

Original article

Predictors of Remission following IVIG in Newly Diagnosed Childhood Immune Thrombocytopenia

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Abstract

Immune Thrombocytopenia (ITP) is the most common acquired autoimmune bleeding disorder in children, and only 20-25 % progress to chronic ITP. Intravenous immunoglobulin (IVIG) is recommended as one of the first-line therapeutic options for those with significant mucosal or life-threatening bleeding in ITP. Predictors of remission following IVIG therapy have not been fully explored yet. Now trying to individualize IVIG therapy for ITP children who have special demographic, clinical, and therapeutic predictors of remission following IVIG therapy. Aim: To evaluate the demographic, clinical, and laboratory predictors of remission following IVIG therapy in newly diagnosed ITP children. This retrospective observational study included 142 children with newly diagnosed ITP aged 1-9 years who were treated with IVIG as initial therapy and admitted to Benghazi University Children's Hospital from January 2019 to April 2024. We revised their medical records to demographic, clinical, and laboratory characteristics at diagnosis and during follow-up to 1 year post-IVIG therapy. Results: $\frac{3}{4}$ (75.4%) of our study ITP children were ≤ 5 years old, with male predominance 91 (64.1%). Only 12.7% (n=18) of our study group developed chronic ITP, while the majority, 87.3% (n=124), were complete responders and achieved disease remission. Our study confirmed that children ≤ 5 years ($p = 0.037$) and an abrupt onset of the disease ($p = 0.028$), in addition to platelet counts $>100 \times 10^9/L$ at one month ($p = 0.036$) and at three months ($p = 0.000$) after IVIG therapy, are good predictors of remission following IVIG therapy in newly diagnosed ITP children. Our study concluded a higher remission rate (87.3%) following an initial course of IVIG therapy for ITP. In addition, children ≤ 5 years, an abrupt onset of the disease, platelet count $\geq 100 \times 10^9/L$ at 1 and 3 months, are good predictors of remission following IVIG therapy in newly diagnosed ITP.

Keywords. Children, Immune Thrombocytopenia, Intravenous Immunoglobulin.

Introduction

Primary immune thrombocytopenia (ITP) is a primary acquired hematological autoimmune disease characterized by low platelet counts (peripheral blood platelet count $<100 \times 10^9/L$) without underlying causes of thrombocytopenia, with bleeding risk [1]. The pathophysiological mechanism of ITP is explained by immunological destruction of platelets in the spleen and liver, as well as autoantibody-mediated inhibition of megakaryocyte poiesis in the bone marrow, which plays a key role, especially in patients with chronic ITP [2-4]. Although a few cases are asymptomatic, ITP children usually present with acute bleeding symptoms, often occurring as a post-infection or post-vaccination sequel [5]. There is no standard diagnostic test for ITP; the diagnosis is based only on clinical and laboratory evaluation to rule out secondary causes of thrombocytopenia [1,6].

Primary immune thrombocytopenia (ITP) was classified based on the duration of illness into 3 categories by the International ITP Working Group (IWG) 2009: newly diagnosed ITP, which is recently diagnosed up to 3 months, persistent ITP that lasts from 3 to 12 months post diagnosis, and lastly chronic ITP, which persists for more than 12 months [1]. The bleeding presentation of ITP ranges from common mild skin and subcutaneous bleeding to moderate, insignificant mucosal membrane bleeding and quite significant, even serious and life-threatening bleeding, including gastrointestinal (GIT) and central nervous system (CNS) bleeding; the latter constitutes 0.1% - 0.5% [7,8]. Only 3 - 5 % had significant active bleeding that required urgent therapeutic intervention regardless of platelet count [9]. Management of newly diagnosed ITP depends on regular follow-up with monitoring of platelet count [10,11].

Generally, there is controversy about a clear-cut decision-making for the best therapeutic approach to be started in childhood, for newly diagnosed ITP [12]. Recently, efforts have been made to individualize thrombocytopenia therapy for each patient [13,14]. IVIG is one of the first-line therapeutic options for newly diagnosed ITP, as recommended by the 2019 American Society of Hematology (ASH) guidelines, for a newly diagnosed ITP patient who has non-life-threatening mucosal bleeding and or reduced health-related quality of life, when corticosteroids are contraindicated, and Anti-D immunoglobulin is not preferred because it induces hemolysis [15,16]. The main advantage of IV immunoglobulin (IVIG) is that it increases platelet counts more rapidly within 24-48 hours post-therapy than other therapeutic agents such as steroids [17], making it the best therapeutic option in the ITP emergency with clinically significant or life-threatening bleeding, as well as for those with very low platelets, due to a high risk of serious bleeding. However, some patients have short-term remission following IVIg treatment, while other patients get long-term remission

and final disease recovery [18]. There is a controversy on the predictors of remission following IVIG therapy in newly diagnosed ITP children [19, 20].

Recently, scientists have shown interest in evaluating predictors of IVIG response in ameliorating ITP [21]. Not only do the clinical bleeding manifestations differ among children, for unclear reasons, but their response to treatment does. The identification of predictors of remission following IVIG therapy in newly diagnosed ITP children would help to target the therapy to those who have positive predictive factors, and individualized management of ITP. Our findings can be applied as a guide for the individualization of IVIG therapy for ITP patients who have the positive predictors of remission following IVIG therapy in newly diagnosed ITP children.

Method

This retrospective study included 142 children, 1-9 years old, of newly diagnosed primary immune thrombocytopenia who received IVIG as the initial therapy at diagnosis. These cases were admitted to University Benghazi Children's Hospital and followed up for 1 year at the pediatric hematology clinic from January 2019 to April 2024. Our study cases were assessed for demographic, clinical, and laboratory predictors of remission following IVIG therapy in newly diagnosed ITP children at diagnosis, and during follow-up to 1 year post-IVIG therapy by revising their medical records.

The diagnosis of primary ITP is based on the International Working Group ITP definition criteria.[1], Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count $<100 \times 10^9/L$) in the absence of other causes or disorders associated with thrombocytopenia. Secondary ITP includes all forms of immune-mediated thrombocytopenia except primary ITP. Secondary forms include thrombocytopenia that is due to an underlying disease or to drug exposure (as disease-induced ITP, including SLE and other diseases, infection-induced (Hepatitis B, C, HIV, and helicobacter infection), congenital, genetic causes, drug-induced), and Severe ITP should be used only in patients who have clinically relevant bleeding. This is defined by the presence of bleeding symptoms at presentation sufficient to mandate treatment, or by the occurrence of new bleeding symptoms requiring additional therapeutic intervention with a different platelet-enhancing agent or an increased dose [1].

The demographic, clinical, and laboratory evaluation

The medical record of the study group were evaluated for the demographic data including age at presentation and sex, detailed clinical history including onset of disease either abrupt which defined as onset < 2 weeks, gradual those >2 week, preceding infection within last 4 weeks, preceding vaccination including MMR and DPT vaccination, bleeding presentation, either cutaneous, mucus membrane bleeding including epistaxis, gum bleeding, no patient of our study group had experienced severe life-threatening bleeding including genitourinary tract (GUT), and central nervous (CNS) bleeding, the laboratory data including complete blood count, focusing on Hemoglobin(HB), mean platelet volume(MPV), platelet count at diagnosis, platelet count at 1,3 months and at 1 year post IVIG therapy, treatment response, and outcome.

IVIG therapy regimen

All patients were treated with IVIG in a dose of 1 g per kilogram of body weight for 2 days, or 400 mg per kilogram of body weight for five consecutive days, generally as a total of 2 gram per kg in both protocols with or without intravenous methylprednisolone (IVMP) as an adjunctive therapy in a few cases. IVMP was given in a dose of 30 mg/kg/day for 3 days. IVIG was used when there was moderate mucus membrane or severe bleeding, regardless of platelet count, or when platelets were less than $20 \times 10^9/L$

Inclusion Criteria

All children with newly diagnosed primary ITP aged 1-9 years who received IVIG as an initial therapeutic option and were admitted to the Benghazi University Children's Hospital and followed up at the hematology clinic from January 2019 to April 2024.

Exclusion criteria

In addition, those with secondary thrombocytopenia, older than 9 years, those with missing data, and those who had only observation or received other therapy rather than IVIG with or without methyl prednisolone were excluded.

Response to Therapy

In our research, IVIG therapy response was defined according to the ITP International Working Group (ITP IWG) definition of treatment response [1]. A complete response (CR) was defined as a platelet count of $\geq 100 \times 10^9/L$ and the absence of bleeding, and no response (NR) was defined as a platelet count $30 \times 10^9/L$ or less than 2-fold increase of baseline platelet count or bleeding. The other treatment responses, such as response (R) and partial remission (PR), were not included in the studied variables.

Outcome (phases) of ITP Immune thrombocytopenia (ITP)

It was classified based on the duration of illness into 3 categories by The International ITP Working Group (IWG) 2009: a newly diagnosed ITP that is recently diagnosed up to 3 months, persistent ITP that lasts from 3 to 12 months post diagnosis, and lastly chronic ITP, which persists for more than 12 months [1,8]. The demographic, clinical, and laboratory characteristics of the study population were compared between the complete response group (newly diagnosed and persistent ITP) and the chronic (non-respond) group to assess the predictors of remission following IVIG therapy

Data analysis

A comprehensive data analysis approach to assess patient characteristics and treatment effects by using SPSS version 24 [22]. Descriptive statistics were utilized to summarize patients' demographic and clinical characteristics, providing insights into their baseline profiles. For the analysis of qualitative data, inferential statistics were applied, specifically using the Chi-Square test or Fisher's Exact test, to explore potential associations between categorical variables. To compare means of quantitative data, an independent t-test was used to identify differences between groups. The significance level for type I error was set at 5%, with the statistical power of 80%, ensuring that the study was adequately powered to detect meaningful differences.

Results

This retrospective study included 142 patients with newly diagnosed ITP who received IVIG as initial therapy; various demographic, clinical, and laboratory characteristics, treatment response, and outcome were analyzed. Here's a summary of the key findings: Table 1 shows the demographic, clinical, and laboratory characteristics of children with ITP. Demographic characteristics of the study population: Up to 3/4th (75.4%) of our study group are aged ≤ 5 years at diagnosis, with males constituting 64.1%, and the M: F ratio is 1.8:1.

Clinical characteristics

Most patients experienced an abrupt onset (71.8%), while an insidious onset was less common (28.2%). Preceding infections were reported in 97.2% of the cases, while only 1.4% of cases followed vaccination. All patients had skin bleeding (100%), with gum bleeding (10.6%) and epistaxis (9.2%) also noted. The majority received only IVIG (89.4%), while a small proportion received both IVIG and methyl prednisolone (10.6%). The received dose of IVIG was predominantly 1 g/kg/day over 2 days (78.2%), and only 21.8% received 400 mg/kg over 5 days.

Laboratory characteristics

As shown in Table 1, Laboratory findings show a mean Hb level of 11.3 ± 1.02 g/dL, MPV 12.1 ± 8.5 , platelet counts at diagnosis averaging 17.7 ± 6.5 , at 1 month, platelet counts averaged 114 ± 47.6 , and at 3 months of treatment, mean platelet counts increased to 223 ± 94.5 . Disease course (outcome): As shown in (Table 1), approximately $\frac{3}{4}$ (73.9%) of the cases are newly diagnosed, while (13.4%) had a persistent, and only (12.7%) had a chronic ITP.

Table 1. Distribution of children with ITP according to their demographic, clinical, and laboratory characteristics and outcome

Variable		Number	Percent (%)
Patient characters			
Categories of age at diagnosis	≤ 5 years	107	75.4
	> 5 years	35	24.6
Gender	Male	91	64.1
	Female	51	35.9
Onset	Abrupt	102	71.8
	Insidious	40	28.2
Preceding infections	Yes	138	97.2
	No	4	2.8
Preceding vaccinations.	Yes	2	1.4
	No	140	98.6
Bleeding site	Skin	142	100
	Epistaxis	13	9.2
	Gum bleeding	15	10.6
Medication:			
Received medication	IVIG alone	127	89.4
	IVIG +IVMP	15	10.6

Dose of IVIG	1g/kg/2 days	111	78.2
	400 mg/kg/5 days	31	21.8
Laboratory findings			
Hb level (g/dL)	11.3 ±1.02		
Platelet counts at diagnosis(x10 ⁹ /L), mean(±SD)	17.7±6.5		
Platelet counts at 1month(x10 ⁹ /L), mean(±SD)	114.4±47.6		
Platelet counts at 3month(x10 ⁹ /L) mean(±SD)	223±94.5		
MPV	12.14±8.5		
Disease course (Outcome)			
	Newly diagnosis	105	73.9
	persistent	19	13.4
	Chronic	18	12.7

Abbreviations: IVIG: intravenous immunoglobulin; IVMP: intravenous methyl prednisolone, g: gram, mg: milligram, kg: kilogram.

Table 2 showed the comparison between the complete response group (newly diagnosed and persistent) and the chronic ITP group patients' characteristics. We compared ITP patients' characteristics according to IVIG response at 1year post-therapy between the complete response group, which included newly diagnosed and persistent, and the chronic (no response) group, which did not achieve remission. There is statistically significant differences between the complete response and chronic ITP groups in terms of age at diagnosis ($p= 0.037$), with a higher proportion of patients diagnosed at age ≤ 5 years in the complete response group, and with abrupt disease onset more common among responders($p =0.028$), No significant differences were observed in gum bleeding status (p -value =1), epistaxis ($p = 0.216$), preceding infection, preceding vaccination, or received medication, as indicated by their higher p -values or lack of significance between the two groups. Additionally, the dose of IVIG showed a trend toward significance ($p = 0.06$), suggesting a possible difference that warrants further investigation, although it does not reach the conventional threshold for statistical significance.

Table 2. Comparison between the complete response group and the chronic ITP group according to patients' characteristics

Variables		Complete Response (124)	Chronic ITP (18)	Level of significance
Categories of age at diagnosis	≤ 5 years	97	10	0.037**
	> 5 years	27	8	
Gender	Male	82	9	0.183
	Female	42	9	
Onset	Abrupt	93	9	0.028**
	Insidious	31	9	
Gum bleeding	Yes	13	2	1
	No	111	16	
Epistaxis	Yes	10	3	0.216
	No	114	15	
Preceding infection	Yes	120	18	1
	No	4	0	
Preceding vaccination	Yes	2	0	1
	No	122	18	
Received medication	IVIG alone	109	18	0.217
	IVIG + IVIG +IVMP	15	0	
Dose of IVIG	1g/kg/2 days	100	11	0.06
	400 mg/kg/5 days	24	7	

Abbreviations: IVIG: intravenous immunoglobulin; IVMP: intravenous methyl prednisolone, g: gram, mg: milligram, kg: kilogram.

In Table 3, the comparison between the complete response group and the chronic ITP group at 1 year of IVIG treatment according to their laboratory findings. The laboratory findings show no significant differences between the complete response and chronic ITP groups, for hemoglobin levels ($p = 0.606$) and MPV at diagnosis ($p =0.689$), with similar means and standard deviations. However, platelet counts at diagnosis do not differ significantly ($p = 0.333$). In contrast, there is a significant difference in platelet counts at 3 months

post-treatment ($p = 0.000$), with the complete response group showing a much higher mean count ($243.9 \times 10^9/L$) compared to the chronic ITP group ($79 \times 10^9/L$), indicating better recovery in the complete response group. Platelet counts at 1 month also show a significant difference ($p=0.036$), favoring better recovery in the complete response group, although the difference is less pronounced at 1 month than at 3 months.

Table 3. Comparison between the complete response group and the chronic ITP group at 1 year of IVIG treatment according to their laboratory findings

Laboratory findings		Complete response	Chronic ITP	Level of significance
Hemoglobin (HB) at diagnosis	Mean	11.33	11.47	0.606
	Standard deviation	1.05	0.76	
MPV at diagnosis	Mean	12.25	11.38	0.689
	Standard deviation	9.1	1.18	
Platelet count at diagnosis	Mean	17.5	19.1	0.333
	Standard deviation	6.50	6.48	
Platelet count at 1 month	Mean	117.66	49.07	0.036**
	Standard deviation	92.2	28.8	
Platelet count at 3 months	Mean	243.9	79	0.000**
	Standard deviation	82.1	15.3	

Abbreviations: ITP: immune thrombocytopenia; MPV: mean platelet volume.

Discussion

Each therapy has a unique effect on the primary ITP outcome, especially the initial therapeutic agent started at the diagnosis. This thesis was evaluated in the literature. There are significant differences in predictors of remission following IVIG therapy in newly diagnosed ITP children in the literature, generally showing no effect, and others show various effects on the disease outcome. In the current study, we evaluate demographic, clinical, and laboratory predictors of remission following IVIG therapy in newly diagnosed ITP. Our study reports that a high proportion of our study group, (87.3%) show complete response resulting in disease remission, and only 12.7% developed chronic ITP, which is consistent with the previous research reports that treatment with IVIG results on lower rate of chronic disease and a higher rate of remission [23-25], It is in agreement with a study by Ay Y et al. (2020), which demonstrate that initial IVIG treatment less likely to get chronic disease [23], the pediatric ITP Cases randomized controlled trial by Heitink-Polle et al.(2018) [24], demonstrated the initial IVIG had resulting in high disease remission and lower chronic ITP rate compared to follow-up without therapy as well as Tamminga R et al (2009) study, it was found that children who received IVIG were platelet count recovery 6 months after diagnosis than children not receiving IVIG (odds ratio 1.81; 95% confidence interval: 1.25-2.64) [25].

On other hand our study is not in agreement with a study of predictive factors for remission of childhood immune thrombocytopenia in Thailand, it was found that pediatric ITP patients who were followed without treatment or who received steroids alone had less chronic ITP than those who received combined IVIG and methylprednisolone therapy [26] and Söğüt G et al, 2020, have found that IVIG therapy has a higher rate of chronicity than those receiving methylprednisolone [27]. In Turkey, a pediatric ITP study by Aslan M et al. 2019 [28], a retrospective evaluation of patients diagnosed with acute immune thrombocytopenic purpura and comparison of high-dose methylprednisolone and intravenous immunoglobulin.

The study results suggest that HDMP and IVIG treatments have similar effects on disease progression to chronicity. Although the previously mentioned data indicated that IVIg influences the ITP outcome, David E et al.'s 2021 [29], a recent randomized controlled trial (RCT) showed that IVIg has no role in chronic ITP development. Our study found that the ITP patients aged ≤ 5 years at presentation served as a positive predictor of remission following IVIG therapy in newly diagnosed ITP children; these findings are compatible with other research, which revealed that the younger age of the patient, the higher remission rate, and the lower chance of chronic ITP following IVIG therapy in newly diagnosed ITP [30-31]. However, this difference in therapy response in different age groups should be considered in any research as shown in our study, the lower rate of chronic ITP also can be explained by the low-risk age 1-9 years of the studied population, as previously reported studies have shown that the risk factors for chronicity in primary ITP in children were age >10 years, the platelet counts $\geq 20 \times 10^9/L$ at diagnosis [32] and the other confirm the children with ITP under 9 years of age had a higher remission rate.[33]. Similar reports in the literature found that the younger the age group, the higher the rate of ITP remission, as shown by Kühneet al 2003 study, which reports better IVIG therapy response in the infant age group and recommends that infants are more likely to be treated with IVIG, and corticosteroids are used most frequently in older children and adolescents [34].

As well as Fujisawa K et al 2000 and Shirahata A et al., Japanese 2006, studies which show children younger than 25 months tend to have a better response to IVIG, and have a higher chance of disease

remission, and older children, ≥ 25 months, show lower therapy response and are more likely to progress to chronic disease [35, 36]. In another study, Min Gi Sakong et al. (2022) show that patients older than 6 years and those who received IVIG doses less than 2 g/kg are most likely to progress to chronic ITP [37]. Our study reveals that abrupt disease onset is another positive predictor of remission following IVIG therapy in newly diagnosed ITP children, as reported, 84.5% of our complete response group had an abrupt disease onset and subsequent disease remission. This is consistent with the research that reports chronic ITP more in patients with an insidious onset [38-42]. However, our study is inconsistent with Al Fawaz in Saudi Arabia, who shows no association between the onset of disease and the remission in Saudi ITP patients [43].

The laboratory data in this study indicated that a platelet count of $\geq 100 \times 10^9/L$ at both 1 and 3 months is a reliable laboratory predictor of remission following intravenous immunoglobulin (IVIG) therapy in children with newly diagnosed immune thrombocytopenic purpura (ITP). These findings are consistent with other studies, reports show that early platelet count recovery at 1 and 3 months after IVIG treatment predicts a shorter disease duration and a favorable outcome in children with newly diagnosed ITP [44-46]. Choi HS et al., 2015 retrospectively analyzed 72 children newly diagnosed with ITP who received IVIG treatment, demonstrating that early platelet count recovery at 1 and 3 months after IVIG treatment predicts a short disease duration and a favorable outcome in children with newly diagnosed ITP [44]. Jae Yeob Jung et al., A retrospective study evaluating the clinical course of childhood immune thrombocytopenia (ITP) and assessing risk factors for developing chronic ITP, 2014.

In total, 45 patients (70.3%) received intravenous immunoglobulin (IVIG) as first-line therapy; older age, absence of prior infection, and insidious onset of symptoms were significantly associated with the development of chronic ITP. Among patients who received IVIG, those with platelet count $< 45 \times 10^9/L$ at 1 month after therapy had a significantly higher incidence of chronic ITP than those with platelet count $\geq 45 \times 10^9/L$ (88.8% vs. 44.4%, $P < 0.01$) [45]. In a multicenter randomized trial, Heitink-Pollé KMJ et al. 2018 [46] showed that chronic ITP occurred in 18.6% of patients in the IVIg group and 28.9% in the observation group (relative risk [RR], 0.64; 95% confidence interval [CI], 0.38-1.08). Platelet counts lower than $100 \times 10^9/L$ at 12 months (current definition of chronic ITP) were observed in 10% of children in the IVIg group and 12% in the observation group (RR, 0.83; 95% CI, 0.38-1.84).

Complete response rates in the first 3 months were significantly higher in the IVIg group [46]. Platelet count recovery $\geq 100 \times 10^9/L$ at 1 and 3 months, age at diagnosis ≤ 5 years, and abrupt disease onset are positive predictors of remission following IVIG therapy; these findings are consistent with Jung JY et al.'s 2018 study [47]. While other parameters, including gender, prior infection, prior vaccination, hemoglobin level, MPV, and platelet count at diagnosis, did not serve as remission predictors following IVIG therapy in newly diagnosed ITP children.

Conclusion and recommendation

We concluded that approximately 87.3% of ITP children experienced disease remission within 1 year of initial IVIG therapy at diagnosis. These patients experienced a higher recovery rate, which was linked to the younger age group ≤ 5 years, and to abrupt disease onset and platelet count recovery $\geq 100 \times 10^9/L$ at 1 and 3 months after IVIG therapy; these are good predictors of remission following IVIG therapy in newly diagnosed ITP children. So we recommend IVIG as the best therapeutic option for young pediatric patients with newly diagnosed ITP ≤ 5 years and those with an abrupt onset of the disease, as well as we recommend using the platelet count recovery $\geq 100 \times 10^9/L$ at 1 and 3 months as positive predictive factors of the ITP remission following IVIG as initial therapy. Further research with a larger population and a prospective cohort study will be required to explore these findings and provide precise treatment decisions. Strengths and Limitations The strengths of this study were the use of the New American hematology guideline for ITP children and the fact that all cases were followed up for 12 months. Our study was limited by its retrospective design with a relatively small number of ITP children ($n = 142$).

Author Contributions

This work was carried out in collaboration between all authors. Author Haloom Abdelsalam Elhashmi is the corresponding author, designed the study, wrote the protocol, wrote the first draft of the manuscript, submitted the manuscript, and made revisions. Nadia AM Eldarogi performed the statistical analysis and revisions. Hana Abdullah Misbah Alshibani contributed to data collection.

Informed Consent Statement

Patient consent was waived due to the study's retrospective nature, which was approved by our Institutional Review Board.

Conflicts of Interest

The authors declare no conflict of interest.

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