



# Recurrence rate in patients with acute immune thrombocytopenic purpura in Ahvaz, southwest of Iran: Corticosteroids versus intravenous immunoglobulin

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## Abstract

**Introduction:** Immune thrombocytopenic purpura (ITP) is known as the most important cause of sudden drop in platelet count among children. The acute form of unexpected drop in platelet count in children calls for treatment with medications such as corticosteroids, intravenous immunoglobulin (IVIg), and Rho(D) immunoglobulin (anti-DIG). Most of the previous studies have accordingly compared short-term therapeutic outcomes of steroids with those of IVIg. In some cases, IVIg has led to better results. However, there are few studies on the long-term treatment effects of both medicine categories.

**Objectives:** This study was aimed to evaluate the therapeutic effects and recurrence rate (RR) of corticosteroids, IVIg, or both in the long-term to find the best and most effective treatment for these patients.

**Patients and Methods:** A total of 188 children diagnosed with acute ITP were admitted to the hematology departments of Shafa and Baghaei hospitals of Ahvaz, Khuzestan, Iran. The therapeutic consequences and RRs of corticosteroids, IVIg, or both were compared within one year.

**Results:** Comparing treatments employing corticosteroids and IVIg in children having acute ITP in terms of the long-term treatment outcomes showed no statistically significant difference. In addition, the findings revealed that 34% of the patients had experienced recurrence within one year with no remarkable difference between both drug groups.

**Conclusion:** The long-term therapeutic outcomes in both medicine categories were not significantly different. Therefore, given the world's current economic conditions and inadequate supply of all medicines, it seems more rational to use the least expensive drugs.

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## Introduction

Immune thrombocytopenic purpura (ITP) is known as one of the most common acquired blood disorders in children, with a prevalence rate of 6.4 cases per 100 000 people each year. Although this condition can be found in all age groups, it is particularly common among children between 2 and 6 years. ITP refers to an autoimmune condition that impairs platelets through antibodies and then destroys megakaryocyte platelet production (1). Recent experimental and clinical observations have also revealed abnormal autophagy in ITP patients. Accordingly, the role of autophagy in megakaryopoiesis, thrombopoiesis, and platelet function is being gradually discovered. The abnormal autophagy in ITP patients may be caused by deletion of autophagy-related genes such as ATG7 and disrupted signaling due to over-expression of the mechanistic target of rapamycin (mTOR), ultimately

## Key point

In a study to compare therapy methods employing corticosteroids and intravenous immunoglobulin (IVIg) in affected children, we found no significant difference between long-term treatment outcomes for immune thrombocytopenic purpura (ITP).

diminishing the function and the quantity of platelets and leading to the onset of ITP. After platelet destruction, small hemorrhages also occur on the skin and in the mucosa in forms of petechiae and purpura. However, there might be internal bleeding such as intracranial hemorrhage if the platelet count drops dramatically. Diagnosis in this respect is based on platelet counts below 100,000/ $\mu$ L in peripheral blood samples in the absence of any cause for thrombocytopenia (2). Recently, ITP has been classified as acute (lasting up to three months from onset), persistent (3-12



months), and chronic (>12 months). Most acute forms in children occur seasonally following a viral infection and are often self-limiting and improve within a few weeks to six months (3). Several treatments have been thus far suggested for this condition, including medications such as corticosteroids, anti-Rh<sub>0</sub> (D) immunoglobulin (anti-D IG), and intravenous immunoglobulin (IVIg) as well as surgical procedures (e.g., splenectomy). Some patients treated with corticosteroids, IVIg, or anti-D IG may experience recurrence of the disease a few weeks after treatment. Fortunately, most patients respond to initial treatments positively/successfully. However, those who do not have a positive response need to be treated with alternative methods. In most studies, short-term therapeutic outcomes related to corticosteroids and IVIg groups have been examined individually or together. However, the long-term recurrence rate (RR), specifically in these two types of treatments, whether separately or in combination, has received less scholarly attention. Most investigations have compared short-term therapeutic outcomes of steroids and IVIg. Although in some cases, IVIg has been associated with better results, there are few studies on the long-term effects of these two drugs (4). On the other hand, there are other investigations addressing the combination of steroids and IVIg. In the present study, most patients were treated with a combination of steroids and IVIg.

## Objectives

The most commonly used ITP treatments in Iran are corticosteroids and IVIg. This study was aimed to compare the differences between these two treatment options in terms of the RR of these two treatments as the costs and side effects of both treatments are different.

## Patients and Methods

### Study design

This retrospective descriptive-analytic study was conducted between 2012 and 2016 at Shafa and Baghaei hospitals, in the city of Ahvaz, Khuzestan, Iran. The participants of this study included a total of 188 hospitalized children diagnosed with acute ITP and treated with corticosteroids or IVIg or both. Patient data were also extracted based on age, gender, platelet count at baseline and upon discharge, recurrence within one year after treatment, and type of treatment including the use of corticosteroids, IVIg therapy, or both.

In the current study, the diagnosis of ITP was determined based on the patients' history and their physical examination which included a complete blood count (CBC) revealing isolated thrombocytopenia (platelets below 30 000/ $\mu$ L), normal hemoglobin concentration, white blood cell count, and peripheral blood smear. Inclusion criteria were included absence of underlying conditions and malignancy cases. Bone marrow aspiration was performed in children presenting with typical

features of acute ITP, mainly to rule out other roots of thrombocytopenia. All patients also had indications for the initiation of treatment, and they had been then hospitalized to receive treatment (5). The required dose of steroids and IVIg as well as duration of treatment were the same for all of the patients. Additionally, the criterion of recurrence was defined as a patient's platelet count below 100 000/ $\mu$ L within one year of treatment. It should be noted that all the patients and their families were informed about the type and the side effects of treatment. Besides, there were no striking adverse effects during treatments.

### Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, approved this research project (IR.AJUMS.REC.1398.006). Accordingly, as mentioned earlier, a written informed consent was taken from all the parents before the study. This research was part of a pediatrics residency thesis financially supported by a grant from Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (Grant#Th-9801).

### Statistical analysis

The baseline characteristics of the study population were summarized using descriptive statistics. To examine the effects of the treatments, patient characteristics and outcomes were also compared across five groups using chi-square test or Fisher's exact test for categorical variables. The analysis of variance (ANOVA), F-test, or Kruskal-Wallis test were additionally employed for continuous variables. Either the Student *t* test or Wilcoxon rank-sum test was used to compare continuous variables in both groups. Data management and statistical analysis were performed using the SPSS version 25. *P* values less than 0.05 were considered statistically significant.

## Results

In this study, a total of 188 hospitalized children diagnosed with acute ITP were recruited. Petechiae, purpura, and ecchymosis (64.9%) were the most frequent clinical signs in this study. Other symptoms included bleeding (5.3%) and fever (3.2%). Of all patients, 91 (48.4%) were male and 97 (51.6%) were female. However, there was no significant difference between genders in terms of the RR (Table 1). The patients were compared in two groups of infancy (i.e., those under the age of 2 years; 53%) and childhood (i.e.,

**Table 1.** Comparison of the duration of hospitalization based on sex (Mann-Whitney Test)

| Gender | Number | Mean rank | Sum of rank |
|--------|--------|-----------|-------------|
| Boy    | 91     | 89.42     | 8137.50     |
| Girl   | 97     | 99.26     | 9628.50     |
| Total  | 188    |           |             |

those aged above 2 years; 47%). No significant difference was observed between these two groups regarding the time of the initiation of ITP (Table 2). Accordingly, the seasons of onset of symptoms in this study were spring (19.7%), summer (15.4%), fall (33%), and winter (31.9%). However, there was no significant difference between seasons ( $P=0.21$ ). Most patients had been hospitalized for a short period, and most of them (98%) had less than 10 days of hospital stay. They also had an increased platelet count after receiving a course of treatment during admission. As far as the duration of remission was concerned, the ITP patients were compared based on three subgroups according to their remission length, namely three months, three months to 12 months, and more than 12 months. Since this study was performed over a 12-month period, all patients had RRs shorter than 10 months, and most of them had experienced recurrence during the first three months. The patients were also compared in three groups based on time of recurrence, including less than three months (93.5%), 4-7 months (4.9%), and 8-10 months (6.1%). However, most patients' recurrence was less than three months of treatment (namely, platelet loss below 100,000/ $\mu\text{L}$  within one year after treatment). Of 188 patients, 64 cases had recurrence (34%) and 124 (66%) had no recurrence until one year later. The used treatments were divided into five categories: corticosteroid, IVIg, corticosteroid + IVIg, prednisolone, and platelet infusion. The most frequent treatment was corticosteroid + IVIg treatment with a frequency of 141 patients with 50 recurrences. Prednisolone and platelet infusion were each used in only one individual and both cases did not have recurrence. There was no significant difference in RRs (relapse rates) among the remaining three treatment methods ( $P=0.49$ ) (Tables 3 and 4). As far as gender was concerned, 31 (48.4%) and 33 (51.6%) cases respectively from 60 males and 64 females had recurrence in this study. No significant relationship was found between gender and RR ( $P>0.05$ ) (Table 5). Also, based on the  $P$  value (0.96),

no significant relationship was observed between age group and RR (Table 2).

Normality of two quantitative variables (i.e., duration of hospitalization and RR) was assessed, and the result showed that they were not normal. Therefore, non-parametric tests such as Kruskal-Wallis test and Mann-Whitney U test were used.

Kruskal-Wallis analysis was used to compare the duration of hospitalization across age groups ( $P=0.24$ ) and type of treatment ( $P=0.36$ ) and to compare recovery time across age groups ( $P=0.85$ ) and type of treatment ( $P=0.66$ ). Results showed no significant relationship (Table 4).

Mann-Whitney U analysis was used to compare the duration of hospitalization and recovery time in terms of the sex variable ( $P=0.194$  and  $P=0.3$ , respectively). No significant difference was observed (Table 1).

### Discussion

Numerous studies have been so far conducted to compare the efficacy of various medical therapies in ITP. However, most treatments have been followed up in the short term, and little research has reviewed the long-term therapeutic outcomes. Regarding the duration of recovery, this study involved three groups of less than three months (93.5%), 4-7 months (4.9%), and 8-10 months (6.1%). In some investigations, the patients had been monitored only for a short period of time (18). In Beck et al (5), the patients

**Table 4.** Comparison of the duration of hospitalization based on type of treatment (Kruskal-Wallis test)

| Treatment                 | Number | Mean rank |
|---------------------------|--------|-----------|
| Methylprednisolone        | 40     | 91.18     |
| IVIg                      | 5      | 106.90    |
| Methylprednisolone + IVIg | 141    | 94.73     |
| Prednisolone              | 1      | 44.50     |
| Platelet                  | 1      | 183.50    |
| Total                     | 188    |           |

**Table 2.** Distribution of treatment methods in various age groups

| Age group      |     | Corticosteroid | IVIg | Corticosteroid + IVIg | Prednisolone | Platelet infusion |
|----------------|-----|----------------|------|-----------------------|--------------|-------------------|
| Infancy <2 y   | No. | 19             | 2    | 65                    | 0            | 0                 |
|                | %   | 22.2           | 2.3  | 75.5                  | 0.0          | 0.0               |
| Childhood >2 y | No. | 21             | 3    | 76                    | 1            | 1                 |
|                | %   | 20.6           | 3    | 74.5                  | 0.9          | 0.9               |

**Table 3.** Recurrence rate in children with ITP based on different therapeutic methods

| Treatment method      | Frequency | Frequency% | Recurrence | Recurrence% | $P$ value |
|-----------------------|-----------|------------|------------|-------------|-----------|
| Corticosteroid        | 40        | 21.3       | 11         | 17.2        | 0.49      |
| IVIg                  | 5         | 2.7        | 3          | 4.7         |           |
| Corticoateroid + IVIg | 141       | 75         | 50         | 78          |           |
| Prednisolone          | 1         | 0.5        | -          | -           |           |
| Platelet infusion     | 1         | 0.5        | -          | -           |           |
| Total                 | 188       | 100        | 64         | 100         |           |

**Table 5.** Comparison of different therapies based on gender

| Gender |     | Corticosteroid | IVIg | Corticosteroid + IVIg | Prednisolone | Platelet infusion | P value |
|--------|-----|----------------|------|-----------------------|--------------|-------------------|---------|
| Male   | No. | 17             | 2    | 71                    | 1            | 0                 | 0.57    |
|        | %   | 18.7           | 2.2  | 78.0                  | 1.1          | 0.0               |         |
| Female | No. | 23             | 3    | 70                    | 0            | 1                 |         |
|        | %   | 23.7           | 3.1  | 72.2                  | 0.0          | 1.0               |         |

were followed up for only 48 hours. However, there were other investigations, like the current study, which followed up patients for longer intervals, such as six months and even one year. For instance, in a report by Cheng et al, 157 acute ITP patients were followed up for 10 days, three months, and six months (6). Additionally, Erduran et al (7) examined patients diagnosed with acute ITP for two days and 180 days (six months). In the study by Godeau et al (8), patients were followed up for a long period (i.e., 12 months). Furthermore, Rosthøj et al (9) divided a total of 43 patients with acute ITP into two groups, i.e., methylprednisolone and IVIg, followed them up for 72 hours and then six months. Another variable examined in the present study was the length of hospital stay. In this respect, the vast majority of hospital stays (98%) were fewer than 10 days. The length of stay in about 1.6% of the cases was between 10 and 20 days, and it was from 20 to 30 days in 0.5% of the cases. In the study by Bani Hashim et al (10), responses to treatments with prednisolone, RhoGAM (anti-D IG), and IVIg were investigated. The length of stay of those treated with RhoGAM was significantly shorter than that of the rest (less than five days). However, in the study by Celik et al (11) on three treatment groups of methylprednisolone, RhoGAM, and IVIg, no significant difference was observed among the three groups in terms of length of stay. However, Yasuyuki Arai et al (12) reported that only about 13% of the patients were discharged from the second to the third days. This might be due to higher cut-off point specified for treatment responses (i.e., platelet count over 50000/ $\mu$ L). For this reason, the patients had been hospitalized and monitored for a longer period than the desired one. Another variable that was examined in the present study was the disease RR in different seasons, with the highest incidences being reported in fall and winter, which was not consistent with results of other studies (13,14) where RR was not significantly different in terms of seasons. For instance, in the study by Ramyar and Kalantari (15) at a pediatric medical center in the city of Tehran, Iran, the prevalence rates of ITP had been 28.2%, 24.7%, 19.3% and 27.7% in summer, fall, winter, and spring, respectively. We also examined RR in individuals based on their gender (60 males and 64 females), and results showed there was no significant relationship between gender and RR, with 48.4% in males and 51.6% in females. This variable was not included in other studies (10,16,17). The proportion of males was higher only in two studies. In the study by Ramyar and Kalantari, RR was more common among male

cases compared with their female counterparts, and by the same token, Holt et al (18) reported that 23 out of the 32 children examined in their study were male. These results could be attributed to the smaller sample size in these studies compared with the present study. In terms of age, the patients in this study were divided into two groups, i.e., infancy (under the age of 2 years) (53%) and childhood (aged above 2 years) (47%). Other studies have reported similar results, revealing no significant association of age with ITP incidence and RR. Petechiae, purpura, and ecchymosis (64.9%) were also found as the most frequent clinical signs in this study. Other symptoms, such as hemorrhage (5.3%) and colds (3.2%), were reported in the patients of the current study. Although studies investigating these symptoms are limited, they all confirm the results of our study. The long-term treatment outcomes also did not differ significantly among the groups. Additionally, gender and age did not vary in terms of RR and type of treatment practiced.

#### Limitations of the study

Since the sample size of this study was small, inferences about treatment effects are somewhat limited. The scientific literature review was limited and inconsistent.

#### Conclusion

Given the different treatments practiced for ITP, it is necessary to compare the effectiveness of these treatments over time and to choose the best one, taking into account side effects, the costs, and the complications of different treatments. Since there was no significant difference between the treatment groups in terms of the presence of specific adverse effects, RR, and length of hospital stay (both had fewer than ten days), it is better to use corticosteroids because of their cost-effectiveness compared with other treatments (such as IVIg) and their availability.

#### Authors' contribution

AA, AS and FA were the principal investigators of the study. AA, AS and FA were included in preparing the concept and design. AA and AS revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

#### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

**Conflicts of interests**

The authors declare that they have no competing interests.

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