

Low Dose Intravenous Immunoglobulin for Acute Immune Thrombocytopenic Purpura in Children

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Acute immune thrombocytopenic purpura (ITP), previously known as idiopathic thrombocytopenic purpura, is a common cause of thrombocytopenia in children. Acute ITP is diagnosed when a child presents with abnormal bleeding diathesis due to isolated thrombocytopenia, with increased megakaryocytes in bone marrow aspirates, and absence of other known disorders.¹ Acute ITP is caused by self-limited autoimmunity to platelets, leading to platelet destruction in the spleen.² Although thrombocytopenia spontaneously resolves in most cases within 6 months after diagnosis, platelet count is often very low with the associated risk of spontaneous bleeding, thus necessitating treatment. Most experts agree that treatment is indicated when children with acute ITP have spontaneous bleeding or have platelet count below 20,000/ μ l.¹

Intravenous immunoglobulin (IVIG) is one of the most effective treatments for acute ITP in children. It is believed that large

SUMMARY Acute immune thrombocytopenic purpura (ITP) is a self-limited autoimmune disorder to platelets. The disease responds well to intravenous immunoglobulin (IVIG) treatment. We studied the efficacy of low dose (1 g/kg) IVIG to treat acute ITP in children. Of 17 children with ITP and platelet counts < 20,000/ μ l, 13 (76%) had rapid platelet count recovery, reaching safe level (> 50,000/ μ l) within 4 days after 1 g/kg IVIG. Four children needed a second dose. In 5 of 15 patients, platelet counts recovered to normal without recurrence, while in 10 patients, platelet counts declined again 2-3 weeks after the initial treatment; 6 of whom (40%) needed re-treatment. All but one patient had complete recovery of the platelet count by 6 months. Adverse effects of low dose IVIG were minimal. We recommend that for childhood ITP, 1 g/kg IVIG should be tried initially. If inadequate response is seen (platelet count < 30,000/ μ l) by 48 hours, a second dose is needed.

amount of immunoglobulin acts by saturating Fc receptors on phagocytic cells, thus preventing them from attacking auto-antibody-coated platelets.² IVIG at 2 g per kg body weight over 5 days or 48 hours has been shown to be superior to treatment with high-dose prednisolone and to no treatment in several trials.³⁻⁶ However, despite its efficacy, the cost of IVIG is often too high to be used in medical practice in the developing world.

To find an economical way to use IVIG, we investigated the use of IVIG at lower doses for the

treatment of acute ITP in children.

PATIENTS AND METHODS

Newly diagnosed and previously untreated patients with acute ITP between 3 months and 15 years of age with severe thrombocytopenia (platelet count <20,000/ μ l) and a bone marrow aspirate that

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revealed normal cellularity with normal or increased megakaryocytes, without other abnormalities, were included in the study. Patients with diseases known to be associated with thrombocytopenia¹ from peripheral destruction of platelets, including HIV infection, and hemangioma, were excluded. Patients who had prior treatment with corticosteroid and patients who had a history of allergy to IVIG or IgA deficiency were also excluded from this study.

The IVIG preparation used in this study was I.V. Globulin®. I.V. Globulin® was purified from volunteer plasma from Thai donors at the National Blood Center, Thai Red Cross Society, using Kohn fractionation provided by the Korea Green Cross Corporation, Seoul, Korea. The supplied batch (lot number 1180149, manufacturing date 18 February 1998, expiration date 7 February, 2000) was tested to have the following properties: pH 6.4-7.2, IgG content 100%, anti-complement ≤ 20 units, pyrogen test: temperature reaction $< 1.3^{\circ}\text{C}$, absence of hepatitis B surface antigen (HBsAg), anti-HIV, anti-HCV, and presence of measles antibody titer of 22 units/150 mg.

All patients whose parents consented to this treatment regimen were admitted to Chulalongkorn Hospital, Bangkok, Thailand, and infused with IVIG at 1 g/kg body weight continuously over 24 hours. Each 2.5 g vial IVIG was reconstituted with 50 ml sterile water for injection and infused at the prescribed rate. Complete blood counts (CBC) were determined using a Technicon H*3 automated CBC analyzer followed by manual confirmation of platelet counts under phase contrast microscopy. In each case, CBCs were determined before

and daily after IVIG infusion until a platelet count of $>50,000/\mu\text{l}$. If the platelet count did not rise above $50,000/\mu\text{l}$ by 96 hours after the start of the infusion, a second dose of IVIG was infused at 1 g/kg body weight as continuous infusion over 24 hours, and the platelet count was followed daily. When the platelet count reached $> 50,000/\mu\text{l}$, the patient was discharged and the CBC was checked once weekly for four consecutive weeks. If the platelet count declined again below $20,000/\mu\text{l}$, the patient was re-treated at the physician's discretion, either with a repeat dose of IVIG, or with oral prednisolone starting at 2 mg/kg/day.

The following symptoms and signs were recorded during IVIG infusion: body temperature, pulse rate, blood pressure, presence or absence of rash, headache, or other signs of anaphylactoid reactions. If any sign of an anaphylactoid reaction occurred, the infusion was immediately stopped, and symptoms were treated at the physician's discretion. If the symptoms resolved spontaneously, IVIG infusion was then resumed at a lower rate.

Data were recorded in Excel 5.0 spreadsheets. Survival curves were plotted using SPSS® 10.0.1.

RESULTS

Early response to IVIG treatment

Between September 1998 and February 2000, 22 children met the inclusion criteria for diagnosis of acute ITP and had platelet counts below $20,000/\mu\text{l}$. Five patients were excluded from the study because of treatment with corticosteroids before

referral. Seventeen children, 8 males and 9 females, with a median age of 2 years and 6 months, were treated with IVIG and followed prospectively. The median platelet count prior to treatment was $6,000/\mu\text{l}$. After 24-hour IVIG infusions, platelet counts rose above $20,000/\mu\text{l}$ by the end of infusions in the majority of cases (12 of 17, Fig. 1A). The median time for platelet counts to rise above $50,000/\mu\text{l}$ was 2 days after starting IVIG. In most cases (13 of 17, 76%), platelet counts rose above this level within 4 days after initiation of IVIG infusion (Fig. 1A). Re-treatments with additional IVIG at 1 g/kg were given in 4 cases whose platelet counts did not rise above $50,000/\mu\text{l}$ within 4 days (Fig. 2). All but one case had prompt resolution of thrombocytopenia within 1, 2, and 5 days after initiation of the second dose. We found that all of the patients who responded to IVIG 1 g/kg, but none of the 4 patients who eventually needed IVIG 2 g/kg, had platelet counts above $30,000/\mu\text{l}$ at 48 hours after initiation of IVIG infusion.

Duration of efficacy

Duration of efficacy of low dose IVIG treatment was evaluated in 15 of 17 cases who had been followed up for at least 4 weeks. The median peak platelet count after IVIG at 1 g/kg was $144,000/\mu\text{l}$ in the second week. Nine cases had complete resolution of thrombocytopenia (platelet counts above $150,000/\mu\text{l}$) by the second week after treatment (Fig. 1A). In one third (5 of 15) of the patients, platelet count continued to rise. However, in most cases (Fig. 2), platelet counts declined again in the 2nd week (6 cases), or in the 3rd week (4 cases), after initial treatment. In

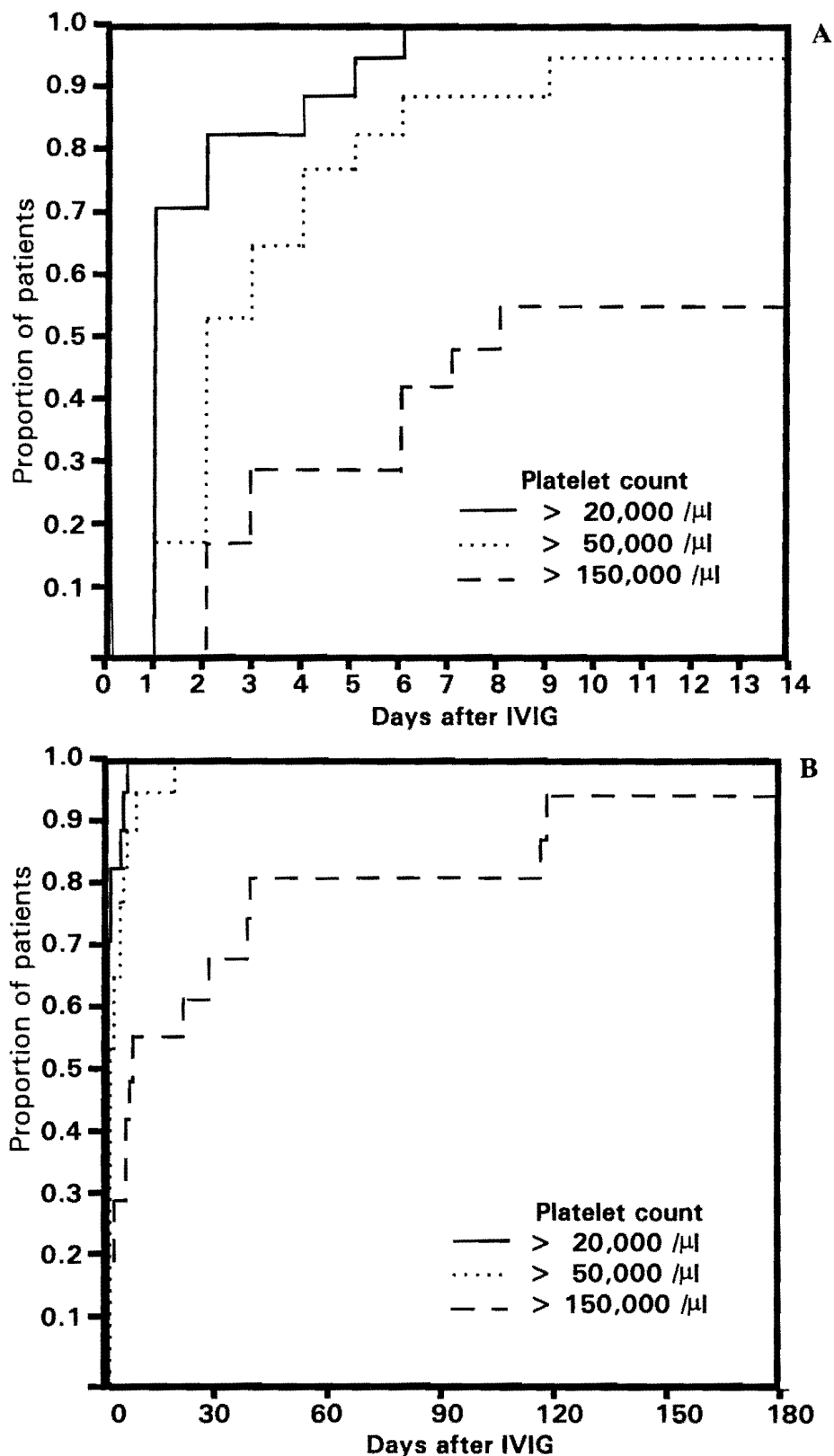
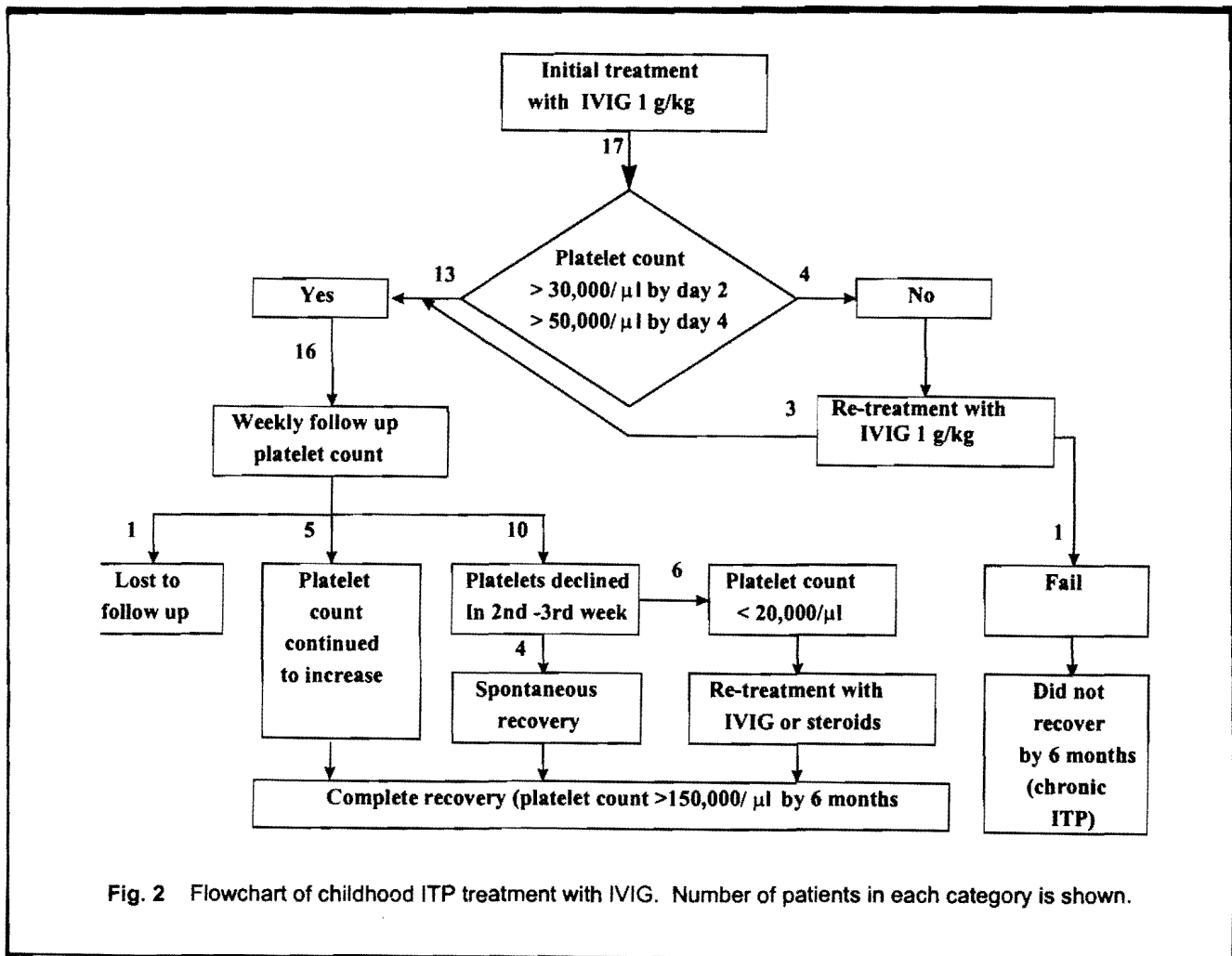


Fig. 1 Proportion of patients with platelet recovery to various level. A. in the first two weeks, B. up to 6 months after diagnosis.



6 cases (40%, Fig. 2), the platelet counts fell below 20,000/ μ l, necessitating re-treatments with either IVIG (2 cases) or oral prednisolone (4 cases). Three patients needed re-treatment in the second week, while the other three were re-treated at day 17, 21, and 39 after the initial treatment. In all but one cases treated with oral prednisolone, satisfactory responses were obtained, although the patients needed a maintenance dose of prednisolone for 2-4 months. The two patients who were re-treated with IVIG, had prompt but temporary responses. They were switched to oral prednisolone treatment at the subsequent recurrences.

Long-term follow-up

Thirteen patients were followed for at least 6 months to study the natural history of the disease. The median time to resolution (platelet count above 150,000/ μ l) was 7.5 days after the initial treatment (Fig. 1A). Thrombocytopenia completely resolved within 6 months in all but one patients (Figs. 1B and 2). This patient did not respond well to IVIG or oral corticosteroid treatment.

Safety of IVIG infusion

During the 24-hour IVIG infusion, each patient was moni-

tored for vital sign changes and observed for known adverse reactions. Only one case had a transient erythematous macular rash, which resolved after a temporary discontinuation of IVIG infusion. IVIG treatment was resumed at a slower rate without antihistamines or other medications, and the rash did not recur. No patient developed fever, abnormal vital signs, or headache.

DISCUSSION

Childhood ITP is a self-limited disease. Treatment is indicated only when platelet count is very low (< 20,000/ μ l) and/or the patient has clinical evidence of

bleeding such as purpura,¹ to minimize the risk of intracranial hemorrhage- a complication that occurs in approximately 1% of children with ITP.^{7,8} Although oral prednisolone is the drug of choice to raise the platelet count in ITP patients who need treatment, it results in several adverse effects⁵ including excessive weight gain (up to 6% of original body weight), epigastric discomfort, behavioral change, transient glycosuria, hypertension, and transient suppression of the immune system. IVIG has been used for treatment of childhood ITP since 1981.³ The use of IVIG in acute ITP is to temporarily raise platelet count while allowing the abnormal immune response to platelets subside spontaneously. IVIG has been shown to be superior to oral prednisolone in several trials.⁴⁻⁶ When platelet count is above 50,000/ μ l, the risk of bleeding is low and the patient can be safely watched at home.¹

I.V. Globulin® is an IVIG preparation that derived from plasma donations from Thai volunteers, followed by a standard fractionation procedure by the Korean Green Cross. Safety and efficacy of other IVIG products of the Korean Green Cross has been established. Because the source of plasma is from local volunteer donation, the cost of this IVIG preparation is considerably less than many other preparations available internationally.

In most pediatric studies, IVIG was given at 2 g/kg body weight over 48 hours^{5,6} or 5 days.^{3,4} Because of high cost of IVIG, we studied whether IVIG at 1 g/kg body weight could be used. Our results showed that the lower dose IVIG could raise platelet counts to a safe range in most cases (Fig. 2). In this study, the median time to

recover platelet counts above 50,000/ μ l is 2 days, which is comparable to other studies using 2 g/kg IVIG⁵ or a lower dose (0.8 g/kg) IVIG.⁶ By 96 hours, 76% of patients had platelet counts above 50,000/ μ l, which was also comparable to the low dose arm of the Blanchette study (83%, n = 35).⁶ We found that only a quarter of our patients needed treatment with 2 g/kg IVIG to successfully raise the platelet count. Our result was similar to a study by Bussel and colleagues⁹ who reported that 3/12 cases of their previously untreated patients failed to respond to 1 g/kg IVIG. We found that in patients who needed high dose IVIG, platelet counts did not reach 30,000/ μ l by 48 hours after the start of the infusion. Therefore, the decision to give the second dose could be made as early as 48 hours after starting the first dose using this platelet count criteria.

In most trials, platelet counts remained high above the safe range for 3-4 weeks as the immunoglobulin level declined. In higher dose IVIG studies, the platelet count also declined below the safe level (< 20,000/ μ l) within 28 days after diagnosis.^{5,6} Re-treatment was necessary in 12-22% of cases. In our study, 40% of patients required re-treatments, a rate comparable to the lower dose arm (32%) of the Blanchette study,⁵ and the 5/12 (42%) patients in the Bussel study.⁹ In 3 of our cases, re-treatment was needed in the second week, earlier than expected in high-dose IVIG regimen. This phenomenon might be due to lower doses of IVIG raising serum immunoglobulin just above the effective level to block platelet destruction, resulting in a temporary rise of the platelet count. Subsequently, serum immunoglobulin soon fall below

the effective level with the low dose IVIG, resulting in shorter duration of safe platelet counts.

In our cohort, there was only one patient whose thrombocytopenia did not resolve by 6 months after initial diagnosis, thus meeting the diagnostic criteria for chronic ITP.¹ This proportion seems lower than the 10-30% reported from larger cohorts in Western countries.^{3,5}

Adverse effects of IVIG are common (15-75%), particularly with high-dose infusion in 48 hrs,⁵ but are generally mild. These include headache, backache, nausea, and fever. Aseptic meningitis may occur.¹⁰ Alloimmune hemolysis is reported rarely.¹¹ There were very few adverse effects in our study; only one case of transient rash that seemed to be associated with the rapid infusion rate. There was no febrile reaction, and no complaints of other symptoms. This may be explained by the relatively young age of children in our study. Serial CBCs, which included hemoglobin level, did not show a significant anemia after IVIG infusion in any case. Other trials with 1 g/kg IVIG similarly reported few adverse effects.⁹

IVIG preparations are expensive. At the time of preparation of this report, the relative cost ratio of most IVIG preparations in Thailand (total 2 g/kg) to oral prednisolone therapy (2 mg/kg/day for 28 days) was calculated to be 240 to 1. The use of local plasma donor-derived IVIG preparations (I.V. Globulin®) infused at 1 g/kg would bring this ratio down to 60 to 1. The cost of therapy must be balanced against reduction in anxiety among parents and physicians, and

the shortened hospital stay. The clinical practice guideline developed by the American Society of Hematology now recommends a low dose IVIG over the standard 2 g/kg for the treatment of acute ITP.¹ However, for most patients in Southeast Asian countries, where cost of treatment is an important factor, IVIG may not be the most cost-effective way to manage ITP, even at a lower dose. Because of low cost and acceptable efficacy, oral corticosteroid therapy has been recommended by the Thai Society of Hematology¹² as the treatment of choice for childhood ITP that needed treatment. A bone marrow aspiration is also required to establish the diagnosis of ITP before steroid treatment. Pre-treatment bone marrow aspiration is optional, however, for children selected to be treated with IVIG, but should also be done for IVIG non-responders for whom corticosteroid treatment is planned.

IVIG is also useful for treatment of chronic ITP to delay or avoid splenectomy.¹³⁻¹⁶ Because of good but transient responses, multiple dosing is required as 'maintenance dose'. This can be achieved with 0.5 to 1 g/kg IVIG every 2-3 weeks.¹⁶ In addition, IVIG is particularly useful for predicting response to splenectomy.¹⁷ Children with chronic ITP who respond well to IVIG treatment will usually have complete resolution of thrombocytopenia after splenectomy.¹⁷

In conclusion, our results suggested that when IVIG is considered for initial treatment for childhood acute ITP, an initial dose of 1 g/kg IVIG may be used. If inadequate response is observed (platelet count not reaching 30,000/ μ l) by 48 hours, another dose of 1 g/kg may be repeated. Platelet count should be followed at least

weekly for 4 weeks as re-treatment may be necessary in some cases.

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