Original article

Treatment outcomes of children with newly diagnosed immune thrombocytopenia in a tertiary care hospital

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Abstract:

Background: *Many clinical practice guidelines in newly diagnosed immune thrombocytopenia (nITP) and treatment options are based on clinicians' decision. The different treatments have different outcomes and complications.* ***Objective:*** *To evaluate treatment outcomes and the incidence of chronic ITP (cITP) among different treatments.* ***Materials and Methods:*** *We reviewed the patients' medical records diagnosed with nITP aged 3 months to 15 years at Siriraj Hospital from 2006-2010.* ***Results:*** *Ninety-seven patients were treated in 5 different treatment strategies, observation (obs) 13.4%, prednisolone 2 mg/kg/day (P2) 24.8%, prednisolone 4 mg/kg/day (P4) 27.8%, pulse methylprednisolone (MP) 5.1% and intravenous immunoglobulin (IVIg) 28.8%. The median response times were in obs: 55, P2: 15, P4: 12, MP 12 and IVIg 3 days. In the IVIg group was significantly faster than in obs and P2 (p = 0.002 and 0.01) and P4 was significantly faster than obs (p = 0.03) but those among other groups were not significant. Sixty-four patients completed one year follow-up and 28.1% developed cITP: 71.4% in obs, 40% in P2, 26.3% in P4, 20% in MP, and 5.6% in the IVIgG group developed cITP. The patients with cITP in the IVIgG group were significantly fewer than in obs and P2 (p = 0.002 and 0.03) but among the other groups were not significant.* ***Conclusion:*** *The response time in the IVIgG group was faster than obs, P2 and P4. The prevalence of cITP in IVIG is lower than in the obs and P2 group. The results may be applied to treat each patient's conditions.*

Keywords : ● *Immune thrombocytopenia* ● *Children* ● *Treatment*

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นิพนธ์ต้นฉบับ

ผลการรักษาโรคเกล็ดเลือดต่ำจากภูมิต้านทานในเด็กในโรงพยาบาลตติยภูมิ

บุญชู พงศ์ธนากุล ยุทธพล ทิตอร่าม ณัศวีร์ วัฒนา นัทธี นาคบุญนำ และ ชญามน ทักษ์ประดิษฐ์
สาขาวิชาโลหิตวิทยาและออนโคโลยี ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

บทคัดย่อ

ความเป็นมา *แนวทางการรักษาโรคเกล็ดเลือดต่ำจากภูมิต้านทาน (newly diagnosed immune thrombocytopenia; nITP) มีหลากหลาย ขึ้นกับการตัดสินใจของแพทย์ผู้รักษา การรักษาที่แตกต่างกันส่งผลต่อผลของการรักษาและภาวะแทรกซ้อน* ***วัตถุประสงค์*** *เพื่อศึกษาผลการรักษา และอุบัติการณ์การเกิด chronic ITP (cITP) ในผู้ป่วยที่ได้รับการรักษาในรูปแบบต่าง ๆ* ***วัสดุและวิธีการ*** *ทำการศึกษาโดยการทบทวนเวชระเบียนย้อนหลังในผู้ป่วย nITP ที่มีอายุระหว่าง 3 เดือน ถึง 15 ปี ที่ได้รับการรักษาที่โรงพยาบาลศิริราช ระหว่างปี พ.ศ. 2549-2553* ***ผลการวิจัย*** *มีผู้เข้าร่วมการศึกษา 97 ราย ที่ได้รับการรักษาด้วยยาที่แตกต่างกันทั้งหมด 5 ชนิด ประกอบด้วยการรักษาแบบเฝ้าระวัง (observation; obs) ร้อยละ 13.4, prednisolone 2 มก./กก./วัน (P2) ร้อยละ 24.8, prednisolone 4 มก./กก./วัน (P4) ร้อยละ 27.8, pulse methylprednisolone (MP) ร้อยละ 5.1 และ intravenous immunoglobulin (IVIG) ร้อยละ 28.8. ค่ามัธยฐานของระยะเวลาการตอบสนองต่อการรักษา ในกลุ่ม obs: 55 วัน, P2: 15 วัน, P4: 12 วัน, MP 12 วัน และ IVIG 3 วัน ผู้ป่วยในกลุ่ม IVIG มีการตอบสนองต่อการรักษาที่เร็วกว่าในกลุ่ม obs และ P2 อย่างมีนัยสำคัญทางสถิติ ($p = 0.002$, 0.01) และผู้ป่วยในกลุ่ม P4 มีการตอบสนองต่อการรักษาที่เร็วกว่าในกลุ่ม obs ($p = 0.03$) การตอบสนองต่อการรักษาในผู้ป่วยกลุ่มอื่น ๆ ไม่พบความแตกต่างอย่างมีนัยสำคัญ ผู้ป่วยจำนวน 64 ราย มีการติดตามการรักษาครบ 1 ปี มีผู้ป่วยร้อยละ 28.1 เป็น cITP โดยพบว่าเป็นผู้ป่วยในกลุ่ม obs ร้อยละ 71.4, กลุ่ม P2 ร้อยละ 40, กลุ่ม P4 ร้อยละ 26.3, กลุ่ม MP ร้อยละ 20 และ ร้อยละ 5.6 ในกลุ่ม IVIG โดยพบผู้ป่วย cITP ในกลุ่ม IVIG น้อยกว่าในกลุ่ม obs และ P2 อย่างมีนัยสำคัญทางสถิติ ($p = 0.002$ and 0.03) แต่ไม่พบความแตกต่างอย่างมีนัยสำคัญ ในผู้ป่วยกลุ่มอื่น ๆ* ***สรุป*** *การรักษาผู้ป่วยเด็ก nITP ด้วยยา IVIG มีการตอบสนองที่เร็วกว่าการรักษาในกลุ่ม obs, P2 และ P4 อุบัติการณ์การเกิด cITP ในผู้ป่วยที่ได้รับการรักษาด้วย IVIG พบน้อยกว่าการรักษาด้วยวิธี obs และ P2 ผลการรักษานี้สามารถนำมาปรับใช้ในผู้ป่วย nITP ที่มีสภาวะแตกต่างกันได้*

คำสำคัญ : ● *เกล็ดเลือดต่ำจากภูมิต้านทาน* ● *เด็ก* ● *การรักษา*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2562;29:223-30.

Introduction

Immune thrombocytopenia (ITP) is the most common acquired platelet disorder among children. This disease is caused by antibody-mediated destruction of platelets and impaired platelet production of megakaryocytes[1]. ITP is typically self-limited. When thrombocytopenia does not last longer than 3 months, it is classified as newly diagnosed ITP (nITP); however, in some cases, thrombocytopenia will last between 3 and 12 months from diagnosis (persistent ITP), or greater than 12 months from diagnosis (chronic ITP: cITP)[2]. Many clinical practice guidelines are available to manage childhood ITP. The most popular two guidelines were from the International Working Group published in 2010[3] and from The American Society of Hematology in 2011[4]. The decision to treat newly diagnosed patients is based on several factors including ceasing bleeding symptoms, increasing the platelet count, preventing bleeding and inducing remission. Many medications are recommended in the treatment guidelines including prednisolone, dexamethasone, intravenous immunoglobulin (IVIg) and observation. Current first line therapy is a course of corticosteroids. Treatment of patients with nITP is aimed at rapidly obtaining a safe platelet count to prevent or stop bleedings and to ensure an acceptable quality of life with minimal treatment-related toxicity. Although this treatment increases the platelet count in most patients, a high relapse rate after discontinuation of corticosteroid therapy can occur. This study aimed to evaluate the treatment outcomes of nITP and remission rate among treatment paradigms in a tertiary care hospital setting.

Materials and Methods

We retrospectively reviewed children's medical record being treated for nITP at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital from 1 January 2006 to 31 December 2010. The inclusion criteria consisted of children diagnosed with nITP aged between 3 months to 15 years. We evaluated the treatment outcomes including platelet count increment during 48 to 72 hours, 2 weeks, 1 month and 6 months among different treatment paradigms and continued to follow up these patients until 1 year since diagnosis. We also recorded the grade of bleeding severity as previous described[3] and side effects of the different treatments. The definition of treatment response was based on the criteria for assessing response to ITP treatments as proposed by the International Working Groups[2]. We excluded patients with a diagnosis of secondary ITP including ITP from human immunodeficiency virus, other autoimmune diseases such as systemic lupus erythematosus, Evans syndrome and antiphospholipid syndrome. The statistical analysis was performed by nonparametric analysis. The study was approved for human research ethics by The Siriraj Institutional Review Board (SIRB).

Results

Ninety-seven patients meeting the inclusion criteria were enrolled in this study. Fifty-seven (58.8%) and 40 (41.2%) patients were male and female (1.4:1), respectively aged between 3 months to 14.8 years and median age was 2.7 years. The bleeding symptoms that presented at diagnosis included petechial hemorrhage (92.8%), mucocutaneous bleeding (16.5%), gastrointestinal bleeding (9.3%), epistaxis (8.2%), hematuria (1%) and ecchymosis on the forehead (1%). Some patients presented more than one bleeding symptoms. Regarding bleeding severity, 26.8, 48.4, 19.6 and 5.2% presented bleeding grades 1, 2, 3 and 4, respectively. The platelet counts at diagnosis range from 0 to 86 $x10^9$/L with median platelet counts at 9 $x10^9$/L.

Treatment paradigms in nITP in this study included observation (obs), prednisolone 2 mg/kg/day for 14 days and tapered over 21 days (P2), prednisolone 4 mg/kg/day for 4 days without tapering off (P4), pulse methylprednisolone 30 mg/kg/day with maximum dose 1 gm per day for 3 days followed by 20 mg/kg/days for 4 days (MP) and IVIg 0.8-1 gm/kg/day for 1 to 2 days (IVIG). In all, 13 (13.4%), 24 (24.8%), 27 (27.8%), 5 (5.2%)

Table 1 Demographic data

	Number
	Total 97 (%)
Gender	
Male	57 (58.8)
Female	40 (41.2)

Treatment	**Number (%)**	**Bleeding severity**				
		Grade 1 (%)	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Platelet ($x10^9$/L) min-max (median)**
Observation	13 (13.4)	10 (76.9)	2 (15.4)	1 (7.7)	0	20-86* (41)
Prednisolone 2 mg/kg/day	24 (24.8)	8 (33.3)	14 (58.3)	2 (8.4)	0	3-37# (13.5)
Prednisolone 4 mg/kg/day	27 (27.8)	7 (25.9)	10 (37.1)	9 (33.3)	1 (3.7)	3-46** (7.0)
Pulse methylprednisolone	5 (5.4)	0	5 (100)	0	0	2-11 (7)
Intravenous immunoglobulin	28 (28.8)	1 (3.6)	16 (57.2)	7 (25.0)	4 (14.2)	0-23#,** (4.0)

*p-value < 0.001 between observation and every treatment; # p-value < 0.001; **p-value = 0.01

Table 2 Time to complete response in different treatment paradigms

Treatment	**Median response time (days)**	**Total cases**	**Response rate (%)**				
			48-72 hr	**2 weeks**	**1 month**	**6 months**	**1 year**
Observation*,#	55.0	13.0	8	23	31	74	83
Prednisolone 2 mg/kg/day**	15.0	24.0	21	46	67	88	96
Prednisolone# 4 mg/kg/day	12.0	27.0	30	60	71	87	91
Pulse methylprednisolone	12.0	5.0	40	60	80	80	80
IVIG*,**	3.0	28.0	54	65	79	97	97

*p value = 0.002, **p value = 0.01, #p value = 0.03

and 28 (28.8%) patients were treated with obs, P2, P4, MP and IVIG, respectively. The platelet counts at diagnosis were 20 to 86 (median 41 $x10^9$/L) in obs, 3 to 37 (median 13.5 $x10^9$/L) in P2, 3 to 46 (median 7 $x10^9$/L) in P4, 2 to 11 (median 7 $x10^9$/L) in MP and 0 to 23 (median 4.5 $x10^9$/L) in the IVIG group. The platelet counts in the obs group was significantly higher than other treatments ($p < 0.001$). Regarding platelet counts among the P2, IVIg, P4 and IVIg groups, Both P2 and P4 were significantly higher than the IVIg group, $p < 0.001$ and $p = 0.01$, respectively. The demographic data, treatment paradigm and severity of bleeding among different treatments are shown in Table 1.

Time to response among different treatments and median response time were 55, 15, 12, 12 and 3 days in the obs, P2, P4, MP and IVIg group, respectively. Time to response in the IVIg group was significantly faster than in the obs and P2 group ($p = 0.002$ and $p = 0.01$). In the P4 group, time to response was significantly faster than in the obs group ($p = 0.03$). No statistically significant difference was observed in time to response among the other groups of treatment. Time to response among different treatments is shown in Table 2 and Figure 1. Some patients needed more than one course of treatment because of nonresponse or relapsed state after the first course of treatment. In the obs group, 12 patients (92.3%) did not need any medication and only

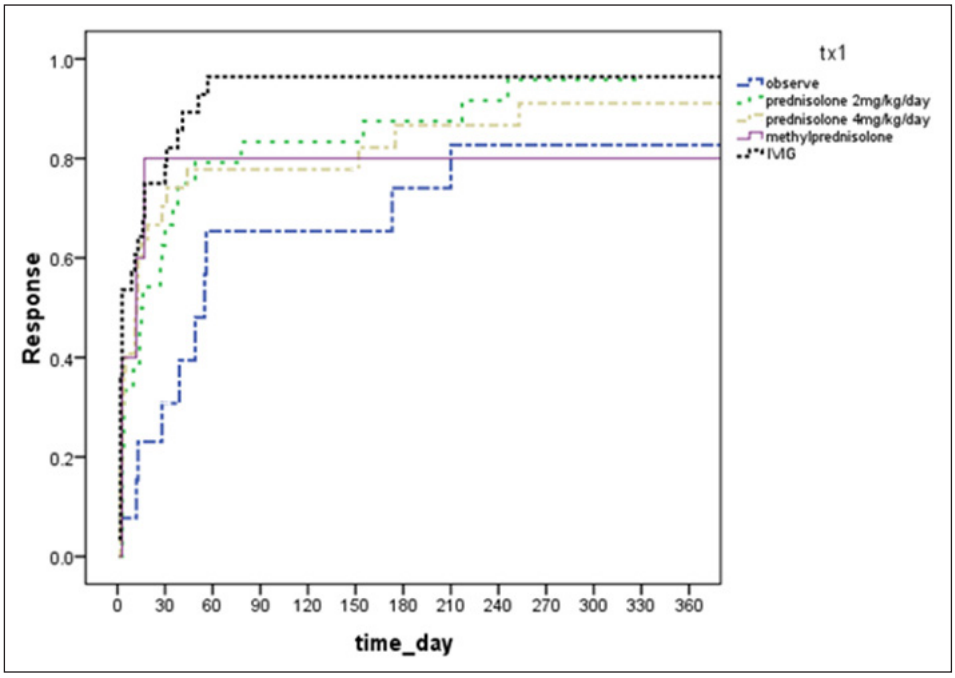

Figure 1 Treatment outcome according time to response in different treatments in newly diagnosed ITP

Table 3 Number of treatments in different treatment paradigms in newly diagnosed ITP

Treatment	No medication N (%)	1 course N (%)	2 courses N (%)	> 3 courses N (%)
Observation	12 (92.3%)	0	1 (7.7%)	0
Prednisolone 2mg/kg/day	0	14 (58.4%)	5 (20.8%)	5 (20.8%)
Prednisolone 4mg/kg/day	0	18 (66.7%)	4 (14.8%)	5 (18.5%)
Pulse methylprednisolone	0	4 (80%)	0	1 (20%)
IVIG	0	17 (60.7%)	4 (14.3%)	7 (25%)

one patient required two courses of treatment. In other treatment groups, most patients (58.4 to 66.7%) needed only one course of treatment. The number of treatments in different treatment paradigms is shown in Table 3.

Regarding bleeding complications after treatment, no bleeding complications were observed in the obs group. regarding bleeding complications in the P2 group, one patient for each in grades 2 (petechiae), 3 (epistaxis) and 4 (intracerebral hemorrhage) were found. One patient with intracerebral hemorrhage died. He presented chronic ITP at that time and had a history of head injury. In the P4 group, three patients presented bleeding complications, and all were grade 3 (bleeding per gum, epistaxis and hematuria). In the MP and IVIg groups, one patient in each group presented bleeding complications. Both were grade 3 (hematuria and bleeding per gum). Regarding side effects of treatment, 67 patients received corticosteroid and only 5 patients reported side effect. Three patients experienced significant weight gain (two in P2 and one patient in the P4 group). One patient presented hypertension (in P2) and one patient had gastrointestinal discomfort (in P4). No patient experienced side effects with IVIG treatment.

Sixty-four patients (65.9%) completed one year follow-up for 1 year since diagnosis; of these, 18 patients (28.1%) developed chronic ITP. Stratifying each treatment paradigm revealed 5 of 7 (71.4%), 6 of 15 (40%), 5 of 19 (26.3%), 1 of 5 (20%) and 1 of 18 (5.6%) patients in the obs, P2, P4, MP and IVIg groups, respectively developed chronic ITP. Comparing the rate of developed chronic ITP in each group, the IVIg group had significantly fewer patients with cITP than in the obs and P2 group

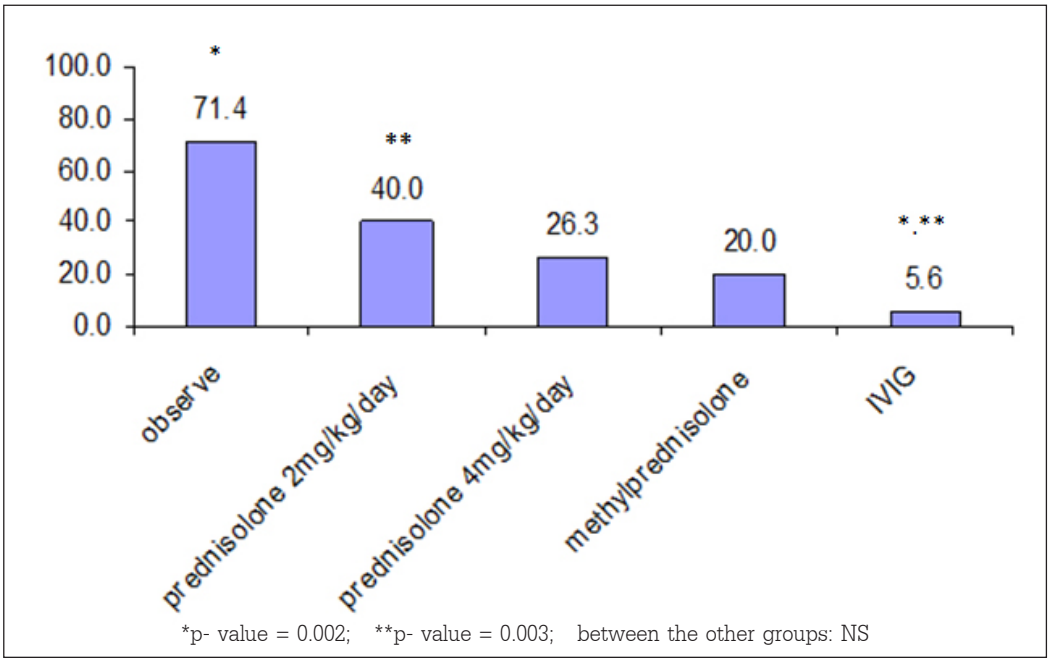

Figure 2 Rate of developing chronic ITP in different treatment paradigm

(p = 0.002 and p = 0.03, respectively). However, those among the other groups were not significant. The rate of developing chronic ITP among different treatments is shown in Figure 2.

Discussion

ITP is an acquired autoimmune platelet disorder. Regarding the epidemiological data of childhood nITP, our study showed that males were more predominant than females at a ratio of 1.4:1. In Thailand, Satthawisut S, et al. reported the male to female ratio was 1.06:1[5]. That boys with nITP were more common than girls was also found in Shirahata A, et al.'s[6] report from Japan (1.24:1) and Zafar H, et al.'s[7] from Pakistan. However, among older patients aged > 10 years, females with ITP were more prevalent than males at a ratio of 2.6:1.[6] Most of our patients (75.2%) presented clinically mild bleeding symptoms of bleeding severity grades 1 to 2. A large study group also reported that more than one half of the patients had no or only mild bleeding episodes.[8]

Regarding the treatment of nITP, our study showed that most childhood nITP (86.6%) required pharmacologic treatment whereas only 13.6% could be treated by watch and wait strategy. This result was similar to that of Satthawisut S, et al.[5] in Thailand reporting that only 15% of children with nITP could be treated by observation alone. One reason might be that nITP is also treated by general pediatricians and only complicated cases are referred to a pediatric hematologist. Our data was collected at a tertiary care center and showed a complicated initial presentation for this cohort. However, in our data, the patients treated by watch and wait strategy had higher platelet counts and less bleeding severity (bleeding grade 1) at diagnosis than those of the pharmacological treatment group. Shirahata A, et al.[6] also reported that patients with platelet counts at diagnosis ≥ 20 $x10^9$/L did not require aggressive treatment.

Among different pharmacological treatment paradigms, treatment with IVIg had the fastest time to response (3 days) compared to corticosteroid. This result was similar to the report from Blanchette V, et al.[9] that response time of IVIG was faster than prednisone. In our data, patients with more severe bleeding symptoms (bleeding grade 3 to 4) also were treated with IVIg (39%) because this group of patients needed a shorter time to increase platelet counts to stop bleeding.

Among the three different regimens of corticosteroid (P2, P4 and MP), the time to response of these treatments did not differ significantly (15, 12 and 12 days, respectively). Between the P2 and P4 groups, the number of

courses of treatment were did not differ. Therefore, The International Working Group and the American Society of Hematology recommended that when corticosteroids are chosen as the initial treatment, no evidence supports any one dose, or dosing regimen, over others.[10] Long term corticosteroids should be avoided among children with nITP because of side effects.

For cITP, 28.1% of our cohort developed cITP. However, patients completing one year follow-up totaled only 65.9%, which may have affected the prevalence of cITP. The prevalence of childhood cITP in Thailand among other studies varied. Studies conducted by Chotsampancharoen T et al.[11] and by Satthawisut S, et al.[5] reported patients showed cITP at 34.1%. Another study by Champatiray et al.[12] from India, and by Mushtaq et al.[13] from Pakistan, showed 14 and 5.3% of patients developed chronic ITP, respectively. The various rates of cITP might be due to complicated initial presentation. Being female, older age at presentation and absence of preceding infection or vaccination were identified as risk factors for developing chronic ITP.[14] The study by Chotsampancharoen T et al.[11] showed that factors influencing remission of cITP included platelets count > 60×10^9/L at the onset of cITP and treatment with IVIg. One multicenter randomized trial conducted among children with nITP, randomly assigned subjects to receive either a single infusion of 0.8 g/kg IVIg or observation. Chronic ITP occurred among 18.6% of the patients in the IVIg group and 28.9% in the observation group (relative risk 0.64; 95% confidence interval, 0.38 to 1.08).[15] Our study also showed that patients receiving treatment with IVIg developed cITP significantly less than those in the obs and P2 groups .

In our cohort, bleeding complication was very low especially in the obs group (0%). One patient died from intracerebral hemorrhage but he developed cITP and had a history of head injury. Side effects related to treatment especially occurred in the corticosteroid group, 5 of 67 patients (7.5%). Most were mild side effects: weight gain, hypertension, gastrointestinal discomfort and no reports of Cushing's syndrome. No side effects related IVIG treatment were found in our study.

Summary

Regarding treating children with nITP, the response time in the IVIg group proved faster than in the obs, P2 and P4 groups. Observation or watch and wait strategy in nITP without severe bleeding symptoms is safe and possible. The prevalence of cITP in the IVIG group was lower than in the obs and P2 groups. This result may be applied to treat each patient's conditions. A future prospective study is recommended to show the effect of different treatment outcomes.

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