Evaluation of clinical characteristics, diagnosis and management in childhood immune thrombocytopenic purpura: a single center's experience

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Diagnostic evaluation and management in childhood immune thrombocytopenic purpura (ITP) are controversial. We reviewed the files of 162 children with ITP to evaluate clinical characteristics, response to treatment and outcome. History of antecedent infection, vaccination and serologic evidence for acute viral infection were present in 48%, 5% and 17% of the patients, respectively. At diagnosis, two-thirds of the patients had a platelet count of <10,000/μl but only 10% had major bleedings. Intracranial hemorrhage was seen in two patients (1.2%) with a mortality rate of 0.6%. Sixteen percent developed chronic ITP. The rate of platelet recovery with mega-dose methylprednisolone (30 mg/kg/d for 3 and 20 mg/kg/d for 4 days) was similar to that obtained with intravenous immunoglobulin or oral prednisolone. Four of seven patients with ITP responded to splenectomy. These data show that mode of treatment has no effect on the clinical course and prognosis of childhood ITP.

Key words: children, immune thrombocytopenic purpura, treatment.

Childhood immune thrombocytopenic purpura (ITP) is generally considered to be a benign disorder with mild bleeding symptoms and a high rate of spontaneous recovery. Serious bleedings generally occur when platelet count (PC) falls below 20,000/μl. The most feared problem is intracranial hemorrhage (ICH), which is reported to occur in less than 1% of patients. The incidence of serious bleedings or ICH shows wide variations in different series[1-5]. The rationale for treatment with steroids or intravenous immunoglobulin (IVIG) is to increase PC rapidly over the safe level (>20,000) and minimize the risk of fatal bleedings. However, the need for therapeutic intervention and choice of therapeutic substance have always been a subject of great debate, since there is no evidence that initial therapy can prevent fatal bleedings or chronic course of the disease and the therapeutic substances are not entirely safe[1,6-8].

There are several reports comparing effectiveness of oral prednisolone (OP), mega-dose methyl prednisolone (MDMP), IVIG and anti-D immunoglobulin in childhood ITP[9-14]. Although IVIG appears to be slightly better than the others in increasing PC rapidly[9,11,12], lower cost of treatment and ease of administration have led to widespread use of steroids[10,13]. Practice guidelines reported by several expert groups are discrepant in regard to diagnostic evaluations, criteria for treatment and choice of therapeutic agent[8,15-17]. The objectives of this study were to assess the frequency and risks of serious bleedings, the value of diagnostic procedures, effectiveness of various treatment regimens and outcome in childhood ITP.

Material and Methods

Files of children with ITP were retrospectively reviewed. There were 143 children with newly diagnosed ITP and 19 children with chronic ITP whose initial diagnosis had been made elsewhere. The diagnosis of ITP was based on the exclusion of other causes of thrombocytopenia by detailed history, physical examination, complete blood count with blood smear and

bone marrow examination. Blood counts were done by a Coulter Hematology Analyzer. Throat culture, direct Coombs tests and serum immune globulin levels were performed in all children at initial presentation. In some of the patients, antinuclear antibodies and antibodies to cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus, rubella, Parvovirus B19, human immunodeficiency virus, and hepatitis A, B and C viruses were also tested.

Major hemorrhage was defined as 1) ICH, 2) prolonged epistaxis requiring cautery or nasal packing, 3) macroscopic hematuria, 4) widespread mucosal bleedings at more than one site, and 5) any bleeding causing anemia[18].

Prior to 1987, all children with newly diagnosed ITP (n: 17) were treated with OP (1 mg/kg/d) until PC rose above 150,000/μl for a maximum period of three weeks. After 1987, MDMP 30 mg/kg for 3 days followed by 20 mg/kg for 4 days was used in all but 29 children, who received IVIG in doses of either 400 mg/kg for 5 consecutive days or 800 mg/kg for 2 consecutive days. Children (n: 15) with a PC over 20,000/μl were not given any treatment (NT group) unless they had a major bleeding symptom. Response to treatment was defined as partial response (PR) (PC between 20,000-150,000/μl) and complete response (CR) (PC > 150,000/μl). Persistence of thrombocytopenia more than six months after diagnosis was defined as chronic ITP[11].

Statistical Analysis

Data were analyzed using an SPSS program, and the results were shown as mean and standard deviation (mean ± SD). Mann-Whitney U and Kruskal-Wallis tests were used for statistical analysis, and $p < 0.05$ was accepted as the significance level.

Results

Clinical and laboratory findings at presentation in 162 children with ITP are shown in Table I.

Table I. Clinical and Laboratory Characteristics of Patients with Acute and Chronic ITP

	Acute ITP (N: 143)	Chronic ITP (N: 42)
Age (years)		
Mean	6.4 ± 3.8	7.4 ± 4.1*
Range	(2 months-16 years)	(1-15 years)
Sex		
(Female/male)	0.93 (69/74)	1.2 (23/19)
Initial platelet counts (μl^{-1})		
Mean	7640 ± 6240	21750 ± 25970*
Range	(0–27,000)	(2000–99,000)
<10,000	86 (72%)	22 (52%)
10-20,000	27 (22%)	7 (17%)
20-50,000	7 (6%)	6 (14%)
>50,000	0	7 (17%)
History of preceding viral infection	69 (48%)	5 (12%)**
History of vaccination	6 (44%)	1 (2.4%)
BCG	2 (1.33%)	
MMR	1 (0.77%)	1 (2.4%)
DPT-P	3 (2%)	
Dry hemorrhage	77 (54%)	13 (31%)
Mean PC	5.285 ± 3.960	10.875 ± 11.600
Wet hemorrhage	54 (38%)	23 (55%)
Mean PC	10.175 ± 11.400	14.400 ± 15.500
Major Bleeding	10 (7%)	5 (12)
ICH	1 (0.7%)	1 (2.4%)

ITP: Immune thrombocytopenic purpura. BCG: Bacille bilié Calmette Guérin. MMR: Measles-mumps-rubella. DPT-P:Diphtheria, pertussis, tetanus-polio. PC: Platelet count. ICH: Intracranial hemorrhage.
*$p<0.05$.
**$p<0.001$.

In 143 children with newly diagnosed ITP, the presenting symptoms were simple skin petechiae (11%), ecchymoses (17%), petechiae and ecchymoses (34%), gingival bleeding (9%) and epistaxis (32%). Fourteen (9.8%) of 143 children presented with major bleedings as epistaxis requiring nasal package (n: 4), macroscopic hematuria (n: 3), extensive gingival bleeding (n: 3), gross gastrointestinal system bleeding (n: 2), and menorrhagia causing anemia (n: 2). There was history of an antecedent viral infection in 69 (48%), vaccination in 6 (4%) and bee sting in 1 (0.7%) children. PC during major bleeding episode was under 5,000/μl in 10 patients (71%), 6,000 in 2, 12,000 in 1 and 34,000 in 1 patient(s). The latter case had normal coagulation screen but further investigations of hemostatic function were not done.

Intracranial hemorrhage occurred in 2 (1.2%) of 162 patients (1 with acute and 1 with chronic ITP). PC was <3,000/μl during ICH in both cases. The first case was a five-year-old boy who presented with widespread mucosal and retinal bleedings 10 days after chickenpox and developed fatal ICH 16 hours after admission. The other case was an 11-year-old boy with chronic ITP unresponsive to steroid and IVIG. He developed ICH shortly after a strenuous exercise and showed complete recovery after emergency splenectomy.

Initial laboratory investigations for antinuclear antibodies and Coombs test were negative in all patients. Seven (5%) of 143 patients had abnormalities in serum immune globulin levels. Viral screen was performed in 40 patients, and serologic evidence for recent viral infection (elevated IgM) was found 7 (17%) (rubella in 3, EBV in 2, hepatitis A and CMV in 1 patient each).

Treatment Response in Acute ITP

A total of 82 children with newly diagnosed acute ITP were given MDMP treatment (Table II). The proportions of complete and partial responders were 23% and 79% on day 4 and 72% and 97% on day 8, respectively. Of the two patients in whom PC did not increase from baseline within the first week, one achieved CR in the third week while the other did not respond to further treatment with IVIG and became chronic ITP. At the end of week 4, 66% of children still had normal PCs. None of the children experienced a major bleeding episode or fatal bleeding after the start of MDMP treatment.

Twenty-nine children were given IVIG as the preference of the consultant physician. As seen in Table II, the rates of platelet recovery on day 4 and day 8 were not significantly different from that obtained with MDMP. There were 17 children who were treated with 1 mg/kg OP and 15 children who were observed without treatment. Although the number of subjects in these groups was not sufficient for a sound statistical comparison, the rate of platelet recovery was close to that observed in MDMP and IVIG groups.

Table II. Platelet Response, Recurrence and Retreatment in Various Treatment Groups of Acute ITP

	MDMP n (%)	Prednisolone n (%)	IVIG n (%)	No therapy n (%)
Number of patients	82	17	29	15
Platelet > 20,000/μl				
4th day	65 (79)	14 (82)	21 (72)	13 (86)
8th day	80 (97)	15 (88)	26 (89)	13 (86)
1st month	82 (100)	16 (94)	26 (89)	15 (100)
Platelet > 150,000/μl				
4th day	19 (23)	10 (59)*	6 (20)	1 (7)
8th day	59 (72)	10 (59)	15 (51)	8 (53)
1st month	66 (80)	8 (47)	15 (51)	9 (60)
Recurrence (PC < 150,000/μl)	18 (22)	3 (18)	7 (24)	2 (13)
Retreatment during follow-up	6	2	2	1
Chronicity (16%) (n: 23)	14 (17)	2 (12)	5 (17)	2 (13)

*p<0.001.
MDMP: Mega-dose methyl prednisolone. IVIG: Intravenous immunoglobulin. PC: Platelet count.

Relapses

Thirty children who had achieved CR relapsed. Relapse rate was 22% in MDMP group, 18% in OP group, 24% in IVIG group and 13% in NT group (Table II).

Side Effects of Treatment

Adverse effects observed in the MDMP group included transient hypertension in 3 (3.6%), hyperglycemia in 2 (2.4%) and weight gain in all cases. Allergic reactions were seen in 2 (6.8%) and aseptic meningitis in 1 (3.4%) of 29 patients treated with IVIG.

Chronic ITP

Of the 143 children with acute ITP, 23 (16%) were still thrombocytopenic six months after diagnosis and defined as chronic ITP. These patients were analyzed with 19 children who were admitted with previously diagnosed chronic ITP, making a total of 42 patients with chronic ITP. As seen in Table I, mean age and female/male ratio were higher in patients with chronic ITP as compared to children with acute ITP. Therapy in chronic ITP group consisted of MDMP in 20, IVIG in 8, OP in 5, vincristine in 2, and IVIG plus MDMP in 7 patients. Responses to treatment and recurrence rate are shown in Table III.

Splenectomy

A total of 7 patients with chronic ITP underwent splenectomy. Three were unresponsive to steroid and 4 were unresponsive to both steroid and IVIG. Splenectomy produced CR in 4 (57%), PR in 2 (28%), and no response in 1 (15%).

Discussion

Immune thrombocytopenic purpura is the most common cause of acute onset thrombocytopenia in otherwise healthy children[19]. The diagnosis can be made by history, physical examination, complete blood count and careful review of peripheral blood smear in a typical case[8]. Bone marrow examination at presentation is generally considered to be unnecessary if there is no sign of marrow failure or infiltration and steroid treatment is not planned[14]. Confirmatory bone marrow examination disclosed a different diagnosis in five of the 127 cases (3.9%) with initial diagnosis of ITP in one study[20]. Another retrospective analysis did not reveal a single case of leukemia in 332 cases with typical hematological features of ITP[21]. Over the period of our study, bone marrow examination confirmed ITP in all children but revealed acute lymphoblastic leukemia in only one case despite clinical and laboratory findings being consistent with acute ITP. Therefore, bone marrow examination is still justified if steroid therapy is contemplated. Other routine investigations such as direct Coombs test, antinuclear antibodies and/or DNA antibodies were negative in all patients. These tests are considered to be unnecessary during the initial evaluation of ITP by the American Society of Hematology (ASH) and British guidelines[8,15].

Clinical characteristics of our patients were typical for childhood ITP; mean age at onset was 6 years, males and females were equally affected, and the disease followed an infection or vaccination in 48% and 6% of the patients, respectively. EBV appears to be the most common viral infection associated with ITP, as reported in 32.4% of children with ITP[22-24].

Table III. Platelet Response to Treatment and Recurrence in Children with Chronic ITP

	MDMP (n)	OP (n)	IVIG (n)	VCR (n)	Combination (n)
Platelet count >150,000	14	2	4	–	–
Platelet count 20,000-150,000	5	2	2	2	3
No response	1	1	2	–	4
Recurrence					
(PC<20,000/μl) time after complete or partial response					
1 to 2 weeks	5	–	2	–	–
3 to 4 weeks	1	–	1	1	–
1 to 6 months	7	6	3	1	5
>6 months	1	1	–	–	2

MDMP: Mega-dose methyl prednisolone. OP: Oral prednisolone. IVIG: Intravenous immunoglobulin. VCR: Vincristine. PC: Platelet count.

We found serological evidence for a recent viral infection with common viruses including rubella, EBV, CMV and hepatitis A in 17% of patients at diagnosis. Interestingly, one case of acute ITP developed after bee sting, which has not been noted previously.

The true incidence, timing, specific sites and risk factors for major bleedings in childhood ITP are not precisely known. Frequency of so-called clinically significant or major bleedings ranges from 3 to 17% in different reports[2,18,25,26]. One of the reasons for this discrepancy may be the lack of a uniform definition for these bleedings[2,18]. In the present study, we used the same criteria for major bleeding described by Medeiros and Buchanan[18] and found a similar incidence figure (9.8% vs. 11%). The incidence of ICH in their study (0.8%) and in ours (0.6%) was also similar. This complication has been observed in 0.1% and 1.2% of children with ITP[1-5] and at least one study indicates that it is more common in adolescents[27]. There is usually a precipitating factor such as use of aspirin, head trauma, strenuous exercises or accompanying bleeding disorder in cases of ICH. Strenuous exercise seemed to be the cause of ICH in one of our patients while the other case had had varicella infection, which is considered to be a risk factor for ICH[9,28]. Acute onset with widespread mucosal bleedings from multiple sites and retinal bleedings in the latter case are alerting signs of forthcoming ICH. The incidence of ICH among our 42 patients with chronic ITP (2.3%) was much lower than the figure of 11.2% ICH in chronic ITP previously reported from Turkey[27]. We have not observed this complication within the last 10 years, probably due to general improvement in medical care.

Management of childhood ITP has always been a subject of enormous controversy. Most experts believe that PCs spontaneously increase to hemostatic levels (PC>20,000/μl) in the majority of children within a week or so and that the initial treatment has no effect on the chronic course of the disease[1,6,7]. However, many physicians prefer to give treatment to shorten the risky period[8]. ASH guidelines recommend that children with PC <20,000/μl and significant mucosal bleedings and those with counts <10,000/μl with minor purpura should be treated with IVIG or glucocorticoids. British and German guidelines however, do not recommend IVIG or sustained steroid treatment for a PC <10,000/μl without active bleeding and state that IVIG be reserved for life-threatening bleeding[15-17]. Thus, the issue of treating the majority of acute ITP cases presenting with PC <10,000/μl and minor bleedings like simple petechiae or bruising symptoms remains equivocal. In our study group, nearly two-thirds of major bleedings occurred when PCs were less than 10,000/μl and both cases of ICH occurred with a PC of 3,000/μl, a finding consistent with the recommendation that patients with PC <5,000/μl should receive IVIG or steroid to prevent life-threatening bleedings.

There currently are no clear criteria for selecting IVIG or corticosteroids as the first-line therapy, since both medications raise PCs over 20,000/μl within a short period of time. Treatment with MDMP in a small number of patients has been shown to produce remission rates close to that obtained with IVIG[10,13]. Thereafter, MDMP therapy gained widespread acceptance in Turkey, essentially due to its lower price and ease of administration as compared to IVIG. Our experience with MDMP in 82 cases of acute ITP was essentially similar to previous reports[10,13]. The rate of CR on day 7 (72%) was comparable to that obtained by Ozsoylu et al.[10]; however, it was lower in our study (23%) than theirs (60%) on day 3. However, attainment of safe platelet level (>20,000/μl) was achieved within 72 hours and 7 days in 79% and 97%, respectively. These results are comparable with those obtained with IVIG by other investigators[9,11].

The rates of CR among patient groups treated with MDMP and IVIG and the NT group were not significantly different, albeit a significantly higher response rate was obtained on day 4 with conventional dose OP. However, this is not a controlled study and the numbers of patients in each group were not sufficiently comparable to reach a firm conclusion about the relative efficacy of each management option.

There would be less conflict about the treatment of ITP with the commonly used drugs if they were entirely safe and inexpensive. In almost all children treated with MDMP, side effects (transient glycosuria, hypertension) were rare (6%) and tolerable, and neither more frequent nor serious than those associated with IVIG therapy (aseptic meningitis, allergic reactions) (10%).

In conclusion, severe bleedings are rare in childhood ITP despite the fact that the majority of patients present with severe thrombocytopenia. As the prognosis is irrespective of the initial treatment modality, it is important to arrange therapy according to the patient's symptoms rather than the PC alone. Our experience with MDMP is consistent with others, reporting that its efficacy and safety profile are equal to IVIG. MDMP provides a cheaper alternative to IVIG in countries which are not self-sufficient in blood products and where availability of IVIG is limited.

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