Intravenous Gamma Globulin for Treatment of Chronic Idiopathic Thrombocytopenic Purpura in Children

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Abstract

A prospective and descriptive study was carried out in 17 children with chronic ITP. Five-day course of Intraglobin (400 mg/kg/d x 5) was given intravenously to 10 children with the age of 4-16 years (5 males and 5 females). Two-day course of Venoglobulin-I (1 g/kg/d x 2) was given intravenously to 7 children with the age of 3-15 years (3 males and 4 females). Intraglobin and Venoglobulin-I were effective in treating children with chronic ITP. All of the patients had transient increased in their platelet counts during the first 2 weeks. The two-day course of Venoglobulin-I was superior to the five-day course of Intraglobin. Mild adverse effects were observed in a greater percentage of patients treated by Venoglobulin-I than in patients treated by Intraglobin. Intravenous immunoglobulin was one of the choices of treatment in children with chronic ITP, but the cost of immunoglobulin or gamma globulin is quiet high.

Key word : Immunoglobulin, Gamma Globulin, Chronic ITP, Children

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Idiopathic or immune thrombocytopenic purpura (ITP) is a disorder in which antiplatelet autoantibodies cause the destruction of platelets, resulting in thrombocytopenia. In children, chronic idiopathic thrombocytopenic purpura accounts for 10-24 per cent of ITP and is characterized by thrombocytopenia for at least 6 months[1-8]. Corticosteroid therapy is designed to reduce the autoimmune

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and/or inhibit the splenic sequestration of antibody-sensitized platelet[9]. Short-term corticosteroid therapy is useful in children with chronic ITP who have acute exacerbation of clinical bleeding[3,4]. Splenectomy should be considered in children with chronic ITP who have persistent severe thrombocytopenia and increased bleeding manifestations despite corticosteroid therapy. Unfortunately, the response to splenectomy cannot be predicted[1,10] and the procedure is not risk-free[11]. Splenectomy, however, entails a risk of overwhelming sepsis due to encapsulated microorganisms especially in infants and children under the age of five years[4]. Furthermore, at least 10 per cent of children with chronic ITP fail to have any response to splenectomy[12]. Many reports have indicated that intravenous administration of gamma globulin (IVIG) at high doses can produce mainly transient but, in some cases, permanent reversal of thrombocytopenia in children and adults with chronic ITP[13-18], thus providing an alternative choice for the treatment of children with chronic ITP. The majority of studies with IVIG therapy in ITP have used gamma globulin-SRK (Swiss Red Cross) or Sandoglobulin, but there are reports of variable efficacy with other gamma globulin preparations as well[18-22]. The study objective was to assess the efficacy, safety and tolerance of two gamma globulin preparations, Intraglobin (Biotest Pharma GMBH, Germany) and Venoglobulin-I (Alpha therapeutic Corporation, USA), which are commercially available in Thailand for the treatment of children with chronic ITP.

PATIENTS AND METHOD

Entry criteria and patients

Established entry criteria included a clinical diagnosis of chronic ITP with platelet count less than 50 x 10^9/L for at least 6 months and normal or increased number of megakaryocytes in the bone marrow. Other hematologic disorders, such as leukemia and hypoplastic anemia, had to be ruled out.

The study was prospective in a single center in the south of Thailand. This study enrolled 17 children with chronic ITP, 9 girls and 8 boys, aged between 3 and 16 years.

Treatment regimen

The first study was done from June 1990 to April 1995 and involved 10 children, 5 girls and 5 boys, aged 4 years to 16 years. two of whom had previous splenectomy who received intravenous Intraglobin (Biotest Pharma GMBH, Germany) at 400 mg/kg/day for 5 consecutive days. Intraglobin is a modified gamma globulin which is isolated from large pools of human plasma and treated with ß-propiolactone. This preparation consists of 5 per cent solutions, containing essentially only IgG, minimal IgA and no unspecific complement activity.

The second study was done from March 1996 to August 1997 and involved 7 children, 4 girls and 3 boys, aged 3 years to 15 years who received intravenous Venoglobulin-I (Alpha Therapeutic Corporation, USA) at 1 g/kg/d for 2 consecutive days. Venoglobulin-I is an unmodified gamma globulin which is isolated from large pools of human plasma using a cold alcohol fractionation process and is further purified by polyethylene glycol fractionation and DEAE-Sephadex ion exchange adsorption. This preparation contains at least 90 per cent intact IgG, minimal IgA and low anticomplementary activity.

Complete blood count (CBC), blood urea nitrogen, blood glucose, blood uric acid, serum bilirubin, serum transaminase and serum gamma globulin were monitored on the day prior to gamma globulin infusion and the day after gamma globulin therapy. Platelet count was performed every day during gamma globulin infusion and the day after infusion and then weekly for 4 weeks. Patients who had a persistent platelet count less than 40 x 10^9/L at 4 weeks after gamma globulin infusion, received one booster dose of Intraglobin 400 mg/kg or Venoglobulin-I 1 g/kg. Platelet count was monitored on the day prior to infusion and the day after it ended. Patients' follow-up with platelet count was done every 4 weeks for 4 times and then every 1-3 months. The patients with Intraglobin therapy were followed-up for 20-90 months (median 54 months). The follow-up time in the second study group after Venoglobulin-I infusion was 3-24 months (median 24 months).

Adverse effects or toxicity, which included anaphylaxis, urticaria, rise in temperature, tachycardia, headache, cough, malaise, nausea, vomiting and chills, were monitored during gamma globulin infusion and follow-up.

Treatment response criteria

To determine the efficacy of IVIG therapy, patients were considered excellent responders if platelet counts increased to $\geq$ 100 x 10^9/L within 4

weeks after the initial infusion and remained at that level without any treatment. Patients who had platelet count > 100 x 10^9/L within 4 weeks after the initial infusion but the platelet count decreased to less than 100 x 10^9/L later were considered good responders. Patients were considered fair responders if platelet count increased over the baseline but to less than 100 x 10^9/L. Patients with no increase of the platelet count above the baseline to either the initial infusion or the booster infusion were considered poor responders.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. All patients or their parents signed informed consents. Medication used during or after infusions to alleviate infusion reactions was acetaminophen.

Statistical analysis

Comparison between the groups was made by Students' *t*-test for age of patients and duration of ITP.

Table 1. Patient data.

Patient No.	Age (yr)	Sex	Duration of ITP (months)	Previous medication	Splenectomy	Gamma globulin preparaon	Time of follow-up (months)
1.	5	M	36	PRED, VCR, DNZ	N	Intraglobin	90
2.	10	M	72	PRED, DNZ	N	Intraglobin	90
3.	12	M	84	PRED, DNZ, CTX	Y	Intraglobin	90
4.	16	F	83	PRED	N	Intraglobin	88
5.	14	M	96	PRED	Y	Intraglobin	20
6.	4	M	9	PRED	N	Intraglobin	54
7.	6	F	46	PRED	N	Intraglobin	23
8.	7	F	24	PRED	N	Intraglobin	38
9.	4	F	24	PRED	N	Intraglobin	33
10.	9	F	24	PRED	N	Intraglobin	32
11.	12	F	38	PRED	N	Venoglobulin-I	24
12.	14	M	33	PRED	N	Venoglobulin-I	3
13.	5	M	26	PRED	N	Venoglobulin-I	24
14.	4	F	23	PRED	N	Venoglobulin-I	24
15.	6	F	9	PRED	N	Venoglobulin-I	24
16.	8	F	14	PRED	N	Venoglobulin-I	24
17.	3	M	13	PRED	N	Venoglobulin-I	9

PRED = Prednisolone, VCR = Vincristine, DNZ = Danazol, CTX = Cytoxan, N = No, Y = Yes

Table 2. Response and adverse effects to IVIG therapy in children with chronic ITP.

	Intraglobin (10 cases)	Venoglobulin-I (7 cases)	P value
Age (years)	8.7 ± 4.2+	7.4 ± 4.2+	0.55
Ratio of male to female	5 : 5	3 : 4	
Duration of ITP (months)	49.8 ± 31.2+	22.3 ± 10.9+	0.026*
Degree of response to initial IVIG			
Good	3	6	
Fair	7	1	
Adverse effects			
Rise in temperature	1	6	
Headaches	3	5	
Nausea & vomiting	4	2	

+ mean ± SD

* $p < 0.05$ = statistically significant

RESULTS

Clinical information for the 17 children is given in Table 1. Three of the 10 children had a good response to the 5 day course of Intraglobin therapy and 7 had fair response (Table 2). All 3 patients with good response (Nos 7, 8, 9 in Table 1) received one booster dose of Intraglobin, and the platelet count was increased in all cases, but in only one case (No 8) did the count increase to greater than 100 x 10^9/L (Fig. 1). Good responders had only mild bleeding symptoms and were generally quite well and did not receive any medication. The platelet count in good responders fluctuated during the 3 years follow-up after Intraglobulin therapy (Fig. 1). Patients with prior splenectomy had a fair response to Intraglobin (Fig. 3) (Nos 3, 5 in Table 1). The platelet count increased but to less than 100 x 10^9/L after initial infusion and one booster dose of Intraglobin. Splenectomized patients were quite well with minimal bleeding symptoms after Intraglobin therapy and did not receive any medication. In one patient (No 10 in Table 1) who had a fair response, the platelet count rose to greater than 100 x 10^9/L at 8 weeks without any medication after Intraglobin therapy (Fig. 2). Her platelet count was also greater than 100 x 10^9/L during the 32 months of follow-up. Three fair responders had severe clinical bleeding (No 1, 2, 4 in Table 1) after Intraglobin therapy. One of these patients (No 4) had menorrhagia and responded to a short course of oral prednisolone, premarin and ovural (contraceptive pills). Her platelet count declined with clinical bleeding, however, and did not respond to another two courses of prednisolone oral therapy. Splenectomy was done about 9 months after Intraglobin therapy. She had excellent response to splenectomy with her platelet count greater than 100 x 10^9/L during the 6 years follow-up (Fig. 2). Another two fair responders who had severe clinical bleeding underwent splenectomy 9 months (No 2) and 10 months (No 1) after Intraglobulin therapy. One of these patients (No 1) had a good response to splenectomy; his platelet count fluctuated during the 6 years follow-up after Intraglobin therapy (Fig. 2). He was quite well with no clinical bleeding symptom. Another patient (No 2) had a fair response to splenectomy; his platelet count fluctuated but remained less than 50 x 10^9/L with minimal clinical

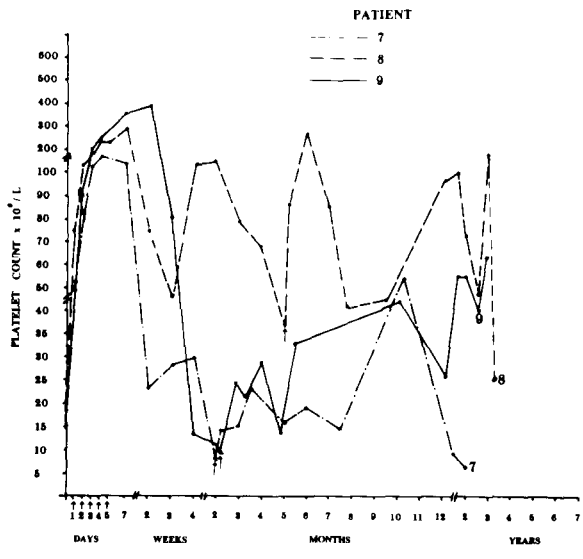

Fig. 1. Clinical course of children with good response to Intraglobulin. Upward-pointing arrows indicate Intraglobulin 400 mg/kg/d.

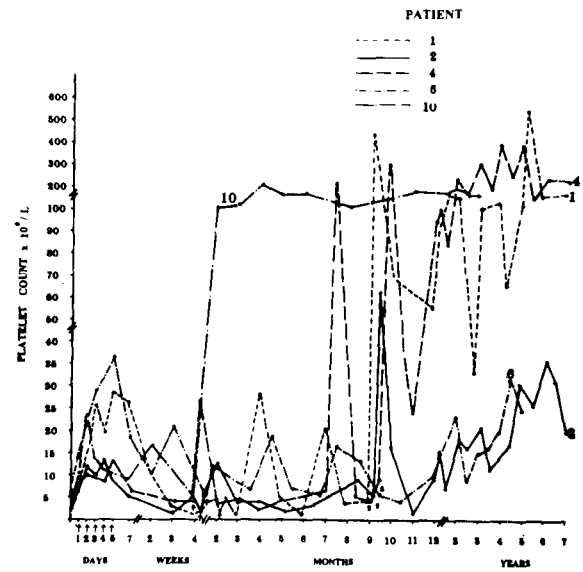

Fig. 2. Clinical course of children with fair response to Intraglobulin. Upward-pointing arrows indicate Intraglobulin 400 mg/kg/d, S = splenectomy.

bleeding (Fig. 2). The last patient (No 6) who had fair response to initial and booster dose of Intraglobin (Fig. 2) was well with mild and severe clinical bleeding symptoms off and on and did not responde to many short courses of prednisolone during the 5 years follow-up after Intraglobin therapy. All of the children had an increase in serum IgG following Intraglobin except one who had undergone splenectomy (No 5). No serious adverse effects necessitating cessation of therapy occurred. Four patients (Nos 1, 3, 4, 7) had nausea and vomiting during the infusion; three had headaches (Nos 1, 3, 4) and one had a transient rise in temperature (No 1).

Six of seven children had good response to the 2 day course of Venoglobulin-I and one case had fair response (Table 2). Four of six children with good response received one booster dose of Venoglobulin-I, and the platelet count increased in all cases, but only in one case did the count increase to greater than 100 x 10^9/L (Fig. 4). A good responder (No 15) who had platelet count greater than 100 x 10^9/L after a booster dose was very well with no clinical bleeding symptoms and her platelet count fluctuated between 68-538 x 10^9/L during the 2 years follow-up after Venoglobulin-I therapy. The rest of the good responders were quite well with minimal bleeding symptoms off and on. Their platelet counts fluctuated during the 2 years follow-up after Venoglobulin-I therapy (Fig. 4). Patient (No 11) who had a fair response to Venoglobulin-I also had a fair response to the booster dose. She was quite well with mild clinical bleeding symptoms off and on and did not receive any medication during the 2 years follow-up after Venoglobulin-I. All of the children had an increase in serum IgG following Venoglobulin-I. No serious adverse effects necessitating cessation of therapy occurred. Six patients (Nos 11, 12, 13, 14, 16, 17) had a transient rise in temperature; five (Nos 11, 12, 13, 14, 16) had headaches and two (Nos 11, 13) had nausea and vomiting. There were no clinically remarkable changes in vital signs during infusions, in physical examination at the time after IVIG therapy, or in laboratory values, other than platelet count in both Intraglobin and Venoglobulin-I study groups.

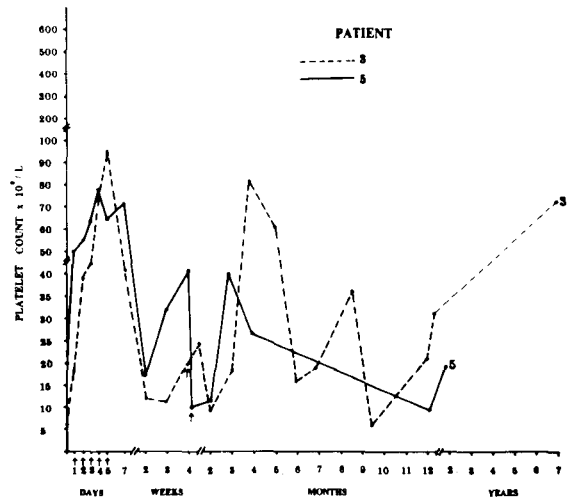

Fig. 3. Clinical course of splenectomized children with fair response to Intraglobulin. Upward-pointing arrows indicate Intraglobulin 400 mg/kg/d.

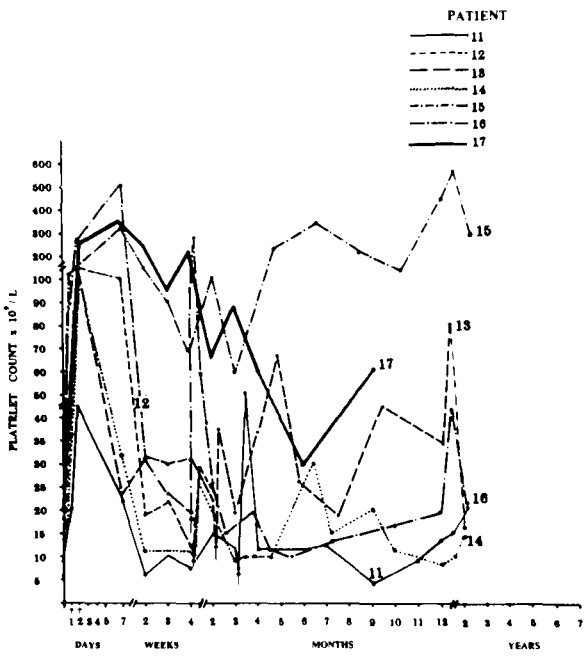

Fig. 4. Clinical course of children with Venoglobulin-I. Upward-pointing arrows indicate Venoglobulin-I 1 g/kg/d.

DISCUSSION

Two preparations of gamma globulin (Intraglobin and Venoglobulin-I) were effective in treating children with chronic ITP in this study. All

of the patients had transient increases in their platelet counts during the first week with the initial 5-day course of Intraglobin or 2-day course of Venoglobulin-I. These effects may be due to blockage of the Fc receptors of macrophages in the reticuloendothelial system, particularly in the spleen[23-26]. In adult patients with ITP who were treated with IVIG, unmodified gamma globulin preparation was superior to modified gamma globulin preparation. Seventy percent of the patients treated with unmodified gamma globulin had a platelet count greater than 100 x 10^9/L compared to only 49 per cent of those treated with modified gamma globulin[22]. Venoglobulin-I (unmodified gamma globulin) was superior to Intraglobin (modified gamma globulin) in the treatment of children with chronic ITP in this study (Table 2). The duration of the disease is a factor to evaluate the response of IVIG therapy in adult patients with ITP; the longer a patient had had ITP, the less he tended to respond to IVIG, especially if the ITP had been diagnosed more than 3 years[22]. The duration of ITP in children who were treated with Intraglobin was longer than that in children treated with Venoglobulin-I ($p < 0.05$) (Table 2). The lower responses in patients treated with Intraglobin in our study may be due to the longer period of ITP (Table 2). The response of ITP patients with prior splenectomy to IVIG therapy has been reported to be variable; all of the three splenectomized children with ITP had good response to Sandoglobulin[15]. Another study showed that one of the two splenectomized children with ITP had good response to Sandoglobulin[16]. Lusher and Warrier showed that two splenectomized children with chronic ITP had fair and poor response to Gamimune[27]. Splenectomized patients (adults and children) with ITP had good responses to Venilon in 56 per cent of the patients[28]. In the present study, chronic ITP children with prior splenectomy had fair response to Intraglobin.

Lusher and Warrier demonstrated that children with chronic ITP who had fair or poor responses to Gamimune had excellent response to splenectomy[27]. But adult patients with ITP who had poor responses to IVIG therapy also had poor responses to splenectomy[29]. Two of our three patients who had fair response to Intraglobin had good and excellent response to splenectomy in this study. A girl who had fair response to Intraglobin had spontaneous remission of ITP without any therapy in this study. High dose intravenous gamma globulin (IVIG) therapy was effective in adult patients with ITP, 64 per cent had peak platelet counts greater than 100 x 10^9/L and 83 per cent had peak platelet counts greater than 50 x 10^9/L[22]. The majority of children with chronic ITP had better outcome to IVIG therapy than did the adults in the previous studies[22]. (Table 3)

Adverse effects of IVIG (Sandoglobulin) therapy in children are common (15% to 75%) but generally mild, including fever, headache, backache, nausea and vomiting[32,33]. In our study,

Table 3. The response to initial IVIG therapy in children with chronic ITP.

Author	Patients (cases)	Peak platelet count x 10^9/L				gamma globulin preparation	No of ref.
		> 100 %	50-100 %	< 50 %	no response %		
Imbach	7	100	-	-	-	Sandoglobulin#	13
Imbach	7	100	-	-	-	Sandoglobulin#	30
Bussel	8	87	13	-	-	Sandoglobulin#	16
Lusher	16	44	25	19	13	GamimuneΔ	27
Lusher	6	67	33	-	-	Sandoglobulin#	27
Mori	20	80	20	-	-	Gammabulin#	17
Uchino	102	72	18	-	10	VenilonΔ	28
Khalifa	8	25	50*	25+	-	NS	31
Present study	10	30	20	50	-	IntraglobinΔ	
	7	86	14	-	-	Venoglobulin-I#	

unmodified gamma globulin, Δ modified gamma globulin
* platelet count 40-100 x 10^9/L
+ platelet count < 40 x 10^9/L
NS = not specified

mild adverse effects were observed with both preperations of gamma globulin (59%), including rise in temperature, headache, nausea and vomiting. The most frequent adverse reaction associated with Venoglobulin-I therapy was rise in temperature (86%) which was higher than that found in patients treated with Intraglobin. Most of the adverse reactions occurred during the gamma globulin infusion and 24 hours after the start of IVIG therapy and were easily controlled by acetaminophen.

In conclusion, Intraglobin and Venoglobulin-I appear to be effective and safe, having only mild adverse effects and are well tolerated by children with chronic ITP. The two-day course of Venoglobulin-I was superior to the five-day course of Intraglobulin. Mild adverse effects were observed in a greater percentage of patients treated with Venoglobulin-I than in patients treated with Intraglobin. IVIG therapy should be one of the choices of treatment in children with chronic ITP, but the cost of gamma globulin is quite high (US $ 600-2,000 for a single course).

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การรักษาเด็กที่เป็นโรคเกร็ดเลือดต่ำที่ไม่ทราบสาเหตุชนิดเรื้อรังด้วยการให้แกมม่าโกลบูลินทางหลอดเลือดดำ

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เด็กที่เป็นโรคเกร็ดเลือดต่ำที่ไม่ทราบสาเหตุชนิดเรื้องรัง (chronic ITP) จำนวน 17 คน อายุระหว่าง 3–16 ปี ได้รับการรักษาด้วยการให้แกมม่าโกลบูลินทางหลอดเลือดดำ การศึกษาแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มแรกมีจำนวน 10 คน อายุระหว่าง 4–16 ปี เป็นเพศชายและหญิงอย่างละ 5 คน และมีเด็ก 2 คนที่ได้รับการตัดม้ามแล้ว เด็กกลุ่มนี้ได้รับการรักษาด้วย Intraglobin ซึ่งเป็น modified gamma globulin ในขนาด 400 มก.นน.ตัว 1 กก. โดยให้ทางหลอดเลือดดำวันละครั้งติดต่อกัน 5 วัน กลุ่มที่สองมีจำนวน 7 คน อายุระหว่าง 3–15 ปี เป็นเด็กชาย 3 คน และเด็กหญิง 4 คน ได้รับการรักษาด้วย Venoglobulin–I ซึ่งเป็น unmodified gamma globulin ในขนาด 1 ก./นน.ตัว 1 กก. โดยให้ทางหลอดเลือดดำวันละครั้งติดต่อกัน 2 วัน ผลการศึกษาพบว่าเด็กทุกคนตอบสนองต่อการรักษาด้วย gamma globulin ทั้งสองชนิด สำหรับเด็กที่ได้รับการรักษาด้วย Venoglobulin–I ตอบสนองต่อการรักษาโดยมีจำนวนเกร็ดเลือดเพิ่มขึ้นมากกว่า 100 x 10^9/ล. มีจำนวนมากกว่าเด็กที่ได้รับการรักษาด้วย Intraglobin เด็กที่ได้รับการตัดม้ามแล้วตอบสนองต่อการให้ Intraglobin ปานกลาง โดยมีการเพิ่มขึ้นของเกร็ดเลือดแต่มีค่าน้อยกว่า 100 x 10^9/ล. เด็กที่ตอบสนองต่อการให้ Intraglobin ปานกลาง โดยมีการเพิ่มขึ้นของเกร็ดเลือดแต่มีค่าต่ำกว่า 50 x 10^9/ล. มี spontaneous remission ของโรคโดยที่ไม่ได้รับการรักษาอย่างอื่นเลยมีจำนวน 1 ราย เด็กที่ตอบสนองต่อการให้ Intraglobin ปานกลาง โดยมีการเพิ่มขึ้นของเกร็ดเลือดซึ่งมีค่าน้อยกว่า 50 x 10^9/ล. แต่ยังคงมีอาการเลือดออกผิดปกติอย่างรุนแรงภายหลังการให้ Intraglobin จึงต้องทำการรักษาโดยการตัดม้ามจำนวน 3 ราย พบว่าผู้ป่วย 2 ราย ตอบสนองดีต่อการตัดม้าม โดยมีจำนวนเกร็ดเลือดเพิ่มขึ้นมากกว่า 100 x 10^9/ล. ผลข้างเคียงจากการให้ gamma globulin ทั้งสองชนิดมีเพียงเล็กน้อยคือปวดศีรษะ คลื่นไส้อาเจียน และมีอุณหภูมิกายเพิ่มขึ้น ซึ่งพบประมาณร้อยละ 59 Venoglobulin–I ทำให้มีการเพิ่มขึ้นของอุณหภูมิกายมากกว่า Intraglobin การให้แกมม่าโกลบูลินทางหลอดเลือดดำในขนาดสูงจึงเป็นอีกทางเลือกหนึ่งในการรักษาเด็กที่เป็นโรคเกร็ดเลือดต่ำที่ไม่ทราบสาเหตุชนิดเรื้อรังแต่ราคาของ gamma globulin ยังแพงอยู่

คำสำคัญ : อิมมูโนโกลบูลิน, แกมม่าโกลบูลิน, โรคเกร็ดเลือดต่ำที่ไม่ทราบสาเหตุชนิดเรื้อรัง, เด็ก

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