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Evaluation of Initial Diagnosis, Clinical-Treatment Features of Children with Acute Immune Thrombocytopenia

Akut İmmun Trombositopenili Çocukların İlk Tanı Başvuru, Klinik ve Tedavi Özelliklerinin Değerlendirilmesi

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Abstract: Primary immune thrombocytopenia (ITP), formerly known as idiopathic thrombocytopenic purpura, is the most common cause of thrombocytopenia in children, defined by an isolated low platelet count (<100,000/mm³) without other etiologies. It has an annual occurrence of approximately 2 to 5 per 100,000 children. Acute ITP presents with mucosal bleeding or skin manifestations at diagnosis, with classifications for acute, persistent, and chronic ITP based on the duration of the condition. Most children (70-80%) experience spontaneous recovery within 12 months. Both primary and secondary ITP exhibit immunological abnormalities, yet secondary cases are linked to identifiable etiological factors. The treatment objectives focus on halting active bleeding and preventing future bleeding, as well as enhancing health-related quality of life (HRQoL). Corticosteroids have been the mainstay of ITP treatment since the 1950s, with recent studies showing a trend toward reducing high-dose methylprednisolone (HDMP) use.This retrospective study was conducted in Turkey, analyzing 40 pediatric patients diagnosed with acute ITP who received intravenous methylprednisolone in two groups with varying doses. The results indicated that both treatment regimens achieved similar response rates, and there were no significant differences regarding relapse rates or the development of chronic ITP between the groups. Overall, while initial treatment response rates did not differ significantly, the study emphasizes the need to investigate dosing strategies for managing acute ITP effectively. The findings support the use of a 'mega dose' of methylprednisolone for the initial treatment phase, but suggest that a lower dose may be equally effective without compromising patient outcomes.
Keywords: acute immune thrombocytopeni, childhood, chronicity, methylprednisolone

Özet: Primer immüntrombositopeni (ITP), daha önce idiyopatik trombositopenik purpura olarak bilinen, çocuklarda trombositopeninin en yaygın nedenidir ve diğer etiyolojiler olmaksızın izole bir düşük trombosit sayısı (<100,000/mm³) ile tanımlanır. Yıllık görülme sıklığı yaklaşık 100,000 çocukta 2 ila 5 arasıdır. Akut ITP, tanı anında mukozal kanama veya cilt bulguları ile kendini gösterir ve durumun süresine bağlı olarak akut, persistan ve kronik ITP olarak sınıflandırılır. Çocukların çoğu (%70-80), tanıdan sonra 12 ay içinde spontan iyileşme yaşar. Hem primer hem de sekonder ITP, immünolojik anormallikler sergiler, ancak sekonder vakalar belirgin etiyolojik faktörlerle ilişkilidir. Tedavi hedefleri aktif kanamayı durdurmaya ve gelecekteki kanamaları önlemeye odaklanmanın yanı sıra, sağlıkla ilgili yaşam kalitesini (HRQoL) artırmayı da kapsamaktadır. Kortikosteroidler, 1950'lerden beri ITP tedavisinin temel itici gücüdür ve son çalışmalar yüksek doz metilprednizolon (HDMP) kullanımını azaltma eğilimini göstermektedir. Bu retrospektif çalışma, Türkiye'de gerçekleştirildi ve akut ITP tanısı almış 40 pediatrik hastayı inceleyerek intravenöz metilprednizolon alan iki gruptaki değişen dozları analiz etti. Sonuçlar, her iki tedavi rejiminin benzer yanıt oranları elde ettiğini ve gruplar arasında relaps oranları veya kronik ITP gelişimi açısından anlamlı bir fark bulunmadığını gösterdi. Genel olarak, başlangıç tedavi yanıt oranlarının anlamlı şekilde farklılık göstermediği, bu çalışmanın akut ITP'nin etkili bir şekilde yönetimi için dozlama stratejilerini araştırma ihtiyacını vurguladığı belirtilmiştir. Bulgular, başlangıç tedavi aşaması için 'mega doz' metilprednizolon kullanımını desteklerken, daha düşük bir dozun da hasta sonuçlarını tehlikeye atmadan benzer şekilde etkili olabileceğini önermektedir.
Anahtar Kelimeler: akut immün trombositopeni, çocukluk çağı, kronikleşme, metilprednizolon.

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1. Introduction

Primary immune thrombocytopenia, previously referred to as idiopathic thrombocytopenic purpura (ITP), is the most common cause of thrombocytopenia in children. ITP is an acquired autoimmune disease defined by an isolated low platelet count (<100,000/mm³) in the absence of other etiologies. It occurs in approximately 2 to 5 per 100,000 children per year (1,2). Cases usually present with a new onset of mucosal bleeding or skin manifestations like petechiae and purpura at the time of diagnosis. Acute (newly diagnosed) ITP is defined as occurring within 3 months of diagnosis, persistent ITP is defined as lasting 3–12 months from diagnosis, and chronic ITP is defined as ITP lasting more than 12 months (3,4). Approximately 70-80% of children with ITP experience spontaneous recovery within 12 months after diagnosis (5,6).

Both primary and secondary ITP share some immunological abnormalities. However, only in secondary cases can the immune defect be triggered by defined etiological factors. Both low platelet production and high removal of platelets from peripheral circulation due to autoreactive antibodies, direct T cell cytotoxicity, NK dysfunction, and abnormal complement activation can account for platelet destruction and impaired megakaryocyte (MK) differentiation (7,8).

The first stage of treatment aims to stop active bleeding in patients who present with bleeding. It also aims to reduce the possibility of future bleeding in patients who have no or minor (skin) bleeding. Recently, improving health-related quality of life (HRQoL) has also gained importance. Corticosteroids have been used in the treatment of immune thrombocytopenia since the 1950s, and they are currently suggested for patients with non-life-threatening mucosal bleeding or reduced HRQoL as a first-line treatment (9,10). The dose and administration regimens of glucocorticoids vary among centers. A dose of 30 mg/kg/day of methylprednisolone for three days (max. 1 g) is commonly preferred for children with active bleeding. This is referred to as "mega" dose methylprednisolone (MDMP) treatment due to the high-dose methylprednisolone (HDMP) (11,12).

Although intravenous methylprednisolone is administered to reduce the side effects of long-term oral corticosteroid use in ITP, we find it worthwhile to examine the effects of reducing the "mega" dose.

2. Materials and Methods

This retrospective single-center, non-randomized, cross-sectional study was performed at a tertiary care hospital in Turkey from January 2018 through December 2023. The study population consisted of 40 inpatients who were diagnosed with acute ITP and received IV methylprednisolone. The diagnosis of acute ITP was based on clinical, laboratory, and bone marrow findings, along with a platelet count of <100,000/mm³. Other causes of thrombocytopenia, such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), connective tissue diseases, or hypersplenism, were excluded. In our clinic, peripheral smears were examined before the initiation of therapy in all cases, and bone marrow aspirates were routinely performed in children with ITP who were determined to require treatment. Each patient included in the study was evaluated for complaints, history of infection, medication, and vaccination. Detailed systemic physical examinations of all patients were conducted, and any evidence of bleeding, organomegaly, lymphadenopathy, presence of bone pain, and infection focus were investigated. All patients with a platelet count below 20,000/mm³ who had wet purpura or complaints of active bleeding (i.e., epistaxis, gingival bleeding, hematuria, melena) were treated. The treated patients were randomly divided into two treatment groups. In group 1, IV methylprednisolone (20 mg/kg/day for three days, followed by 10 mg/kg/day for four days) was administered as a single dose in the early morning. In group 2, IV methylprednisolone (30 mg/kg/day for three days, followed by 20 mg/kg/day for four days) was administered as a single dose at a similar time. To determine the response rates of both groups, they were recorded and compared on the days when the platelet count exceeded 20,000/mm³, 50,000/mm³, and 100,000/mm³. Additionally, information about patients presenting with a platelet count <20,000/mm³ and/or significant clinical bleeding was noted.

Data from 40 children with acute ITP were reviewed from their medical records. Numeric data were analyzed using descriptive statistics, including frequency (number and percentage), and mean and standard deviation (SD) for normally distributed data, or median and range for non-normally distributed data, as appropriate. Demographic features were compared using ANOVA (with

Tukey's test used for pairwise comparisons if a statistical difference was determined). Qualitative data were compared using the Chi-Square test. Variables affecting event-free survival (EFS) were analyzed using Cox regression (enter method for univariate analysis and backward likelihood ratio method for multivariate analysis). The Statistical Package for the Social Sciences (SPSS) program, version 17.0 (SPSS Inc., Chicago, IL, USA), was used. For all analyses, a two-sided p value <0.05 was considered statistically significant.

3. Results

Of the 40 patients, 19 were males and the median age was 8.0 □ 3.9 years (range 1.5 to 16 years) when patients diagnosed with ITP. The study consisted of two groups; 25 patients in group 1 and 15 patients in group 2 were recorded. There was no statistically significant difference between the two groups in terms of mean age at diagnosis, gender, infection-bleeding-vaccination history, physical examination findings (splenomegaly and lymphadenopathy, and blood count results (hemoglobin, white blood cell count, and platelets) (p>0.05).

Demographic features of patients were enrolled (Table-I). To determine the response rate to treatment, we compared the days when the platelet count exceeded 50.000/mm³ and 100.000/mm³ between the two groups. The mean number of days in which the platelet count exceeded 50,000/mm3 and 100,000/mm3 were 3.0 ± 1.1 and 4.3 ±1.5 in group 1, 3.5 ± 1.4 and 4.2 ± 2.0 in group 2. There was no statistical difference between the groups (p>0.05).

In both groups, all patients achieved remission after the initial treatment. However, 12 out of 25 cases (48%) in Group 1 and 10 out of 15 cases (66%) in Group 2 experienced recurrent thrombocytopenia at least once within one year (p> 0.05). Patients who had recurrent thrombocytopenia 11 of 12 (92%) in group 1 and 9 of 10 (90%) in group 2 were need treatment. One patient with recurrent thrombocytopenia from either group did not require treatment. Chronic ITP occured in 5 of 25 (20%) patients in group 1 and 7 of 15 (47%) patients in group 2. There was no statistical difference between the groups (p>0.05) (Table 3).

Table 1. Comparison of clinical and laboratory features of the patients

	Group 1 (n: 25)	**Group 2 (n:15)**	***p***
Age, mean ± SD (year)	7.2 ± 4.3	9.2 ± 2.9	0.128
Gender, male	11 (44%)	8 (53%)	0.579
History of			
infection	12 (48%)	5 (33%)	0.377
bleeding at diagnosis	25 (100%)	14 (93%)	0.177
vaccination	0 (0%)	0 (0%)	-
Initial Diagnosis,			
Hemoglobine, mean ± SD (gr/dl)	12.3 ± 1.1	12.9 ± 1.1	0.108
White blood cell, mean ± SD (/mm^3)	9200 ± 2400	8600 ± 2200	0.415
Platelets, mean ± SD (.000/mm^3)	15 ± 6	16 ± 7	0.941

Group 1: *IV methylprednisolone 20 mg/kg/day for three days, and then 10 mg/kg/day for four days;* ***group 2****, IV methylprednisolone 30 mg/kg/day for three days, and then 20 mg/kg/day for four days were given. (SD: standard deviation) (p<0.05 is significant)*

Table 2. The mean number of days in which the platelet count exceeded 50,000/mm^3 and 100,000/mm^3 in two groups

	≥ 50.000/mm^3	***p***	**≥ 100.000/mm^3**	***p***
Group 1 (n: 25) mean day ± SD	3.0 ± 1.1	0.232	4.3 ±1.5	0.837
Group 2 (n:15) mean day ± SD	3.5 ± 1.4		4.2 ± 2.0	

Group 1: *IV methylprednisolone 20 mg/kg/day for three days, and then 10 mg/kg/day for four days;* ***group 2****, IV methylprednisolone 30 mg/kg/day for three days, and then 20 mg/kg/day for four days were given. (SD: standard deviation) (p<0.05 is significant)*

Table 3. The follow-up process of patients.

	Group 1 n: 25	**Group 2 n: 15**	***p***
Relapsed thrombocytopenia, n (%)	12 (48)	10 (66)	0.084
Need for treatment for relapse, n (%)	11 (97)	9 (90)	0.262
Chronic ITP, n (%)	5 (20)	7 (47)	0.078

Group 1: *IV methylprednisolone 20 mg/kg/day for three days, and then 10 mg/kg/day for four days;* ***group 2****, IV methylprednisolone 30 mg/kg/day for three days, and then 20 mg/kg/day for four days were given. (ITP: idiopathic thrombocytopenic purpura). (p<0.05 is significant)*

4. Discussions

The primary goals of ITP treatment are to reduce or prevent bleeding symptoms and to delay or even prevent the need for splenectomy. Additionally, improving health-related quality of life (HRQoL), which has gained emphasis in recent years, is also a key objective (9,13).

In the studies by Duru et al. (14) and Erduran et al. (15) comparing intravenous immunoglobulin (IVIg) and (HDMP) treatments, no significant difference was found between the average platelet counts of the two groups on the 2nd, 4th, 7th, and 14th days. Similarly, Gungor et al. (16) did not detect a statistical difference among the first-line treatment (IVIg, HDMP, and anti-D) in their study. In this study comparing two different doses of methylprednisolone, no difference was found between the two groups in terms of initial treatment.

Thrombocytopenia may recur after initial treatment for ITP due to infection, other immune effects, or treatment limitations. Chronicity does not occur in all patients who experience recurrence. Approximately 20% to 25% of children with newly diagnosed ITP will develop chronic disease (17,18). Idiopathic thrombocytopenic purpura significantly impacts a child's daily life and activities, making it clinically significant to predict the course of the disease at the time of diagnosis. There is considerable evidence supporting several predictors related to the course of childhood ITP, including gender, age, preceding infection, duration of symptoms, bleeding tendency, and platelet count at diagnosis. Recently, additional predictors have been identified, such as leukocyte count, ANA positivity, and treatment with a combination of corticosteroids and IVIg. Notably, the apparent protective effect of IVIg treatment against the development of chronic disease is remarkable (19,20). Gungor et al. (16) study, the relapse rates of the initial treatments were compared, the rates were found to be significantly higher in patients receiving MDMP therapy compared to those receiving IVIg therapy (16). On the contrary, Chotsampancharoen et al. (21) found that initial treatment with steroid was a positive prognostic marker for remission. In this study, no statistically significant difference was found between the two groups regarding the development of thrombocytopenia again. In addition, no statistically significant difference was found between the two groups regarding the chronicity of ITP when different doses of steroids were used. However, this finding necessitates larger studies to confirm the results due to the small sample size of this study.

The American Society of Hematology (ASH) guideline panel published in 2019 recommends prednisone at 2–4 mg/kg/day; maximum, 120 mg/day for 5–7 days. In line with this recommendation, clinicians apply steroid doses in these amounts (9).

In conclusion, Turhan e al. (22) study suggests that the MDMP therapy in two doses, similar to the oral dosage schedule, as early as possible in consideration of its shorter half-life in the treatment of acute thrombocytopenia in patients with acute ITP. According to our study results, we recommend the first three days 20 mg/kg/day and 10 mg/kg/day for yhe following four days methylprednisolone treatment is succcesful as in comparison to 'mega dose' (30 mg/kg/day for three days and 20 mg/kg/day the following four days) methylprednisolone.

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