IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDHOOD. REVIEW 269 CASES.

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SUMMARY: Our experience with idiopathic thrombocytopenic purpura (ITP) on 269 cases is reviewed and the general lines are resented in this communication.

Presence of antiplatelet antibody both in thrombocytopenic phase and remission was shown in all acute and chronic ITP patients. Abreviation of ITP was therefore proposed to signify immune thrombocytopenic purpura. Because of shorter platelet survival observed in 8 acute 6 chronic ITP cases in remission increased platelet production was considered. As an etiologic factor rubella infection was scrutinized in one epidemic. Low serum IgA levels were documented in one third of acute and chronic ITP cases.

High dose I.V. methyl prednisolane was proposed for the first time and its superiority demonstrated over conventional prednisone administration in ITP.

As a conclusion it appears that high dose of intravenous methyl prednisolon in presently the choise of treatment for ITP.

Key Words: Platelet survival in ITP, Immunglobulin A, Platelet antibodies, High dose of methyl prednisolone treatment in ITP.

Idiopathic thrombocytopenic purpura (ITP) in children usually observed one or two weeks after viral upper respiratory system infections and accepted as a benign self limited disorder with short duration. If it improves in 6 months, is called acute ITP and if the thrombocytopenia persists longer than 6 months those cases are classified as chronic ITP. In ITP cases only platelet counts decreased; hemoglobin level and leukocyte counts are normal; unless large bleeding occurs. Bone marrow reveals increased young megakaryocytes with normal cellularity with some eosinophilia. Hepatosplenomegaly and lymphadenopathy are not present. Throat culture, Coombs test, antinuclear antibody and L. E preparations do not reveal any abnormalities. Since different drugs, including aspirin may cause thrombocytopenia history of drug ingestion, including aspirin, has to be excluded (1).

Because of the high incidence of infection antecedent ITP term has been used for the abbreviation of infections thrombocytopenic purpura. Since autoimmune pathogenesis considered generally ITP term might very well also correspond to immune thrombocytopenic purpura.

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Although ITP usually seen following upper respiratory infections, thrombocytopenia has been observed during or right after specific viral disease epidemics such as measles and rubella. Rubella is often a childhood disease; it might attack susceptible adults with thrombocytopenic complication usually mild and does not cause bleeding diathesis. We observed serologic evidence of recent rubella in 15 acute ITP, cases without clinical evidence of the disease (2).

Fifteen children (8 girls and 7 boys) with the age range of 2.5 to 15 years, seen between September 1975 and May 1976 with the diagnosis of acute ITP blood could be obtained at 2 week intervals, are the subjects of this study. The were all brought to the hospital because of the very recent observation of petechiae, ecchymoses, epistaxis or easy bleeding. In no patient was there a history of drug induced etiology and none of them had received platelet or blood transfusions prior to the study. Skin rash (not petechiae) was not present and no history of upper respiratory infection was obtained from any of the patients.

Blood was obtained from the patients and 15 control children, age comparable to the patients, on their first visit to the hospital and at 2 week intervals, during the same season. Control children seen at the checkup clinic with adequate platelet on blood smear. All serums obtained at

Table 1: Rubella HI Titer Changes In Patients With Acute ITP and In Controls At Two-Week Intervals.

Group	Age (yr)	Rubella HI Titlr	
		First Serum Sample	Second Serum Sample
Controls	9 mos	8	8
	21/2	8	8
	3	8	8
	3	8	8
	4	8	8
	5	32	32
	6	16	16
	8	8	8
	9	9	8
	11	8	8
	11	16	16
	12	16	16
	12	16	16
	13	16	32
	15	8	8
Patients with ITP	9 mos	64 (IgG)	256 (IgG)
	2.5	8	8
	2.5	8	8
	3	8	8
	3	512 (IgG)	256 (IgG)
	4	8	8
	4	8	8
	5	128 (IgG)	256 (IgG)
	5	128	128
	6	128 (IgM, 1:8)	32 (IgG)
	8	64 (IgM, 1:4)	16 (IgG)
	11	8	8
	12	8	8
	12	256 (IgG)	64 (IgG)
	15	32	32

two week intervals were checked for rubella and rubeola antibodies on the same day by standard hemagglutination inhibition (H, I) method in the some run. Sucrose density gradient and complement fixation tests were carried with appropriate controls. No changes in rubeola H.I. antibody titers were found in any of the cases and controls; but serologic evidence of rubella infection was shown one third of the ITP patients (Tables 1 and 2).

In spite of usual benign character of ITP, it has been observed that some women, having recovered from ITP in their childhood, gave birth to children with thrombocytopenia. This could indicate the presence of long lasting serum factor which passes through the placenta and casuses thrombocytopenia in the newborn, even though it did not seem to effect the mother's platelets.

Markedly shortened life span of platelets in ITP cases during the thrombocytopenic phase has repeatedly been

Table 2: Rubella Complement Fixation Titer Changes in Patients With Acute ITP Whose Rubella HI Titer Changes Were At Least One Fold.

	Rubella Complement Fixation Titer	
Age (yr)	First Serum Sample	Second Serum Sample
9 mos	3	64
3	32	256
5	16	128
6	32	256
8	16	16
12	16	32

shown. This is related to the circulating antibodies first suggested in 1971 by Harrington *et al.* (3). The mean life span of the platelets in childhood ITP cases during remission was studied as reported previously (4).

Fourteen children between the ages of 2.5 to 15 years, diagnosed as having ITP were selected for the platelet survival study. They had all been in clinical and hematological remission of 2 months to 6 years duration. Six of the patients had chronic ITP and 5 of them were splenectomized 2 months to 6 years prior to these studies; one went into remission 4 months prior to platelet survival studies. Only two of the cases, both with chronic ITP had received platelet transfusions and one of them in addition had had blood transfusions. The control group consisted of two subgroups:

a. Four hematologically normal children

b. Two children with aplastic anemia.

Autologous platelets were used on two splenectomized case and homologous platelets in the rest.

The mean life span of platelets in four normal controls and in two cases of aplastic anemia were close to each other, being between 8 and 9.2 days. Mean platelet survival was found markedly decreased in ten ITP cases in remission (five acute and five chronic) with the range 1.6 to 4.4 days, moderately shortened in one (5.4 days), questionably decreased in two (7.4 and 7.8 days) and completely normal in one (8.6 days). The mean life span of platelets was also estimated in two chronic ITP cases in relapse (platelet counts 40.000 /ul in both) and was found markedly shortened, being 2.4 and 3.2 days (Tables 3, 4).

Decreased platelet survival of the patients is most likely related anti platelet antibodies which is in IgG fraction. Recently antiplatelet antibodies are determined according to platelet associated immune gloublin G levels (Pa IgG). But we believe that opsonophagocytic test is more specific and appropreiate for this purpose. So far, platelet antibodies has been determined 177 acute ITP (90 in thrombocytopenic phase, 87 in remission; in 54 cases corresponding to both conditions) and 55 chronic ITP (in 35 at the throm-

Table 3: Mean platelet survival and phagocytosis of donor platelets by autologous leukocytes following sensitization by the serums of control cases.

Initials of Name	Sex	AGE in Years	Platelet Count/μl	Platelet Life Span (days)	Phagocytosis of Platelets/cpm	Remarks
S.E.	F	f	8.0			Normal
D.K.	F	9		9.0		Normal
M.C.	M	15		9.2		Normal
N.Y.	M	10		8.6		Normal
M.G.	F	15	48.000	8.0	1325	Aplastic anemia
I.M.	M	12	52.000	8.6	1289	Aplastic anemia
	M	Adult			1536	Bood donor
	M	Adult			1699	Normal
	M	Adult			1682	Normal
	M	Adult			1623	Bood donor

Table 4: Mean platelet survival and phagocytosis of donor platelets by autologous leukocytes following sensitization by the serums of study cases.

Initials of Name	Sex	AGE in Years	Platelet Count/ul	Platelet Life Span (days)			Phagocytosis of Platelets/cpm	Remarks
CHRONIC ITP CASES IN REMISSION								
E.O.	F	15	304 000	8.6		-		
S.E.	F	15	172 000	2.8[x]		2741		
M.G.	M	12	184 000	4.4		2454	Splenectomized	2 years Ago
N.D.	F	15	296 000	3.5	(2319)[xx]	1699		5 years Ago
S.K.	F	11	232 000	2.0[x]	(2279)	2341		6 years Ago
N.S.	F	4	216 000	2.0	(2280)	2174		2 months Ago
H.D.	M	15	248 000	-	(2409)	2140		4 months Ago
								2 months Ago
ACUTE ITP CASES IN REMISSION								
H.K.	F	11	200 000	7.4		2936		
K.E.	M	11	172 000	7.8		-		
E.T	M	11	204 000	2.0		3212		
Z.B.	M	7	140 000	3		2884		
K.K.	M	9	172 000	5.4		-		
N.K.	M	12	396 000	3.0	(2713)[xx]	2134		
Y.K.	M	12	324 000	2.1	-	2809		
E.T.	M	4	236 000	1.6	(2137)	2244		
G.Y.	F	2.5	156 000	-	(1988)	2324		
S.D.	F	6	368 000	-	(1855)	1986		

x Autologous thrombocytes were used, xx With admission serum

bocytopenic period and in 20 during remission; in 8 cases in both conditions). It was also studied in 126 controls (67 normals; 59 thrombocytopenic controls: leukemia: 28 patients, aplastic anemia: 10 patients, Fanconi aplastic anemia: 10 patients, and 11 patients with sepsis and thrombocytopenia). Platelet antibodies were shown in all ITP patients, at presentation and remission, but none in control cases (Figure 1). Antiplatelet antibody levels were found higher statistically in thrombocytopenic phase than in remission, in both, acute and chronic cases: as in acute ITP cases in all 8 patients with chronic ITP in whom anti platelet antibodies were determined in bothphases, remission levels were found higher than remission values (Figure 2). When immunoglobulins were separeted from 13 patients sera in thrombocytopenic phase, antiplatelet antibodies were shown in IgG fraction but neither IgA or IgM (Fig. 3). When the patients sera were incubated with platelets, erythrocytes and lymphocytes the antibodies were adsorbed by platelets but, not with red blood cells or lymphocytes. This indicates the antibody specificity to platelets (Fig. 4) when the four patients' IgG was destroyed with breaking its disulfide bonds by dithiothreital and alkylating them with iodoacetamide the antiplatelet antibody disappeared in all Fig. 5. All these studies indicate that antiplatelet antibodies in the patients' sera is specific to platelets and present only in the IgG fraction (6).

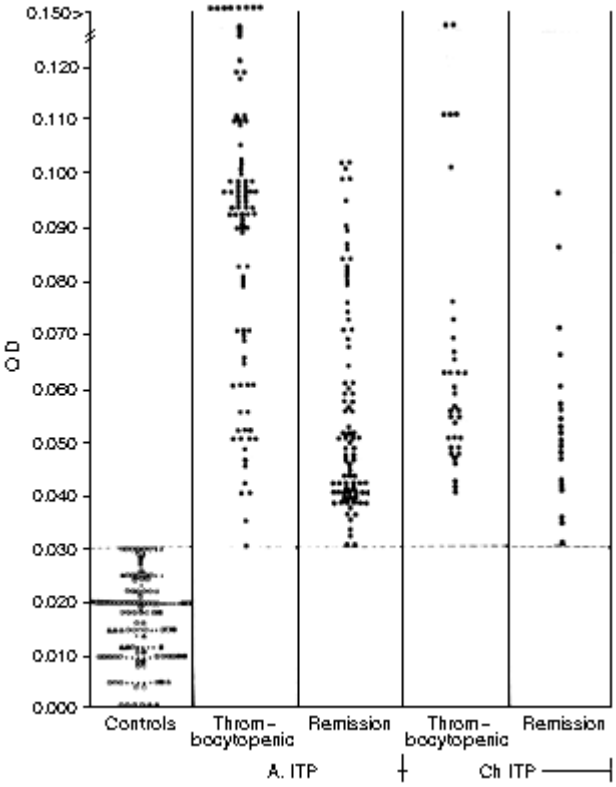

Figure 1: Antiplatelet antibody determined by opsonophagocytic test shows its presence in all ITP (acute and chronic) patients in relaps and remission but not in thrombocytopenic and normal controls.

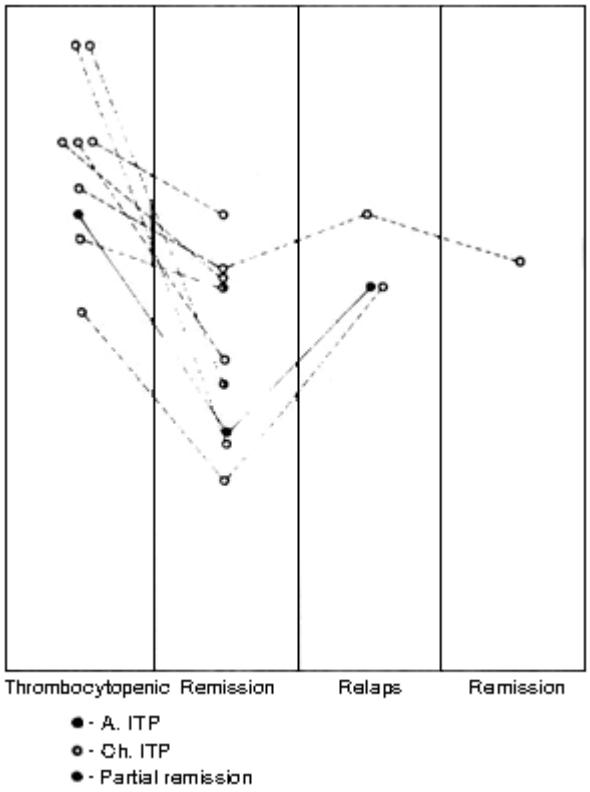

Figure 2: Platelet antibodies corresponding thrombocytopenic phase and remission in ITP patients.

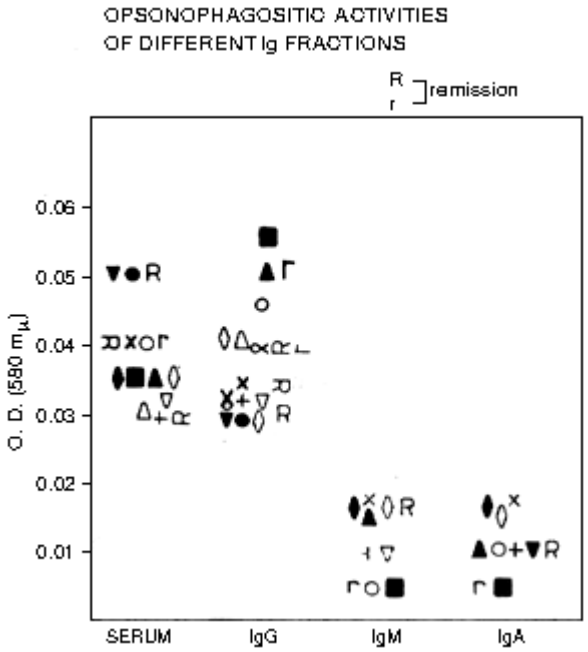

Figure 3: The antiplatelet antibody effect of whole sera is related to the IgG fraction only (Each mark indicates one patients).

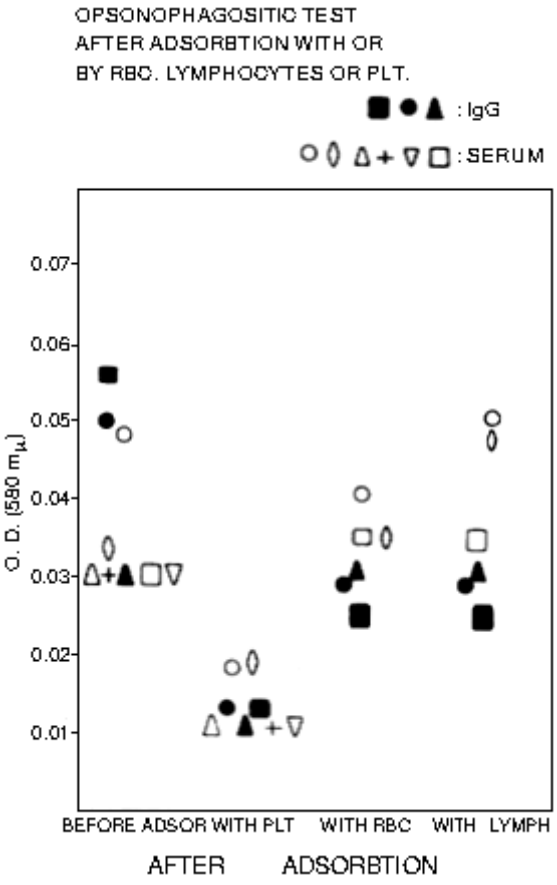

Figure 4: The specificity of antiplatelet antibodies. They are adsorbed only by platelets (plt) but not by red blood cells (rbc) or lymphocytes (lymph).

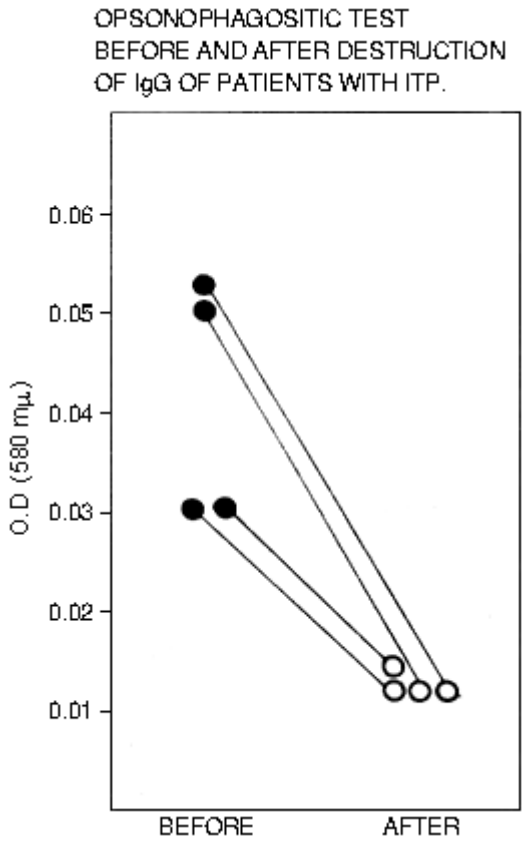

Figure 5: IgG fraction obtained from 4 patients sera loses its antiplatelet effect following treatment with dithiothreitol and iodo acetate.

Since the serum of patients with ITP when incubated with normal platelets, would increase its phagocytosis by normal granulocytes, would increase its phagocytosis by normal granulocytes, NBT reduction of these patients, as index of in vivo granulocyte stimulation was also evaluated. Nine boys and five girls with ITP, with the age range of 8.5 months to 15 years were the subjects of these studies. The ages of the 13 control children (8 boys and 5 girls) who were without infection and hematological problems, ranged from 9 months to 12 years. The results of the quantitative NBT test are summarized in the Table 5. With the exception of phagocytosing values no difference was found between relapse, remission and control values. With this study it is confirmed that sera from ITP patients contain

Table 5: NBT test result in patients with ITP in relapse and in remission.

	Resting	Phagocytizing	OD
Controls	0.097+0.008	0.178+0.007	0.081+0.003
ITP			
In relapse	0.155+0.03	0.222+0.015	0.107+0.007
In remission	0.126+0.006	0.218+0.009	0.092+0.007
P	0.05	0.001	0.05

Table 6: The Results of the EA Rosette Inhibition Tests in Childhood ITP % of Ea (Fc) Inhibition.

	Whole Serum	Supernatant	Sediment
In Acute	56	8	61
Phase	82	0	55
	69	0	53
	66	0	60
	71	14	58
	(X:68.8+9.37)		
In Remission	26	10	23
	75	10	60
	40	N.D	N.D
	35	N.D	N.D
	46	N.D	N.D
	(X:44.4+18.6)		
CONTROLHS (n=20) 0.82 (in two cases only: 4.4. and 12%).			

platelet opsonizing activity in remission as well as in thrombocytopenic phase, platelet opsonizing effect on stimulated granulacytes was not shown by NBT reduction (7).

Circulating immune complexes were determined in five sera of children with ITP in acute phase and in remission. It was shown in acute phase as well as in remission; but less prominent in remission. This finding is compatible with our previous findings that antiplatelet antibodies are present in both phases, being less in remission (8) (Table 6).

Serum IgA levels were determined in 46 and 36 patients with acute and chronic ITP respectively. It was also measured in 32 children who recovered from ITP; 23 from acute and 9 from chronic disorder. Thiry-four (29.8%) of these childeren's IgA level was lower than normal for their ages; four (3.5%) of them had selective IgA deficiency. IgA levels were found higher than normals in 22 (19.3%) of the cases (Table 7); almost one third of these children had IgA deficiency. Since strong relation between IgA deficiency and autoimmunity has been suggested we consider that IgA deficiency makes children more prone to ITP following viral infections.

From the above studies it could be concluded that:

1. Definite antibodies to platelet are present in most, if not all, acute and chronic ITP in childhood;

Table 7: Deficient, decreased and increased serum IgA levels in the study children.

	Deficient	Low	Increased
Acute ITP (46)*	1	12	11
Chronic ITP (3)	1	11	5
In Remission			
From Acute ITP (23)	2	4	5
From chronic ITP (9)	0	3	1
114	4	30	22

*: Indicates number of patients in each group in whom IgA determined.

2. These antibodies could also be shown in almost all cases during remission;

3. Mean platelet survival is short, not only in relapse but also in remission;

4. Therefore, normal platelets counts in remission should be due to compensatory platelet production;

5. Low IgA levels seem to a factor of development of ITP;

6. Although ITP in childhood is usually a self limited disorder its pathogenesis is more likely to be similar to that of adult ITP;

7. If no antecedent is found, serologic evidences of viral infections without disease should be searched, in acute ITP cases.

We have accomplished major development in the treatment of acute and chronic ITP patients.

It has generally been accepted that prognosis of acute childhood ITP is favorable, especially in patients under 10 years of age (9); therefore the use of corticosterioid treatment is controversial (6). Though prednisone (2 mg/kg) is classical approach when treatment considered. The main objective of any from of treatment should be to raise the platelet count rapidly to reduce the risk of bleeding, especially intracranial hemorrhage.

Imbach and co-workerk compared the response to oral corticosteriod and intravenous IgG (i. v. IgG) in the treatment of acute childhood ITP cases, which was found to be identical in all rapid responders (10). Since platelet response with high dose intravenous methylprednisolone (HIVMP) was generally observed in 3 days in chronic ITP cases (11-13), we sought to compare its effect to that of oral corticosteroid in patients with acute ITP. The untreated patients were the control group.

Forthy-nine children with acute ITP of less than a week's duration, ranging in age from three months to 13 years, were seen between April 1986 and October 1987 at Hacettepe Children's Hospital. The first case's group (untreated group) was determined by chance and the other patients were put into the three groups successively one after the other. Sex and ages of the patients in each group are given in Table 8. Patients and the patients themselves (older children) were throughly informed about the disease, its complications and prognosis and were followed closely in the hematology outpatient department. Antiplatelet antibodies were shown in all patients' sera.

Oral Prednisone (2 mg/kg) was given once a day for two weeks. HIVMP was given for 2 to 5 minutes once a day (30 mg/kg daily for 3 days, 20 mg/kg for 4 days and subsequently 10., 5, 2 and 1 mg/kg, for 1 week each). A peripheral smear was obtained every second or third day (smears were not made on Saturday and Sunday). When platelets were seen on the smear, counts were obtained and over 150.000/ul was accepted as success of the treatment.

Anemia (Hct 33%) was present in 2,7 and 3 patients, and leukocytosis (WBC 11.000 /ul) was found in 3,5 and 4 patients in the untreated, oral prednisone and HIVMP groups, respectively; the lowest Hct (16%) was in the HIVMP group and the highest WBC (16.900/ul) in the untreated group.

Ia the first two weeks of the follow - up period, spontaneous remission was observed in 5(24.4%) of the 17 untreated children. Platelet counts were above 150.000/ul in 5 (31.2%) of the 16 patients who had been treated by oral prednisone for 2 weeks. Platelet counts were above 150.000 /ul in 11 of the 16 patients in the HIVMP treatment group on the third days of administration. In another two patients this elevation was observed on the fifty day, and in the other two on the 7th and 11th days of treatment.

In the 4th week the platelet count of 12 (70.6%) of the 17 patients without treatment was over 150.000/ul, of 7 (43.7%) of the 16 Patients who had been given oral prednisone for two weeks and in all 16 (100%) of the group treated with HIVMP (Table 9). The results in the first, second and fourth week were evaluated by the chi-square test and were found to be significantly better only in the HIVMP group (P 0.05 at each evaluation).

Table 8: Age, sex and improvement time of thrombocytopenia ([x]partial remission: 150.000/ul plts 100.000/ul).

	HIVMP	Oral prednisone (2 mg/kg)	Untreated
Number of patients	16	16	17
Mean age (range) in months	46(3-156)	46.5(19-132)	77.5(19-156)
Male/Female	11:5	10:6	7:10
Number of patients in whom plt elevated			150.000/ul
3rd day treatment	11(68.7%)	-	-
1st week treatment	13(81.1%)	3(18.7%)	2(11.7%)
2nd week treatment	15(93.7%)	5(31.2%)	5(24.4%)
4th week treatment	16(100%)	7(43.7%)	12(70.5%)
up to 4 months	7+2(partial)[x] 14+1 (partial)		

Table 9: Age, sex and days of platelet response to HIVMP in children unresponsive to oral prednisone (2 mg/kg). ([x] partial remission: 150.000/ul plt 100.000/ul).

Number of patients	6
Mean age (range) in montths	72 (48-84)
Male/Female	4/2
Number of patients in whom plt	150.000/ul
3rd day	3+1 (partial)[x]
1 week	5 (83.3%)
Unresponsive	1
Number of patients relapsed	2(2 and 6 months later)

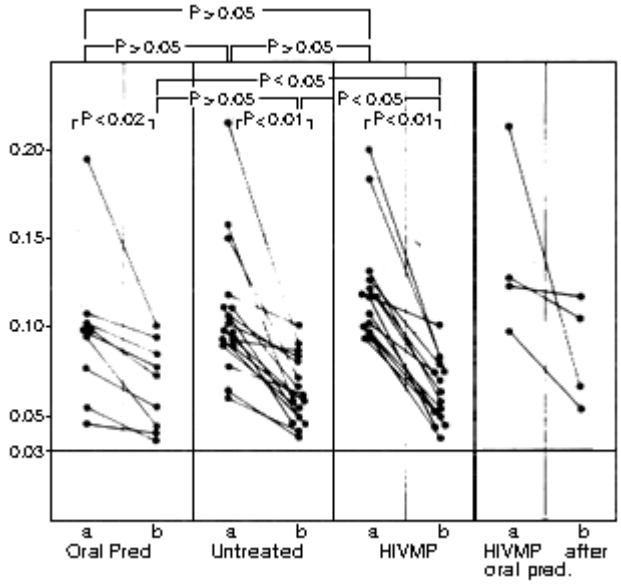

Figure 6: Intial (a) and remission (b) antiplatelet antibodies of the patients to the treatment are shown.

Antiplatelet antibodies also decreased in all treated patients more markedly HIVMP administered group (Figure 6). Five of the 6 patients who were found unresponsive to oral prednisone responded to HIVMP treatment.

The fact that in this study, the improvement of platelet counts occurred in about 70% of the children in the untreated group occurred within 4 weeks and in 88% of these children by the end of four months would support the concept that treatment of this disorder in children may not be mandatory if bleeding is not a problem; however, prediction is not possible. Very early (3 days) platelet response was observed only in the HIVMP group as in chronic ITP. Therefore, if treatment is required because of severe bleeding or life-threatening complications in ITP, we believe HIVMP to be the best choice. It should be taken into consideration that these new platelets were shown to be functional. This treatment is not only cheaper than intravenous gamma globulin administration but much better.

Therapy of chronic ITP, if not responsive to classical prednisone (2 mg/kg), is not easily. When it is symptomatic several approaches have been tried with some hope for improvement of thrombocytopenia. Cyclophosphamide (1), vincristine (14), plasmapheresis, danazol, cyclosporine have been used. Intravenous IgG especially advocated for this condition with some success. We have used high dose intravenous methoylprednisolone (as in the treatment of acute ITP) at 29 children with this disorder, 12 girls and 17 boys (13). Sustained improvement of ITP was observed in 11 (37.9%) patients. Non persistent improvement of thrombocytopenia observed in 13 (44.8%) patients. Response to the treatment was not observed only in 5 (17.2%) patients. Eighty three percent response is the highest response obtained in the treatment of chronic ITP with all alternatives especially sustained response considered.

We believe that HIVMP should be used in the treatment of acute or chronic ITP cases when treatment becomes maridatory.

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