Pediatr Pract Res 2020; 8(2): 38-42
DOI: 10.21765/pprjournal.799176

ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Evaluation of Pediatric Patients with Immune Thrombocytopenia Regarding Clinical Course and Treatment Response: A Retrospective Single-Center Experience

İmmün Trombositopenili Pediatrik Hastaların Klinik Seyir ve Tedavi Yanıtı Açısından Değerlendirilmesi: Retrospektif Tek Merkez Deneyimi

Gülşah Söğüt[1], Göksel Leblebisatan[2], Adnan Barutçu[1], Yurdanur Kılınç[2], Hatice İlgen Şaşmaz[2]

[1]Department of Pediatrics, Çukurova University Medical Faculty, Adana, Turkey
[2]Department of Pediatric Hematology, Çukurova University Medical Faculty, Adana, Turkey

ABSTRACT

Aim: Immune thrombocytopenia (ITP) is the most common cause of acquired thrombocytopenia in childhood. We aimed to investigate the clinical features of the disease and provide insight into how the treatment method is determined accordingly. It is also intended to examine and compare the treatment responses.

Material and Method: Between January 2013 and December 2018, a total of 80 patients diagnosed with ITP, at the Pediatric Hematology Outpatient Clinic were enrolled in the study. During the study period, we recorded data of all patients thoroughly. The results were compared with those undergoing appropriate medical therapy statistically after the exclusion of the causes of secondary thrombocytopenia.

Results: The mean age of the patients was 5 ± 2.3 years; the ratio of females to males was found to be 1 : 2. Among the most common complaints were ecchymosis (63.7%), followed by petechiae (20%). Four (5%) patients received no treatment. Methylprednisolone, IVIG, and dexamethasone were given in 49 (61.2%), 17 (21.2%), and 8 (10%) patients, respectively. Both of methylprednisolone and IVIG were given to only 2 (2.5%) patients.

Conclusion: The ITP patients receiving IVIG have been found to progress to chronicity more than those receiving methylprednisolone. Our study also presents knowledge to be able to predict the development of chronicity in ITP.

Keywords: ITP, thrombocytopenia, IVIG, steroid treatment

ÖZ

Amaç: İmmün trombositopeni (ITP), çocukluk çağında edinilmiş trombositopeninin en yaygın nedenidir. Bu çalışmada, hastalığın klinik özelliklerini ve buna göre tedavi yönteminin nasıl belirlendiğini araştırmayı amaçladık. Ayrıca tedavi yanıtlarının incelenmesi ve karşılaştırılması amaçlanmaktadır.

Gereç ve Yöntem: Ocak 2013- Aralık 2018 tarihleri arasında Çocuk Hematoloji Polikliniği'nde İTP tanısı almış toplam 80 hasta çalışmaya alındı. Çalışma süresi boyunca tüm hastaların verilerinin eksiksiz bir şekilde kayıt altına alınmasını sağladık. İkincil trombositopeni nedenleri dışlandıktan sonra son olarak uygun tıbbi tedavi görenlerin sonuçlarını istatistiksel olarak karşılaştırdık.

Bulgular: Hastaların ortalama yaşı 5 ± 2.3 yıldı; Kızların erkeklere oranı 1 : 2 olarak bulundu. En sık görülen şikayetler arasında ilk sırada ekimoz (%63,7), ardından peteşi (%20) vardı. Dört (% 5) hasta tedavi almadı. Metilprednizolon, İVİG ve deksametazon sırasıyla 49 (% 61,2), 17 (% 21,2) ve 8 (% 10) hastaya verildi. Hem metilprednizolon hem de IVIG sadece 2 (% 2,5) hastaya verildi.

Sonuç: IVIG alan ITP hastalarının, metilprednizolon alanlara göre kronikleşmeye daha fazla ilerlediği bulunmuştur. Çalışmamız ayrıca ITP'deki kronikliğin gelişimini tahmin etmek için de bilgi sunmaktadır.

Anahtar Kelimeler: İTP, trombositopeni, IVIG, steroid tedavisi

Corresponding Author: Adnan Barutçu
Address: Department of Pediatrics, Çukurova University Medical Faculty, Adana, Turkey
E-mail: adnan_barutcu@hotmail.com

Başvuru Tarihi/Received: 23.09.2020
Kabul Tarihi/Accepted: 19.11.2020

INTRODUCTION

Primary immune thrombocytopenia is the most frequent cause of acquired thrombocytopenia in childhood that occurs as a result of the destruction of thrombocytes. It also tends to recover spontaneously in a short period.[1] The purpose of ITP treatment in childhood is to increase existing platelets to the level that will not cause bleeding as soon as possible.

Treatment options in acute ITP are listed as high-dose methylprednisolone, intravenous immunoglobulin (IVIG), anti-D IgG, and platelet transfusion. The platelet transfusion is given only when bleeding cannot be stopped or when urgent surgical intervention is required.[2] Many studies were conducted to compare these pharmacological agents in terms of dosage, effectiveness, side effect, and cost in literature. Some of those show that the platelet count increases fast in children receiving IVIG therapy than in those receiving glucocorticoid therapy (GT) or receiving non-glucocorticoid therapy (NGT). However, what treatment has the best impact on the course of that disease is the subject of debate for the last years.[3]

Here we summarize the clinical features, hematological pictures, and recent and past infections of patients with ITP at the diagnosis. We examine and compare how should the treatment strategy be managed in ITP patients according to the clinical signs, bleeding symptoms, and complaints on presentation. The responses which are given to each ITP treatment are also intended to evaluate and compare.

MATERIAL AND METHOD

Hundred patients with ITP at the Pediatric Hematology Outpatient Clinic of Çukurova University Faculty of Medicine between January 2013-2018 were evaluated. Ethical approval was obtained from the Ethics Committee of Çukurova University Faculty of Medicine on 08 March 2019 (session number: 86, decision number: 09).

The patients aged between 0-18 years, without any additional diseases leading to thrombocytopenia were included in the study. Twenty patients failed to meet the criteria described above, so they were excluded from the study.

At initial examinations of participants, signs and symptoms, age at which thrombocytopenia occurs, the season of application, gender, presence of known systemic disease, history of vaccination and drug use, history of a recent infection before admission, family history, accompanying hematological findings were all recorded. The signs and symptoms included e.g., mucosal bleeding, petechiae, ecchymoses, bone pain, organomegaly, and lymphadenopathy. The 'history of a recent infection before admission' as experiencing an infection in the past 1 to 6 weeks before admission. The type of recent infections (e.g., upper respiratory tract infection (URTI), acute gastroenteritis (AGE), or any disease with rash) experienced by the children before admission 1 to 6 weeks ago were also stated.

We ultimately evaluated patients, either acutely or chronically, in the context of ITP and then compared them according to their clinical characteristics, including the following: gender, presence of a recent infection, history of vaccination, season of diagnosis, complaints at presentation, examination findings and laboratory tests. Thrombocytopenic states of the patients lasting more than 6 months were accepted as chronicity. A serological workup, including viral markers, was also done. We re-evaluated and recorded the platelet count, Hgb, and Htc values of the patients in their follow-ups. Treatment regimens (steroid, antibiotic, immunoglobulin, splenectomy, monitoring without medical treatment) of ITP and the rate of improvement and chronicity of ITP were all remarked. Before treatment, bone marrow aspiration was performed in all patients and malignant diseases were ruled out.

According to the clinical progress of the patients, some of our chronic patients were given eltrombopag treatment. We initiated it at a dose of 25 to 50 mg orally once a day by age groups. The dose was increased up to 75 mg in case of no response. We added Mycophenolate mofetil and cyclosporin to the treatments of unresponsive patients.

Statistical Analysis

SPSS Statistics Versiyon 20.0 package program was used. Measurement variables are expressed in mean ±standard deviation (medians, and minimum and maximum values, where appropriate), while categorical variables were presented in numbers and percentages. We used the chi-square test to compare categorical variables between groups. If assumptions were provided, the comparison of numerical variables between groups was carried out using the Student t-test for independent samples. If not, the nonparametric Mann-Whitney U test was used. All statistical tests were two-sided, and statistical significance was taken as $p<0.05$.

RESULTS

Of the evaluable 80 patients, 62 (77.5%) satisfied the criteria for acute ITP, 18 (22.5%) for chronic ITP. Thirty-six (45%) of the children were male, and 44 (55%) were female. There was no significant difference regarding gender and the rate of the chronicity of the disease between the groups ($p=0.55$). The ages of the patients were as follows: 27 (33.8%) patients; 0-2 years old, 36 (45%) patients; 2-10 years old, 17 (21.2%) patients; >10 years old. Most of the

patients were between the ages of 2-10; 29 (80.6%) of those were acute ITP, and 7 (19.4%) were chronic ITP. There is no significant differences between the two matched groups in terms of age and the rate of the chronicity of the disease (p=0.55).

At the initial examination of our study participants, children with a history of a recent infection before admission accounted for 22.5% of the total number of patients, while 16 (88.9%) of those had a history of upper respiratory tract infection (URTI), and 2 (11.1%) of those had a history of acute gastroenteritis (AGE).

The values of the hematological parameters in acute ITP patients were as follows: mean platelet count 14567±17079 103/µL; mean Htc % 34.6±4.78; mean leucocytes 9452±3912 103/µL; and mean MPV 10.3±1.76 fL. Chronic ITP patients showed similar results with a mean platelet count of 16607±25486 103/µL, mean HTC % 34.7±4.34, mean leucocytes 9638±2516 103/µL, and mean 9.67±1.45 fL. We also found no significant relationship between the hematological findings and acute or chronic clinical course of ITP (**Table 1**).

Table 1. Comparison of patients according to laboratory findings (n=80)

	Acute ITP (n=62) Mean±SD (min-max)	Chronic ITP (n=18) Mean±SD (min-max)	p
WBC (10^3/µL)	9452±3912 (3390-19510)	9638±2516 (6410-14080)	0.64
HCT (%)	34.6±4.78 (22.3-46)	34.7±4.34 (27-43.3)	0.56
PLT (10^3/µL)	14567±17079 (1000-95000)	16607±25486 (1000-113000)	0.71
MPV (fL)	10.35±1.76 (6.7-15.3)	9.67±1.45 (6.75-12)	0.12

WBC:White blood cell; HCT: Hematocrit; PLT: Platelet; MPV: Mean Platelet Volume

After the first attack, 4 of patients were followed without treatment (The platelet values of them were more than 20.000 mm^3, and no significant bleeding symptoms occurred), and no relapse was observed. Seventy-six of patients received the first attack treatment, and 31 of them were cured. In contrast, 45 of those have developed to the need for treatment for the second time due to relapse. Finally, 18 of those have become chronic in 6 months (**Figure 1**).

Four different treatment regimens, including methylprednisolone, IVIG, dexamethasone, and the combination of methylprednisolone and IVIG, were given to the 76 patients at the first treatment. We administered methylprednisolone, IVIG, dexamethasone, and the combination of methylprednisolone and IVIG to 49 (64.5%), 17 (22.4%), 8 (10.5%) and 2 (2.6%) patients, respectively. The combination therapy with methylprednisolone and IVIG was preferred since the patients were resistant to methylprednisolone.

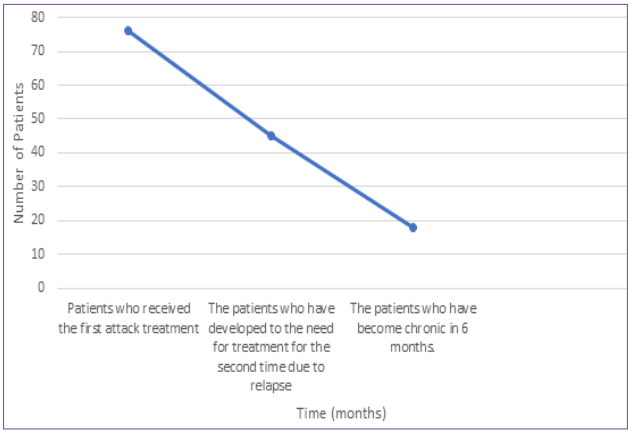

Figure 1. The course of chronicity of patients over time

Among the patients treated, who were given methylprednisolone as the first treatment, while 79.5% of them remained acute ITP, 20.5% became chronic. Of the patients with ITP who received IVIG as the first treatment, 64.7% were observed as acute ITP, 35.3% became chronic. In 75% of the patients who received dexamethasone as the first treatment had an acute clinical course of the disease, whereas 25% of those progressed to chronicity. The effect of dexamethasone on the treatment efficacy as the first treatment option was similar to that of methylprednisolone.

Of the 31 patients who recovered after the first treatment, 19 (61.2%) received methylprednisolone, 7 (22.5%) received IVIG, 4 (12.9%) received dexamethasone, and 1 (3.2%) received the combination therapy with methylprednisolone and IVIG. The chance of cure of patients with methylprednisolone in the first treatment was found to be high; however, this difference was not statistically significant (p=0.49).

We gave 45 patients a second treatment after relapse. IVIG was preferred most frequently in this treatment. In the second treatment, 45% of patients receiving IVIG became chronic. In the second treatment, the patients with IVIG treatment were more likely to progress chronicity than the patients with dexamethasone and methylprednisolone treatments. This difference was also found to be statistically significant (p=0.01) (**Table 2**).

Table 2. Comparison of the second treatments applied to patients after relapse between the groups

	Acute ITP n (%)	Chronic ITP n (%)	Total n (%)	p
Methylprednisolone	4 (100)	0 (0)	4 (100)	0.01
IVIG	12 (54.6)	10 (45.4)	22 (100)	
Dexamethasone	2 (25)	6 (75)	8 (100)	
Dexamethasone+IVIG	0 (0)	2 (100)	2 (100)	
Methylprednisolone+IVIG	9 (100)	0 (0)	9 (100)	
Total	27 (60)	18 (40)	45 (100)	

The number of patients who developed relapses after the second treatment and admitted for treatment for the third time was 37. IVIG was our most preferred agent in the third treatment. In our third treatment, the second most preferred drug was dexamethasone that 63% of patients and 47% of patients who used it had an acute and chronic course of the disease, respectively.

There were two patients aged 5,5 and 16 years who underwent splenectomy, and both of these patients were male. The study patients received dexamethasone, IVIG, methylprednisolone, cyclosporine, and eltrombopag treatments for 19 and 24 months. Twenty-nine patients received no methylprednisolone during all treatment, in whom ITP followed an acute clinical course in 21 (72.4%) patients and a chronic clinical course in 8 (27.6%) patients. Among those with methylprednisolone treatment, 38, 8, and 2 patients received 1, 2, and 3 treatment regimens, respectively.

DISCUSSION

Children diagnosed with ITP have a chance to heal spontaneously regardless of treatment. Platelet count returns to normal in half of the patients within 4-8 weeks and in two-thirds of children, three months after diagnosis. However, in addition to the low platelet counts of some patients at presentation, if they present with bleeding symptoms, treatment should be started.

Many factors, other than platelet counts, should be carefully considered in the treatment decisions of children. For this reason, the same therapeutic patterns should not be applied universally to all patients with ITP. Recommendations of the American Hematology Association in 2011 emphasizes the importance of a less aggressive approach in the management of pediatric ITP patients and observation in the majority of them presenting with symptoms limited to petechiae and ecchymoses.[4]

Even if no treatment is given in ITP, 60% of cases have been shown to improve. The best way of treatment of ITP today can also be "wait and watch" treatment. In increasing the platelet count in the early period of the disease, IVIG was found to be more effective, but in terms of relapse, no significant difference was seen between IVIG and methylprednisolone treatment.[5] In a study by Newland et al.[6] in 2017 with 10814 children and adult patients, treatment for ITP was given to 3388 patients. Of these patients, 1821 (74% of adults, 31% of children) received treatment for more than three months. Corticosteroids, IVIG, and immunosuppressive agents were used as first-line therapy. It was determined that the rate of immunosuppressive drug administration was increased as the age increases. Corticosteroids have become the most preferred agent in the treatment. Splenectomy, rituximab, and TPO therapy were preferred in second-line therapy. In a study comparing the analysis of 211 children with ITP in terms of first response to the treatment and recurrence rate, no significant difference was found between methylprednisolone, IVIG, and monitoring without treatment. Therefore, there is consensus on that treatment may not always be necessary for the first improvement of platelet count.[7]

IVIG is an expensive biological product and fever (38.5°C), meningitis-like findings and injection reaction could be seen as its side effects in the patients. Due to low costs and fewer side effect profiles, steroid use may exceed IVIG use.[8] 18% of ITP patients receiving methylprednisolone treatment, which we most frequently preferred as the first treatment, have become chronic in our study. Besides, 35% of our ITP patients receiving the second most frequently preferred treatment, IVIG, have had a chronic progression of the disease. In the results of Imbach et al.[9] 2540 case reports, the treatment given for ITP has been shown not to affect the chronicity of the disease. In a survey by Güngör et al.[7] with 300 cases in 2018, the relapse rate was significantly higher in cases receiving methylprednisolone ($p<0.05$). In research with 160 patients, developing of ITP to chronicity was detected in 28 of 105 (26.6%) patients receiving methylprednisolone, while in 17 of 55 (30.9%) patients receiving IVIG treatment.[10]

We prefer eltrombopag in the treatment of chronic patients due to its possible oral use, and no side effects as immunosuppressants. Presence of alternative treatments such as mycophenolate mofetil and TPO-RA and being aware of the side effects of splenectomy led to decreased rates of splenectomy in our ITP patients. In this study, only two chronic patients underwent splenectomy, and they were observed to have cured after splenectomy; furthermore, no complications developed during and after the operation.

Approximately 39% of our patients were cured after the first treatment. In the first treatment, we preferred more methylprednisolone, and we have seen that our patients receiving IVIG have become more chronic, which was similar to the literature. The ITP patients in whom we primarily preferred methylprednisolone as the second treatment had an acute clinical course of the disease. When IVIG and dexamethasone treatments were compared with methylprednisolone, they were less likely to become chronic, and methylprednisolone was seen to be more successful than IVIG in reducing the development of chronicity in ITP.

CONCLUSION

As a result, the effect of IVIG treatment on the chronicity of ITP is higher than methylprednisolone therapy. Even if in children with severe bleeding requiring pharmacological treatment, for combined treatments, including also IVIG,

should not be rushed. Although methylprednisolone is preferred in the first treatment, it was found that our patients who received IVIG became more chronic. Further studies are needed to predict the development of chronicity in ITP for elucidating the genetic mechanisms of autoantibodies and immune thrombocytopenia rather than demographic characteristics, clinical findings, laboratory findings, and treatment methods.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Çukurova University Faculty of Medicine on 08 March 2019 (session number: 86, decision number: 09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: None.

REFERENCES

1. Pels SG. Current therapies in primary immune thrombocytopenia. Semin Thromb Hemost 2011;37:621-30.
2. Platelet Disorders of Infancy and Childhood. Nathan and Oski (eds) Haematology of Infancy and Childhood 1993:1552-80.
3. Acquired Platelet Defects. Nathan and Oski (eds) Haematology of Infancy and Childhood, Sixth Edition. Saunders Company, Philadelphia 2003:1597-609.
4. George JN, Woolf SH, Raskob GE. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996;88:3-40.
5. Neunert C, Lim W, Crowther M. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
6. Newland A, Lee EJ, McDonald V, Bussel JB. Fostamatinib for persistent/chronic adult immune thrombocytopenia. Immunotherapy 2018;10(1):9-25.
7. Güngör T, Bilir ÖA, Çulha VK, et al. Retrospective evaluation of children with immune thrombocytopenic purpura and factors contributing to chronicity. Pediatr Neonatol 2018.
8. Neunert CE, Buchanan GR, Imbach P, et al. Intercontinental Childhood ITP Study Group Registry II Participants. Severe hemorrhage in children with newly diagnosed immune thrombocytopenic purpura. Blood 2008;112(10):4003-8.
9. Imbach P, Kühne T, Müller D, et al. Childhood ITP: 12 months follow-up data from the prospective registry I of the Intercontinental Childhood ITP Study Group (ICIS). Pediatric blood & cancer,) 2006;46(3):351-6.
10. Altıntop L, Albayrak D. Oral high-dose methylprednisolone and intravenous immunoglobulin treatments in adult chronic idiopathic thrombocytopenic purpura. Am J Hematol 1997;56(3):191-2.