

Comparing the Outcomes of IVIg with Combination of IVIg and Methylprednisolone in Children with Acute Idiopathic Thrombocytopenia; a Bayesian Logistic Approach

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Abstract

Background

This study aimed to evaluate the effectiveness of Intravenous immunoglobulin (IVIg) and combination of IVIg and Methylprednisolone for childhood Idiopathic (autoimmune) Thrombocytopenia (ITP) treatment; in addition investigate the related factors to develop chronic form of under 15 years ITP.

Materials and Methods

This retrospective study conducted on 88 ITP patients that treated with IVIg or combination of IVIg and Methylprednisolone. Children were treated with IVIg 2 mg/kg/d or combination of IVIg 2 mg/kg/d and Methylprednisolone 20 mg/kg/d for maximum 5 days. The numbers of patients with a platelet count $> 50,000/\mu\text{l}$, after treatment initiation, were the primary outcome. Odds Ratio (OR) as well as 95% Bayesian Credible interval (CrI), were estimated using a Bayesian Logistic regression model.

Results

The median age of subjects was 3.5 ± 4.42 years (Interquartile: 2 8.5). About 13% of patients were discharged from hospitalization in day 2 and day 3. The ITP of 23% of children were progressed to chronic form. The following factors were significantly associated with the development of chronic ITP, combination of IVIg and Methylprednisolone [OR: 3.24, 95% CrI: [1.06 11.11]], and day 2 and 3 of discharge from hospitalization (OR: 7.72, 95% CrI: (1.14 67.16)).

Conclusion

The current results, suggest that the both IVIg and combination of IVIg are equally effective in providing a platelet level $> 50,000/\mu\text{l}$ early. In addition patients how received combination drug were more likely to develop to chronic ITP. Therefore, we suggest that this route must be preferentially used in decision making for treatment childhood ITP.

Key Words: Children, Chronic immune thrombocytopenic purpura, Intravenous immunoglobulin.

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1- INTRODUCTION

Idiopathic (autoimmune) Thrombocytopenia (ITP) is an autoimmune hematologic disorder characterized by low platelet count and bleeding. Its incidence reported between 4 and 5.3 per 100,000 children per year (1). ITP can be fatal when presenting in vital organs (2). Acute form of ITP is seen in 80-85% of children cases, and about 15-20% develop a chronic form of disease (3). Chronic ITP regularly affects primarily adults with remains of thrombocytopenia for greater than 6 months, despite therapy. Treatment of acute childhood ITP is controversial (4). About 80% of ITP children will recover spontaneously before 8 weeks. Clinical severity, as well as platelet count used to define the severity of acute ITP in children, so in almost 80% of children there is no need for treatment (3, 4). For childhood ITP with low platelet count in addition to severe bleeding symptoms, corticosteroids (Prednisolone, Methylprednisolone, Dexamethasone) are first line therapy. Intravenous immunoglobulin (IVIg) is sequence treatment type that should be reserved for patient that not remit to steroids and who have active bleeding. In addition, splenectomy, rituximab anti-D, thrombopoiesis stimulating agents, immunoglobulin and "watch and wait" are used as therapy(5). Dexamethasone treatment is not recommended as first line therapy in acute ITP(3).

Intravenous immunoglobulin is one of the most effective treatments for acute childhood ITP. It is believed that large amount of immunoglobulin acts by saturating Fc receptors on phagocytic cells, thus preventing them from attacking auto-anti body-coated platelets. 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. However, despite its efficacy, the cost of IVIG is often too high to be used in medical

practice in the developing world. Given that at present, treatment decision of patients with acute ITP are really on physician's experience. Moreover the main aim is achieve to optimal outcomes in children. Currently, study focusing on the relationship between treatment selection and longtime clinical response remains scarce, so clarifying results and efficacy of used treatment strategies can be extremely important for future decision making, improve advanced care planning and management adverse events.

The question whether drug treatment at diagnosis of childhood ITP associated with developing the risk of chronic form is unclear. Factors like as age at diagnosis, female gender and platelet count $>20 \times 10^3/\mu\text{l}$, are determined as higher risks for developing chronic childhood ITP(6).

This study aimed to evaluate the treatment outcomes of IVIg with combination of IVIg and Methylprednisolone; in addition investigate the initial treatment may be related to develop of chronic childhood ITP.

2- MATERIALS AND METHODS

In this case-control study, we included all children with ITP into our retrospective study who treated with IVIg or combination of IVIg and MethylPrednisolon in the Hazrat Masoumeh Pediatric Research center of Qom city from 2013 to 2015; and the consecutive sampling method was used. The Patients' progress was followed until 6 month after the treatment as acute ITP, when they were considered into two groups, chronic ITP and non-chronic ITP. Demographic factors, blood sample test results and type of drug used for eligible ITP patients were reviewed retrospectively. Analysis was done on treatment outcomes of 88 children with initial acute ITP.

Each individual with platelet count less than $150 \times 10^3/\mu\text{l}$ was diagnosed as ITP(7). The diagnosis of ITP was made based on

the criteria from the guidelines of the society of pediatric Hematology (3). Clinical severity, in addition to platelet count, was used to define the severity of childhood ITP. Platelet count below 25,000/ μl was defined as severe ITP(8). Children with platelet count below 25,000/ μl or children with platelet count below 50,000/ μl along with severe bleeding symptoms were received treatment. Existing thrombocytopenia (platelet count $<50 \times 10^3/\mu\text{l}$) after 6 months was classified as chronic. The children with splenomegaly, medication that contains aspirin compounds, abnormal clotting factor, Lupus history, systematic Lupus erythematosus and HIV was excluded from analysis. The physician directions and clinical symptoms were used for allocation patients to treatment groups. Data from all under 15 years ITP patients after 6 months of treatment, who received IVIg or IVIg+ Methylprednisolon were used. The blood tests were repeated daily for 5 days as well as within 1 month until 6 months of diagnosis. Children were treated of IVIg 2 mg/kg/d or combination of IVIg 2 mg/kg/d and Methylprednisolon 20 mg/kg/d for maximum 5 days intravenously. Courses were repeated if the platelet count was less than $20 \times 10^9/\mu\text{l}$ on the thirtieth days. The platelets count $> 50 \times 10^3/\mu\text{l}$ was considered as criteria for discharge from hospitalization. Subjects were followed at least for 6 months.

We used Bayesian logit model to study the related factors with treatment outcomes of ITP patients. The Bayesian logit model is a statistical technique for describe response variables with non – normal distribution or binary outcome. The link function is here the log-odds or logit. Bayesian model is robust to outliers, small sample size and different variances within levels of nominal predictors (9). We fitted Bayesian logistic regression with using logit link function for Bernoulli density with

parameter P_i . In this method, we considered Bernoulli prior for response variable. Model with minimum deviance information criterion selected as final model. OpenBUGS 3.2.2 software (Boston, MA 02111-1307, USA) was used to perform data analysis. In significance tests, null hypothesis is rejected if 95% Bayesian Credible interval (CrI) does not include the null value. Convergence was evaluated by visual examination of the autocorrelation plots, posterior density plots, Gelman-Rubin plots, and the trace plots(10). This study was approved by the research committee of Qom University of Medical Sciences (ID Number: 2127800).

3- RESULTS

During the 2013 to 2015, 115 children with ITP were registered. Twenty two as well as five ITP patients were excluded from analysis due to incomplete information and selected exclusion criteria, respectively. The median time of follow up was 8.1 months. The median age of children was 3.8 ± 4.42 years with IQR [2 8.3], 57.8 % (n=54) of them were boy and 41.4% (n=36) of observation disease were mild. The initial platelet counts between two treatment groups was not significant (P=0.582). Thirty-seven (42.5%) of children were received IVIg treatment. Almost 13% of children discharged in the second day and third day. About 23% of patients developed chronic ITP (**Table.1**). Recorded platelet counts from patient between two treatments are demonstrated in **Figure.1**.

The logistic regression results with controlling the effect of other independent variables showed that the gender and treatment type was associated with discharge day. The chance of discharge in the second day and third days were significantly 16 times higher in girls compared the boy (P=0.046). Moreover, it was 9 times higher in combined treatment compared to IVIg group, but it was not

significant. The correlation of days of discharge with age, ITP severity and initial platelet was not significant (**Table.2**).

The Bayesian logistic regression was used to analyzing association of independent variables with chronic ITP. The results showed that, treatment type and day of discharge were significantly associated with prognosis of ITP. The chance of developing to chronic ITP in IVIg group was significantly 3.24 time higher compared the combination treatment (OR=3.242, 95%CrI: [1.06 11.11]),

moreover chance of developing to chronic ITP in group that discharged at second day and third day was significantly 7.72 time higher compared the patients that discharged at fourth day and fifth day (OR=7.72, 95%CrI: [1.14 67.15]) (**Table.3**).

The associations between age, gender, severity of disease, initial platelet, white Blood cell count and hemoglobin with change to chronic form were not significant (P>0.05).

Table-1: Characteristics and demographic information of observations

Variables	Discharge Day		P-value	Prognosis of ITP		P-value	
	2&3	4&5		Acute	Chronic		
Age, year (Mean ± SD)	7.6±4.7	5.4±4.2	0.058	5.18±4.4	6.91±4.2	0.115	
Initial Platelet (Median)[IQR]	12500 [7750 15500]	8000 [6000 14250]	.608	9000 [7000 15000]	10000 [5000 17000]	0.76	
Gender, n (%)	Female	9(24.3)	28 (75.7)	0.072	29 (78.4)	8 (21.6)	0.79
	Male	5 (10)	45 (90)		38 (74.5)	13 (25.5)	
Group, n (%)	IVIg+MP	10 (20)	40 (80)	.24	34(68)	16 (32)	0.02
	IVIg	4 (10.8)	33 (89.2)		33 (86.8)	5 (13.2)	
Primary symptoms, n (%)	moderate	7 (19.4)	29 (80.6)	.475	31 (86.1)	5 (13.9)	0.137
	Sever	7 (13.7)	44 (86.3)		36 (69.2)	16 (30.8)	

*ITP: Idiopathic Thrombocytopenia, IQR: Interquartile.

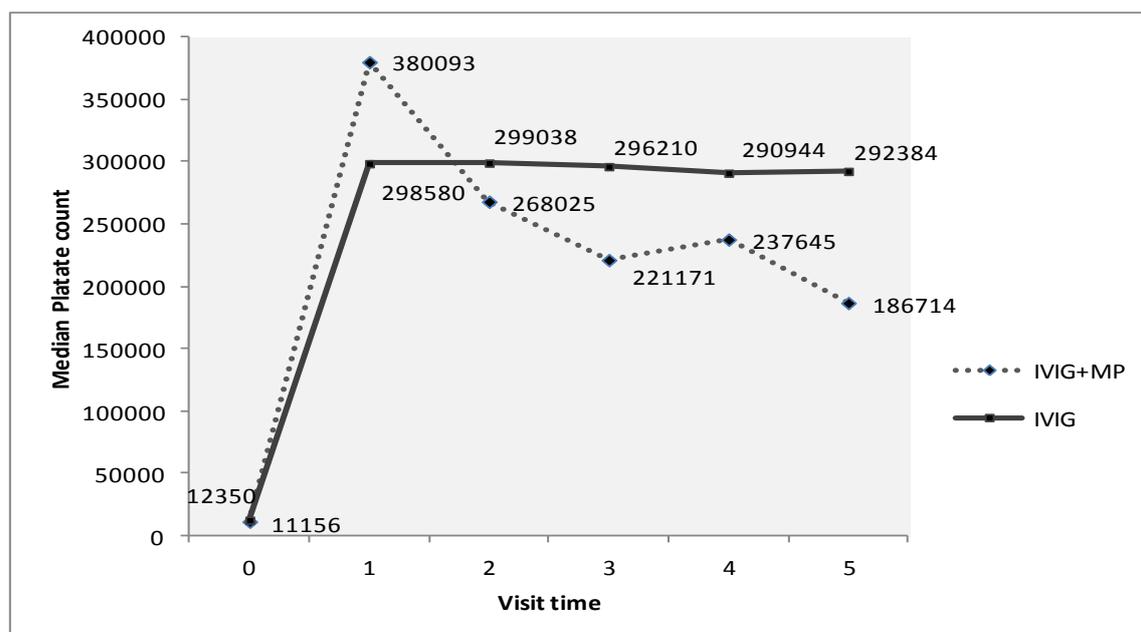


Fig.1: Comparison of placate count during 6 months between IVIG and IVIG+ Methylpredinosolon

Table-2: The associated factors with day of discharge from hospitalization in children with ITP

Variables	Beta	MCE	Odds Ratio	Estimate (95% CrI)	P-value**	
Age (Mean)	-0.0464	0.0021	0.954	0.77	1.19	0.096
Gender (n)	2.97	0.028	16	1.65	46.3	0.046
Treatment type (n)	2.27	0.048	9.71	.992	292.1	0.102
ITP severity (n)	0.743	0.016	2.09	.035	12.81	.56
Initial Platelet (Median)	-0.00004	0.000007	1	0.999	1	.531

*MCE: Minimum classification error; CrI: Bayesian Credible interval; **Adjusted P-value.

Table-3: The associated factors with develop chronic ITP in children

Variables	Beta	MCE	Odds Ratio	Estimate (95% CrI)	P-value	
Age (Mean)	-0.0127	0.002	0.989	0.78	1.23	0.103
Gender (n)	0.942	0.015	2.47	0.384	20.79	0.624
Day	2.08	0.012	7.72	1.14	67.15	0.039
Treatment type (n)	1.196	0.002	3.242	1.06	11.11	0.03
ITP severity (n)	1.094	0.014	2.93	.51	19.07	0.24
Initial Platelet (Median)	-0.00001	0.000005	1	1	1	0.84

*MCE: Minimum classification error; CrI: Bayesian Credible interval.

4- DISCUSSION

In this study we compared the treatment outcomes of ITP with IVIg or combination of IVIg and Methylprednisolone in children. In our experience, the median age of patients with acute ITP was 3.5 years. In addition, slightly, boys affected more than the girls, in line with a previous studies which was about 3-6 years (11, 12). The higher male/female ratio has been reported recently by Farhangi et al. in Iranian children with acute ITP (63%)(13). This may be due to difference in age of study subjects, which it was conducted in 0-2-year- old children.

As results about 23% of cases progress to chronic form which was also in line with a previous studies in Iran, it was 21% in Tehran provinces in Iran from 2005 to 2010 (14), the recent report by Kubota demonstrated that incidence for developing to chronic form was 27% (15). Large cohorts in Western countries reported this proportion between 10-30% for IVIg groups(16). As result, it seems to be needed more attention to management ITP treatment programs for reduction the chronic and other side effects of ITP.

The Bayesian logistic regression analyses from the study revealed that gender was the predictor of early discharge from hospitalization. Some studies demonstrated that boys are as a risk factor for affected sever ITP (14), so this can delays discharge time in this group. The patients in combine group achieving the platelet count $>50 \times 10^3/\mu\text{l}$, as a criteria for discharge from hospitalization, faster than the IVIg group, but this differences, was not significant. This is comparable with other studies that using 2 mg/kg/d IVIg (by 4 days, 76%) (17-19), Celik et al. found that IVIg and Methylprednisolone drugs were equally efficacy in increasing platelet count (20). Koyuncu et al. demonstrated that high dose Methylprednisolone is more effective than IVIg in increasing platelet counts (21). Combination of IVIg and Methylprednisolone may be accelerate this increasing, so it can be good choice for situation that there is emergency need for rapid increasing platelet count.

Other studies, demonstrated that patients with high count of platelet, initial age over 10 years, no viral infection history, female gender, high platelet levels at initial of

diagnosis, and existence of autoimmune disease are risk factor for developing chronic form (6, 22). In our study, chance of patients who developed chronic ITP was significantly higher in combination treatment, this result in keeping with literature (23, 24), the relative risk for developing chronic form in steroids vs. IVIg group was 1.4. Possible cause of this can be due to faster, but slippery increasing of platelet count in patients that treated by combined treatments; while this is contract to some randomized studies that have not demonstrated significant differences between IVIg and other drug treatments (18, 20).

Increasing the platelet count is one of the factors that is associated with discharge from hospitalization (20); in our study the odds of patients who developed chronic ITP was higher in early discharged individuals, which may be due to that patients with higher platelet count in initial of diagnosis reach to safe level rapidly, moreover patients in IVIg+ Methylprednisolone group were discharged minimally faster than IVIg group, so this connection between two variables, may be important to develop chronic ITP. Indeed correlation between day of discharge and develop to chronic form may be due to indirect effects. As result of this study, the trend of platelet count was not stable in combination treatment. In our study, in addition, these differences in results may be due to applied analyzing methods, that Bayesian logistic regression method adjusts existing high autocorrelations among independent variables. This adjustment provides reliable and pure estimation of associations.

We need to apply these results with caution, because this study was hospital-based instead of population-based. Therefore, for example, may be variation among patients not controlled. But this should be confirmed by a larger study population-based analysis.

4-1. Limitations of the study

There are several limitations in this study. First, this is a retrospective study. Treatment decisions were left to each physician's discretion, and therefore the methods of managing the disease have not been standardized. Second, although careful attention was paid to following patients in this regional central hospital, but the missing problem was inescapable. In addition, to date, there is very little published data on the comparing the two methods in adults or children with ITP. Despite these limitations, we yet believe that this study contains useful new information for decision making in ITP management.

5. CONCLUSION

We found that treatment with IVIg is useful for preventing to develop chronic form compared to combination of IVIg and Methylprednisolone. In addition, using low dose IVIg or increasing gradually in platelet count can be important to preventing chronic ITP.

6- CONFLICT OF INTEREST

The authors declare no conflict of interest.

7- ACKNOWLEDGMENTS

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