CLINICAL STUDY

Treatment of Childhood Acute Immune Thrombocytopenic Purpura With High-Dose Methylprednisolone, Intravenous Immunoglobulin, or the Combination of Both

RANI S. GEREIGE, MD*, NILKA J. BARRIOS, MD†

Objective. **To compare the effectiveness of intravenous immunoglobulin (IVIG) alone, high dose methylprednisolone (HDMP) alone and the combination of IVIG and HDMP in the treatment of childhood immune thrombocytopenic purpura (ITP).**

Background. **Acute ITP in children is a self-limited disease with a benign course and low mortality rate. Patients with platelet count less than 20,000 x 10^9/L are at increased risk of bleeding complications, making them candidates for treatment.**

Method. **A 4 year retrospective study of 148 patients hospitalized with acute ITP was conducted to compare the effectiveness of HDMP vs IVIG vs the combination of IVIG/HDMP. Statistical methods used were descriptive statistics and variance analysis utilizing F distribution.**

Results. **The IVIG and the HDMP combination demonstrated to be superior to HDMP alone in raising the platelet count within the first 24 hours. The HDMP and IVIG combination was statistically a superior modality of treatment for patients with platelet count greater than 10,000 x 10^9/L than was IVIG or HDMP alone. Intravenous immunoglobulin had the least effectiveness in patients with platelet count less then 10,000 x 10^9/L within the first 24 hours.**

Conclusions. **IVIG followed by the combination of HDMP and IVIG is the most effective therapeutic modality in rapidly increasing the platelet count to safe levels in children with acute ITP when compared to HDMP alone within the first 24 hours. For borderline low platelet count (> 10,000 x 10^9/L) HDMP and IVIG was superior to IVIG alone.** *Key words: High dose methylprednisolone, Intravenous immunoglobulin, Immune thrombocytopenic purpura, Platelets, Children.*

Immune thrombocytopenic purpura (ITP) in children can be either acute or chronic. In childhood, the acute form of ITP (1) accounts for 85-95% of all cases, while the chronic form accounts for only 10-15% (2). Acute ITP in childhood, usually has a benign course, with 90% spontaneous recovery within 3 months of the diagnosis (3). Chronic ITP has a different course, with spontaneous remission occurring in less than 1% of the cases(4). Severe thrombocytopenia in both acute and chronic ITP carry a risk of serious hemorrhagic complications, particularly intracranial hemorrhage. Many modalities of treatment have been tried over the years with the aim to achieve a rapid rise in platelet count. These have included oral and intravenous steroids in high and low dosages, IVIG, interferon, and splenectomy. We report a 4-year retrospective study comparing IVIG alone, HDMP alone and the combination of IVIG and HDMP in the treatment of childhood ITP.

From the Department of Pediatrics, All Children's Hospital, St. Petersburg, Florida* and the Department of Pediatrics, Hematology/Oncology Section, University Pediatric Hospital†, San Juan, Puerto Rico.

Address for correspondence: Nilka J. Barrios, MD, 644 Collins St., Summit Hills, Río Piedras, Puerto Rico 00920, Phone: (787) 754-4131 Fax: (787) 754-4131.

Materials and Methods

This study was conducted retrospectively; the medical records of 148 patients admitted to All Children's Hospital in St. Petersburg, Florida, with the diagnosis of ITP over a 4 year period January 1989 to December 1992) were reviewed. Age ranged from 6 months to 15 years; the presenting signs and symptoms are summarized in Table 1. Information collected from medical records included age, sex, race, platelet count on admission, significant illness before presentation, signs, symptoms and,

laboratory data during the admission, follow-up platelet counts during hospital stay, treatment modalities and significant side effects.

Inclusion criteria. Patients were included in the study if they met the following criteria:

- ITP diagnosis made by bone marrow aspirate showing adequate cellularity with increased megakaryocytes (findings consistent with ITP) and no evidence of malignancy.
- Platelet counts at diagnosis of less than 20,000 x 10^9/L.
- Patients treated with either HDMP (30 mg/kg/day x 3 days) or IVIG (1 gm/kg/day x 2 days) or a combination of HDMP (30 mg/kg/day x 3 days) and IVIG (1 gm/kg/day x 2 days).
- Patients with recurrent thrombocytopenia occuring more than 2 weeks apart were included as separate admissions, regardless of the previous treatment modality used as long as they were treated with any of the above modalities and were not on outpatient therapy after their last discharge.
- Patients with the inclusion criteria, documented platelet count on admission and follow-up daily platelet counts after therapy was instituted (at least first 24 hours after starting treatment).

Exclusion criteria. Cases were excluded from the study if:

- Other modalities of treatment were used or if different dosages were used in the modalities being tested.
- On follow-up admissions the diagnosis changed to thrombotic thrombocytopenia purpura (TTP) or Evan's syndrome. All previous admissions of these particular cases were excluded.
- Patients with positive antinuclear antibodies (ANA) and Coomb's tests.
- Patients with no documented platelet counts upon admission.
- Patients with no follow-up platelet count after the first dose of treatment (day 1).
- Patients with chronic ITP on other maintenance modalities of treatment during remission periods (interferon, splenectomy, IVIG infusions every 3 weeks).

Statistical methods used were descriptive statistics and variance analysis utilizing F distribution.

Results

One hundred and forty eight admissions were reviewed. Ninety eight patients were treated with either 30 mg/kg/day x 3 days of HDMP or 1 gm/kg/day x 2 days of IVIG or a combination of both. All 98 admissions were diagnosed with bone marrow aspirates and were tested for antinuclear antibodies (ANA). Out of the 98 cases, 9 were excluded because of positive ANA and 3 cases were excluded for not meeting the criteria for follow-up platelet count, leaving us with a study sample of 86 cases. Patient characteristics and presenting signs and symptoms are shown in Tables 1 and 2.

The sample was divided into 2 subsets based on the modality of treatment received: 44 cases received HDMP, 24 cases received both IVIG and HDMP, and 18 cases received IVIG (Table 2). Bruises and petechiae were the most common presenting complaints that brought the patient to medical attention (Table 1).

Table 3 shows a profile of our samples with mean (range), initial (day 0) and follow-up platelet counts (day 1) in each group with the number of patients with platelet counts < 20,000 x 10^9/L.

Table 1. Characteristics of Patients with Acute ITP Treated with IVIG, HDMP or a Combination of Both

	HDMP # (%)	IVIG # (%)	HDMP+IVIG # (%)	Total # (%)
Sex				
Male (%)	26 (59%)	14 (78%)	11 (46%)	51 (59%)
Female (%)	18 (41%)	4 (22%)	13 (54%)	35 ($!%)
Age				
Mean	4ylm	7y3m	1y7m	5y
(range)	(6m-14y)	(16m-15y)	(11m-10y7m)	(6m-15y)
Ethnicity				
white	39 (89%)	16 (89%)	18 (75%)	73 (85%)
black	3 (7%)	0 (0%)	2 (8%)	5 (6%)
Hispanic	2 (4%)	2 (11%)	4 (17%)	8 (9%)
	44	18	24	86

m=month
y=years

When we examined the treatment groups based on available data at the beginning of hospitalization, we found no significant difference in baseline (day) platelet levels between the treatment groups (by F-test, p=0.18 on 2 and 85 degrees of freedom), nor the age of the children (based on proportion 3 years or older, Chi-square=4.13 on 2 degrees of freedom, p=0.13), nor ethnicity (Chi-square=4.30 on 4 degrees of freedom, p=0.37) which made our non-randomized sample very comparable and matched for the above variables.

We then compared the day 11 average levels of platelets among the three treatment groups, initially without adjusting for the level of platelets at presentation, gender, age or ethnicity; we then compared them with these factors included. We also compared the proportions of each

Table 2. Presenting Signs and Symptoms of Children with Acute ITP

Signs /Symptoms	HDMP	IVIG	HDMP+IVIG	Total (%)
Bruises & petechiae	41	15	21	77 (89%)
Upper respiratory infection	8	2	2	12 (14%)
Gingival bleeding	23	3	10	36 (42%)
Hematoma post trauma	6	4	2	12 (14%)
Otitis media	5	3	2	12 (14%)
Epistaxis	3	3	3	9 (10%)
Pharyngitis	2	2	1	5 (6%)
Fever	1	2	1	4 (5%)
Rectal bleeding	1	1	-	2 (2%)
Hematuria	2	-	-	2 (2%)
Aseptic meningitis	1	-	1	2 (2%)
Vomiting	2	-	-	2 (2%)
Sinusitis	1	-	1	2 (2%)
Chickenpox (<2 wks)	1	-	-	1 (1%)
Urinary tract infection	1	-	-	1 (1%)
Diarrhea	-	-	1	1 (1%)
Upper gastrointestinal bleeding		1	-	1 (1%)

treatment group whose platelets were raised above 20,000 x 10^9/L or above 100,0000 x 10^9/L on day 1. In all of these analyses, we reach the same conclusion; namely, that those treated with HDMP had significantly lower levels of platelets by day 1 than did the other two groups. In addition, there was an indication that the combined treatment may not be quite as effective among patients whose baseline platelet levels were extremely low compared to IVIG treatment.

The unadjusted differences in day 1 platelet levels indicated a highly significant benefit for IVIG and the combination of HDMP and IVIG over HDMP alone. The mean for the HDMP group was 34,000 x 10^9/L lower than that for IVIG and 29,000 x 10^9/L lower than the combination. The HDMP mean is more than one full standard deviation lower than those of the other groups (by F-test on 2 and 84 degrees of freedom, p=0.0001). Since we also found that the baseline level of platelets affected day-1 level (R-square=0.21), we performed an analysis of covariance. There was a significant interaction between treatment and baseline platelet count (F=3.59 on 2 and 80 degrees of freedom; p=0.03). This interaction also held up when we considered age, ethnicity, and gender of the patient. No significant side effects or adverse reactions were noticed in our closely monitored patients.

Discussion

Acute ITP in children carries a low mortality rate (<1%) with intracranial hemorrhage, gastrointestinal bleeding, and postsplenectomy sepsis being the leading causes of death (3). The risk of bleeding is highest in children with extremely low platelet counts (< 20,000 x 10^9/L), which usually occurs in the first week following the diagnosis of ITP. When faced with a life-threatening bleeding, it is extremely important to have an effective treatment to which patients respond with an increase in platelet count as soon as possible. Recent reports have indicated that either high-dose steroids or IVIG can increase the platelet count reliably; and in most cases within 72 hours (4,5,6).

The postulated mechanism of action of methylprednisolone is by inhibiting antiplatelet antibody formation or decreasing the amount of antibody present in the platelets. It is also reported to hinder the phagocytosis of platelets by macrophages (3). On the other had, IVIG leads to transient blockade of the immune clearance mechanism mediated by Fc receptors, and is believed to activate T-cells and suppresses B-cells leading to inhibition of formation of antiplatelet antibodies (3).

In the present retrospective study, we compared the three modalities of medical treatment in childhood ITP. From the data collected, HDMP clearly fails to show a significant increment in platelet counts until the second day of treatment (48 hours). This finding was in agreement with previous studies using methylpred-nisolone (7,8,9,10). IVIG showed a superior efectiveness in raising the platelet count significantly within the first 24 hours, a finding in agreement with a previous study (3), so did the HDMP and IVIG combination. However, HDMP and IVIG combination became a statistically superior modality of treatment in cases with borderline low

Table 3. Patients as a Function of Platelet Count and Treatment

Treatment	Day	No. (%) of cases with platelets between 20-30,000 X 10^9/L	No. (%) of cases with platelets from 10-20,000 X 10^9/L	No. (%) cases with platelets <10,000 X 10^9/L	Mean count (Range)
HDMP	0	5 (11.3%)	8 (18.1%)	31 (70.4%)	9 (0-30)
	1	9 (20.4%)	14 (31.8%)	16 (36.3%)	16 (0-65)
IVIG	0	3 (16.0%)	8 (44.0%)	7 (38.0%)	18 (2-24)
	1	2 (11.1%)	2 (11.1%)	3 (16.6%)	50 (2-84)
HDMP+IVIG	0	4 (16.6%)	7 (29.1%)	13 (54.1%)	11 (2-27)
	1	3 (12.5%)	7 (29.1%)	2 (8.3%)	44 (7-108)

initial platelet counts (> 10,000 x 10^9/L), a finding not previously reported. IVIG had the most effectiveness in patients with very low platelet counts (< 10,000 x 10^9/L). These patients have the highest risk for bleeding complications and are the ones that will certainly benefit the most from such therapeutic modality, making IVIG the first-line therapy compared to the other two.

This conclusion has significant therapeutic implications on the use of IVIG in patients with extremely low platelet counts. IVIG, unlike corticosteroids, does not carry the risk of a partial remission effect in acute lymphoblastic leukemia. New patients presenting with significantly low platelet counts, life-threatening bleeding, or hemodynamic instability can be safely treated with IVIG with no risk of 'masking' a leukemia.

When the two treatments are compared in terms of cost we estimate that 30 mg/kg/day/dose of methylprednisolone for a 20 kg child will be $9.43/day and $285 for a 3 day course. IVIG, on the other hand, at 1g/kg/day for a 20 kg child will cost $494.5 per dose and $3,107.96 for a 2 day course. Because of the cost factor, one should weigh closely the benefit and indications for IVIG administration, and it should be reserved for cases at high risk of bleeding.

The lack of secondary effects such as fever, headaches or hypotension from these three modalities of treatment was in agreement with other studies reported in the literature (3).

We conclude from this study that IVIG followed by HDMP and IVIG combination is the most effective therapeutic modality in quickly raising the platelet count to safe levels in children with acute ITP when compared to HDMP. For borderline low platelet counts (> 10,000 x 10^9/L), HDMP and IVIG combination is superior to IVIG alone.

Although our samples were significantly comparable, this study was retrospective and non-randomized. However, there were no indications of imbalance in age, ethnicity, race, and baseline levels of platelet count. Therefore the door is now open for future prospective randomized, controlled trials to evaluate treatment modalities and to monitor short-and long-term side effects. In addition, a long-term follow-up study is needed to evaluate the frequency of recurrence of thrombocytopenia with different treatment modalities.

Acknowledgement

We would like to thank C. Hendricks Brown, PhD from the Moffit Cancer Center in Tampa, Florida for this assistance in the statistics and Jerry Barbosa, MD from the Pediatric Hematology/Oncology Department, All Children's Hospital, St. Petersburg, Florida for his clinical assistance.

References

1. Ozsoylu S, Onat N. Idiopathic thrombocytopenic purpura in infants under 6 months of age. A retrospective study. Clin Pediatr 1992; 31:626-8.
2. Imbach P, D'Apuzzo V, Baumgartner C, Hirt A, Morell A, Rossi E, Schoni M, Vest M, Wagner HP. High dose intravenous gammaglobulin for idiopathic thrombocytopenic purpura in childhood. Lancet 1981;1:1228-31.
3. Barrios NJ, Humbert JR, Mc Neil J. Treatment of acute idiopathic thrombocytopenic purpura with high-dose methylprednisolone and immunoglobulin. Acta Haematol 1993;89:6-9.
4. Dubbeld P, Van der Heul C, Hillen HF. Effect of high-dose Dexamethasone in prednisone-resistant autoimmune thrombocytopenic purpura (ITP). Neth J Med 1991;39:6-10.
5. Bussel JB, Goldman A, Imbach P, Schulman I, Hilgarth I, Hilgartner M. Treatment of acute idiopathic thrombocytopenia of childhood with intravenous infusions of gammaglobulin. J Pediatr 1985; 106:886-90.
6. Dan K, Gomi S, Kuramoto A, Maekawa T, Nomura T. A multicenter prospective study on the treatment of chronic idiopathic thrombocytopenic purpura. Int J Hematol 1992;5:287-92.
7. Jayabose S, Patel P, Inamdar S, Brilliant R, Mamtani R. Use of intravenous methylprednisolone in acute idiopathic thrombocytopenic purpura. Am J Pediatr Hematol Oncol 1987;9: 133-135.
8. Ozsoylu S. High-dose intravenous methylprednisolone for childhood idiopathic thrombocytopenic purpura. Am J Dis Child 1988;142:133-135.
9. Ozsoylu S. Intravenous immunoglobulin or megadose methylprednisolone for the treatment of idiopathic thrombocytopenic purpura. Am J Hematol Oncol 1991;13:364.
10. Van Hoff J, Ritchey AK. Pulse methylprednisolone therapy for acute childhood idiopathic thrombocytopenic purpura. J Pediatr 1988;113:536-8.