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Study on the Factors Influencing the Response to Intravenous Immunoglobulin in Children with Immune Thrombocytopenia Referred to Bahrami Hospital, Iran

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ABSTRACT

Background and Objective: Therapeutic response to intravenous immunoglobulin (IVIG) for the treatment of immune thrombocytopenia (ITP) in children may itself be influenced by various factors. The aim of the present study was to investigate the factors associated with the response rate to IVIG treatment in children with ITP.

Methods: The population of this cross-sectional study included children under the age of 15 who were diagnosed with ITP and admitted to Bahrami Hospital in Tehran from 2021 to 2022. Information on each patient including age, gender, comorbidities, platelet count at diagnosis and duration of treatment at baseline was obtained by reviewing the hospital's data registry. Treatment outcomes, including treatment success and disease recurrence or chronicity, were also recorded. A p- value of 0.05 was considered significant.

Findings: Of the 41 patients examined, 7 (17.1%) cases failed to respond to IVIG treatment and received additional treatment with corticosteroids. There was a significant difference between patients with and without response to IVIG treatment. The mean initial platelet count was 22676.47±18514.07 and 13857.14±7883.07 per cubic millimeter, respectively, indicating a significant difference between the two groups (P value=0.045). An initial platelet count of less than 9,000 was predictive of non-response to IVIG treatment.

Conclusion: In children with ITP, the response rate to IVIG administration was high, with patient gender and initial platelet count influencing the response. Therefore, male gender and a low platelet count on admission are predictive factors for a lower response to treatment in these patients.

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Introduction

Immune thrombocytopenia (ITP) is a bleeding disorder and the most common cause of thrombocytopenia in children [1, 2]. Severe and spontaneous bleeding occurs in patients with <10,000 platelets per microliter. The duration of the disorders can be transient, persistent (3 to 12 months) or chronic (more than 12 months) [3]. A drop in the platelet count to <150,000 is referred to as thrombocytopenia [4]. However, the platelet count threshold for diagnosis has been set at a new value (100,000) instead of the previous limit (150,000) [5]. The incidence of ITP in children is 1.6 to 5.3 per 100,000 [6], in adults 1.9 to 3.9 per 100,000. ITP affects boys and girls equally in children [7].

ITP in children usually begins acutely and occurs shortly after an infection or vaccination [8]. The risk of developing the disease after MMR vaccination is estimated 1 in 24,000 [9]. A large multicenter study collected data from 2031 children with ITP, and represented that the incidence of ITP peaks in the spring and lows in the fall [10]. ITP resolves within 6 months in 85% of children with or without medication [4]. Regarding the clinical symptoms of ITP in children, ITP typically affects a previously healthy preschool child between the ages of 2 and 7 years [11, 12]. The onset of the disease is sudden, with almost all patients affected by bruising and petechial rashes. Epistaxis may occur in about one-third of patients [13]. The clinical examination of the child reveals a healthy appearance with only bruises and petechiae as symptoms of a low platelet count. Organomegaly and lymphadenopathy should be essentially absent. Laboratory examination indicates isolated thrombocytopenia with normal WBC and Hb levels.

Diagnosis and treatment, as with other diseases, depend on understanding the etiology and pathogenesis of the disease [4]. Until 1980, the classical treatment of ITP consisted mainly of treating bleeding episodes with corticosteroid therapy [3]. Treatment is required for moderate to severe thrombocytopenia due to the high risk of bleeding. These treatments include the use of oral or injectable corticosteroids and/or the use of various intravenous immunoglobulins (IVIGs) [15]. Platelet transfusions are generally contraindicated in the treatment of ITP; however, in cases where the patient is at risk of life-threatening bleeding, such as intracranial hemorrhage, platelet transfusions may be considered. In general, the preferred treatment approach will depend on the patient's circumstances, including age, gender, platelet count at diagnosis (severity of thrombocytopenia), whether the disease is acute or chronic, underlying conditions such as autoimmune or other hematologic disorders, and the likelihood of developing complications related to the disease or its treatment [7, 16, 17].

The use of IVIG has increased in recent years. This medication is usually administered and leads to an increase in platelet count in 95% of patients within 48 hours [18]. Based on this approach, extensive global studies have been conducted to compare the effect of IVIG with conventional treatments in different age groups with a focus on adults. However, in pediatrics, fewer studies have been conducted and in some cases, none at all. It seems that a better understanding of the different aspects of treatment may be of valuable help to physicians in selecting the optimal treatment approach in different age groups and in predicting the initial prognosis of the disease [19, 20].

On the other hand, this drug is expensive, assessment of all factors influencing response, which is why we decided to conduct this study.

The aim of the present study was to compare the effect of IVIG treatment in children with ITP in different groups with various risk factors and classifications referred to Bahrami Hospital from 2021 to 2022.

Methods

This cross-sectional study was conducted on children <15 years with ITP, admitted to Bahrami Hospital in Tehran, Iran from 2021 to 2022. The study patients were selected based on clinical signs of petechiae and purpura or sudden onset bleeding, no history of bleeding disorders, and no organomegaly. Laboratory tests of blood cell count performed at Bahrami Hospital confirmed the diagnosis of ITP and were divided into two groups. Patients were administered a single dose of IVIG at a dose of 1 g/kg. Patients in whom the platelet count had not increased after 4 days were treated with

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corticosteroids (prednisolone 1-2 mg/kg). Patients older than 15 years or with thrombocytopenia associated with a decrease in other blood cells or hepatosplenomegaly were excluded from the study. At the time of registration in the hospital's registration system, a declaration of consent was obtained from the parents or legal guardians of the participants regarding the confidentiality of their data and the possible use of the collected data in future research studies.

Information on each patient including age, gender, comorbidities, platelet count at the time of diagnosis and duration of treatment at the start of the study was obtained by reviewing the hospital's data registry and was recorded on a specific form for each patient. An identification code was assigned to each patient to avoid bias in the analysis in subsequent evaluations. Patients were followed up for up to 2 years for disease recurrence or adverse events through contact with their families. Finally, the relationship between response to IVIG treatment and underlying factors such as age, sex, season of disease onset and platelet count at diagnosis was investigated.

Data Analysis

The results were statistically analyzed using SPSS 24. The results were expressed as percentages for qualitative data and as mean ± SD for quantitative data. Changes in symptom severity and patient response to treatment were analyzed. The chi-square test was used to examine the relationship between qualitative variables. To compare quantitative variables, the T-test for independent samples and the Mann-Whitney test were used. A value of 0.05 was considered significant.

Results

In total, 41 patients with ITP were included in the present study. The mean age of the patients was 7.65±2.98 years, ranging from 2 to 15 years. The mean age of the patients at the time of initial admission was 5.63±2.98 years. The mean platelet count of the patients was 21170.73±17418.24 per cubic millimeter. In total, 35 (85.3%) and 6 (14.7%) patients received IVIG treatment and corticosteroids, respectively. The mean time to recovery was 3.19±1.81 days (Table 1).

In comparison between the two groups of patients, the mean age of the patients was 7.91±3.03 years and 6.16±2.40 years, respectively (P=0.189), and the mean age at initial admission was 5.87±3.04 years and 4.18±2.36 years, respectively (P=0.203), representing no significant difference between the two groups.

There was no difference in the distribution of gender (P=0.098) and season (P=0.445) of referral between the two groups. The mean initial platelet (per cubic millimeter) count in the two groups with and without IVIG treatment was 19485.71±11191.83 and 31000.00±37942.06, respectively, and this difference was not significant (P=0.136). Additionally, the mean time to recovery was 3.31±1.87 and 2.50 ± 1.37 days, respectively, which was also similar between the two groups (P =0.317) (Table 2).

Of the 41 patients examined, 6 (14.7%) cases failed to respond to IVIG treatment and received additional treatment with corticosteroids. In terms of baseline characteristics, there was a significant difference between patients with and without response to IVIG treatment. In terms of background characteristics, in patients with and without response to IVIG treatment, first, the frequency of boys was 14.3% and 73.5%, and the frequency of girls was 85.7% and 26.5%, respectively, and this difference was significant (P value=0.003).

Regarding the referral season, 14.3% and 14.7% were referred in the fall, 42.9% and 47.1% in the spring, 28.6% and 14.7% in the summer, and 14.3% and 23.5% in the winter, with no difference between these two groups.

The mean initial platelet count (per cubic millimeter) was 22676.47±18514.07 and 13857.14±7883.07, respectively, which revealed a significant difference between the two groups (P=0.045). Moreover, the mean time to recovery was 3.85±3.33 days and 3.06±1.36 days in patients with and without response to IVIG treatment, respectively, suggesting no significant difference between the two groups (P=0.227). Based on these findings, male gender and low initial platelet count on admission were identified as factors associated with failure to respond to IVIG treatment. Based on the analysis of the area under the receiver operating characteristic

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(ROC) curve (AUC), an initial platelet count of less than 9,000 (AUC of 0.72, sensitivity of 67.6%, and specificity of 42.9%) was predictive of non-response to IVIG treatment.

Overall, 5 (12.1%) patients had a relapse of the disease and developed a chronic form. In patients with and without a chronic form of the disease, there was no significant difference between the two groups in terms of gender and referral season. In the two groups with and without the chronic form of the disease, the mean age was 5.74 ± 3.38 and 5.61 ± 2.98 years, respectively, which had no difference between the two groups (P value equal to 0.963). The mean age at the time of admission was 5.74 ± 3.38 years and 5.61 ± 2.98 years, which was similar between the two groups (P=0.931).

The mean initial platelet count (per cubic millimeter) was 26400.00±15076.47 and 20444.44±17785.13, respectively, indicating no difference between the two groups (P=0.931). Besides, the mean time to recovery was 3.00±1.58 and 3.22±1.86 days, respectively, indicating no significant difference between the two groups (P=0.481).

Thus, none of the primary indicators predicted the disease recurrence and chronicity. In the patients with and without response to IVIG, the frequency of recurrent and chronic cases was 14.3% and 0%, respectively with no significant difference. Therefore, the administration of IVIG did not lead to a reduction in disease recurrence and chronicity (P=0.323) (Table 2).

Analysis of the ROC curves showed good diagnostic accuracy for predicting time to treatment, with an AUC of 0.77 (P=0.72, 95% CI 0.60-0.95). The optimal cut-off value for platelet count to predict time to treatment is 14,000, with a sensitivity of 100% and a specificity of 51.4% (Figure 1).

Table 1: Background characteristics in two groups of patients with and without IVIG treatment

Characteristics		Total N(%)	With IVIG treatment N(%)	Without IVIG treatment N(%)	P value
Gender distribution	Boy	26(63.4)	24(68.6)	2(33.3)	0.098
	Girl	15(36.6)	11(31.4)	4(66.7)	
Referral season	Fall	6(14.6)	5(14.3)	1(16.7)	0.445
	Spring	18(46.3)	16(45.7)	3(50)	
	Summer	7(17.1)	5(14.3)	2(33.3)	
	Winter	9(22.0)	9(25.7)	0(0)	

Table 2: Background characteristics in two groups of patients with and without disease recurrence

Characteristics		Disease recurrence%	No disease recurrence%	P value
Gender distribution	Boy	80	61.1	0.636
	Girl	20	38.9	
Referral season	Fall	0	16.7	0.361
	Spring	80	41.7	
	Summer	0	19.4	
	Winter	20	22.2	

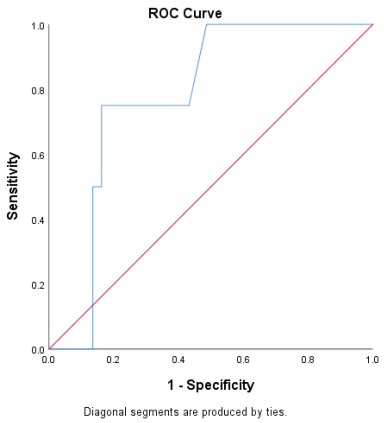

Figure 1. ROC curve analysis of platelet count in immune thrombocytopenia to predict time to treatment in children

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Discussion

The aim of the current study was to investigate the factors associated with the response rate to IVIG treatment in children with ITP and concluded that in children with ITP, the response rate to IVIG administration was 82.9% and treatment failure occurred in only 17.1% of patients. This response rate has varied greatly in different studies. For example, Higashide et al. reported that 69.7% of patients responded to IVIG treatment [21], and in the study by Heitink-Polle et al., 68.7% of patients responded completely to IVIG treatment within one week [22]. The results of the present study have suggested that IVIG treatment leads to complete improvement of symptoms and successful control of the disease in the majority of patients with ITP that is not self-limiting.

These factors included male gender and a low platelet count at the time of admission. Although chronicity and relapse of the disease were considered, none of the underlying parameters were able to predict relapse or chronicity of the disease. Similar and sometimes contradictory results have also been reported in other studies. In a study by Higashide et al. age ≥23 months and platelet count <9 million per liter were considered unfavorable factors for short-term response [21]. Interestingly, their results on the value of a decreased serum platelet count as a predictive factor were consistent with our study.

Morimoto et al. pointed out that a lower white blood cell (WBC) count was the only unfavorable factor for response to IVIG treatment and the development of chronic ITP. Patients with a WBC count <7 million/L were associated with reduced thrombocytopenia- free survival and an increased risk of progression to a chronic form of ITP [23]. In a study by Yıldırım et al., age ≥25 months, a platelet count <6.9 million per liter and a hemoglobin level <12.4 g/dL were considered factors influencing short- and long-term response [24].

Furthermore, in the study by Heitink-Polle et al., the predictors of full recovery at 12 months were: shorter duration of symptoms before diagnosis, younger age, mucosal bleeding at diagnosis, higher lymphocyte count at diagnosis and higher leukocyte count at diagnosis [22]. Chen et al. found that high IL-4 levels (<3.5 pg/ml), low leukocyte count, and platelet count <12 million per liter at the time of diagnosis were considered unfavorable predictors of patient response to IVIG treatment [25]. Therefore, it appears that the initial platelet count of patients at the time of admission or diagnosis may still be an appropriate proxy for predicting response to IVIG treatment in children with ITP.

Regarding factors to predict the response rate to IVIG in patients with ITP, the following factors were suggested in the summary of studies: Predicting the response to IVIG (intravenous immunoglobulin) in patients with immune thrombocytopenic purpura (ITP) can help to adjust treatment plans and manage expectations. Several factors have been studied to identify predictors of a positive response to IVIG in ITP patients: 1) Age: Younger patients, especially children, respond better to IVIG treatment than older adults. 2) Duration of ITP: Patients with new or acute ITP (less than 3 months) are more likely to respond positively to IVIG. The response is even worse in patients with chronic ITP. 3) Initial platelet count: Patients with a relatively low platelet count are more likely to respond to IVIG than patients with a very low count, which was found in the present study.

Infections that trigger an immune response leads to ITP. These are often viral infections, including the viruses that cause chickenpox, hepatitis C and AIDS, but their diagnosis is expensive, which limited the study.

It is important to note that individual response may vary and continuous monitoring and adjustment of treatment is often necessary. However, it should be noted that these factors could vary greatly in different populations. Therefore, the results of the current study have indicated that two indices - gender and initial platelet count - can predict response to IVIG treatment in children with ITP.

Conclusion

In conclusion, in children with ITP, the response rate to IVIG administration was high, possibly influenced by the patient's gender and initial platelet count. Thus, male gender and a low platelet count at admission are predictive factors for a lower response to treatment in these patients. If the number of

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patients is larger and patients are studied over a longer period of time, better results will be achieved.

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Ethical Considerations

The study was approved by the Ethics Committee of Tehran University of Medical Sciences with the ethical code of IR.TUMS.MEDICINE.REC.1401.651. The principles of the Declaration of Helsinki were observed throughout the study.

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Conflict of interest

The authors declare that there is no conflict of interest.

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