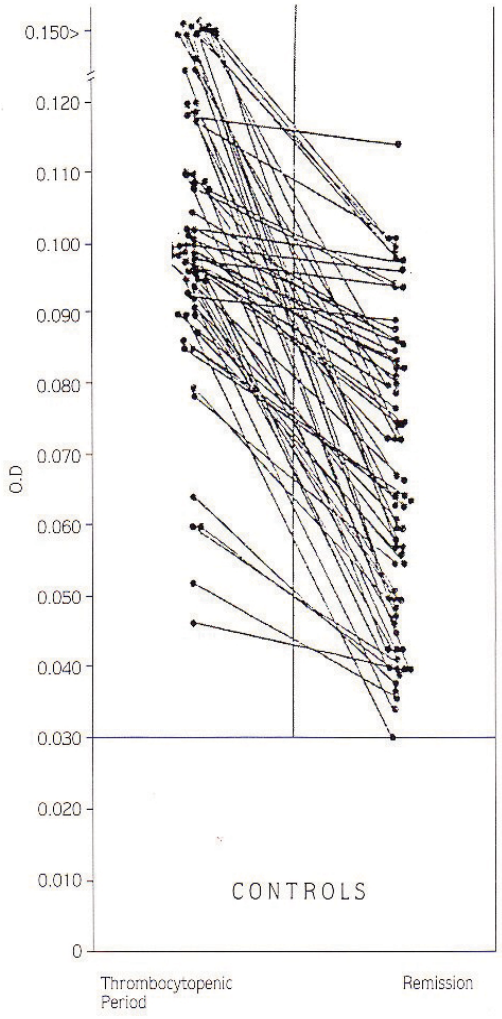

Figure 2: Antiplatelet antibody levels 67 children with ITP in thrombocytopenic period with corresponding remission.

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 fo 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 > 100.000 / μl

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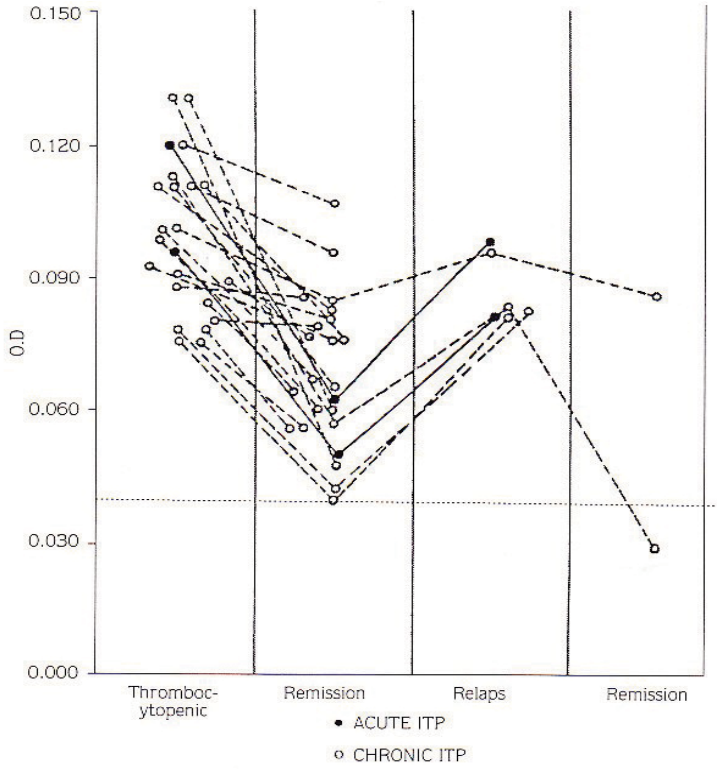

Figure 3: Antiplatelet antibody levels of 21 children with chronic ITP and 2 patients with acute ITP in thrombocytopenic period and in remission are shown. Relaps APA values of 4 chronic ITP patients with their reremission determinations in 2 of them are indicated. Relaps APA values of 2 acute ITP are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

we used 7 days (30 mg/kg for days then 20 mg/kg for 4 days) treatment. Later these doses were given orally and compared with iv treatment which were found not different than each other (Table 5). Since response to iv MDMP was 68.7% in 3 days, oral MDMP (30 mg/kg) for 3 days treatment, was compared with 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 highest physiologically. Although platelet response (>150000/μl) within a week was comparable, recurrences within 4 weeks were observed 50% of the cases who were given 3 days treatment but 12.5% with 7 days administration (Table 6).

Therefore we advise 7 days oral dose regimen at the time being for acute ITP patients, each doses given around 6 AM. We have also compared IVIG (2 g/kg) results with our oral MDMP administration which were found comparable (Table 7), in small number of patients. Chronicity was observed 4 of 59 (6.8%) of patients with acute ITP treated with MDMP and 13 (12.3%) out of 105 (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 as 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 (20,21). The same dose of methylprednisolon (30 mg/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) as of 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 100000/μl during 35 days of treatment, those cases were accepted as none-responsive. If platelet count increased 150000/ l and remained there sustained repsonse and if platelet cound raised over 100000/μl during treatment but decreased later,

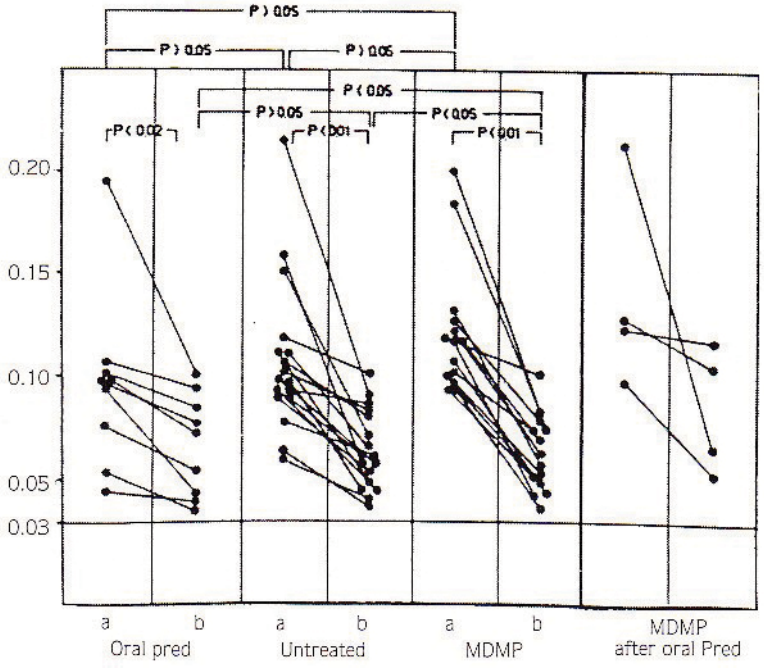

Figure 4: Initial (a) and improvement (b) antiplatelet antibodies of patientsare shown.

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 (21).

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 thrombocyopenia, and the response rate was found comparable to iv MDMP.

MDMP treatment has also been used in adult chronic ITP patients with success (22,23). Because taste of methylprednisolone extremely bitter, each daily oral dose (as powder) was put to a tablespoon and was covered by honey that patients could take it. A glass of milk was given afterwards, as of treatment of acute ITP cases.

Saline nose drops was administered to all patients when MDMP was given, as described by us (24). The major side effect of the treatment was abdominal disomfort

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

No of patients	6
Mean age (range) in months	72 (48-84)
Male: Female	4:2
No fo 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)

* Plt count 150 / μl ** Partial remission: 150.000/μl > 100.000 / μl

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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 (30 mg/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 $\geq$ 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%)
6th 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)
Sustainet response	3 (16.7%)	13 (36%)	16 (37.2%)
Non-persistent response	11(61.1%)	9 (36%)	20 (46.5%)
Unresponsive	4 (22.2%)	3 (12%)	7 (16.3%)

which was observed at least half of the patients but not severe enough to discontinue MDMP administration in any one. Mild cushingoid appearance was observed more than one tenth of the patients with long term (35 days) administration, but rarely with one or two weeks treatment. Other corticosteroids side effects such as hypertension, hyperglycemia, glycosuria, corneal opacities were not seen in patients treated with MDMP for acute or chronic ITP cases as confirmed by the others (25). A 13 year old girl with acquired aplastic anemia had developed diabetes due to deltacortil and testosteron treatment, before referred to us who then was treated with MDMP. Her steroid induced

diabetes as well as aplastic anemia completely cured despite she was insulin dependent prior to MDMP treatment (26).

So far more than 450 patients with different diagnosis have bean treated with MDMP much longer period than ITP cases (27-29). Cataract diagnosed in three of them, two of whom operated, one patient with Diamond-Blackfan anemia (congenital pure red cell anemia). Oral moniliasis was observed in 2 patients who used MDMP long period of time which was treated by local sodium bicarbonate (1%) administration. All patients used saline nose drops prophylactically at least 3 times a day (24). 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 (30, 31). The cost of methylprednisolone is one sixtieth of IVIG (2 g/kg) price for acute ITP patients. Since oral MDMP is administered at home and for IVIG treatment hospital admission is advised, 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 chronic ITP cases,

b. These antibodies could also be shown in all cases during remission, though a lower levels,

c. Mean platelet survival is shorter not only in relapse but in remission in most of the chronic ITP cases,

d. Therefore, normal platelet counts in remission should be due to compansatory over production of,

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,

g. Probably chronicity of acute ITP would be less with MDMP treatment,

h. Oral MDMP treatment is more convenient and cheaper (than other effective treatments)

i. Patient admission is not necessary for MDMP administration which makes it more cost effective, and more convenient for the families.

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