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ARAŞTIRMA / RESEARCH+

Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with immune thrombocytopenia

İmmün trombositopenili erişkin hastalarda birinci basamak tedavide yüksek doz metilprednizolonun etkinliği

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Abstract

Purpose: We aimed to compare the efficacy of high-dose methylprednisolone (HDP) with intravenous immunoglobulin (IVIG) and conventional prednisolone (CDP) as a first-line therapy in adult patients with immune thrombocytopenia (ITP).

Materials and Methods: This retrospective study included 140 adult patients with either previously untreated newly diagnosed ITP (*n*=51) or persistent or chronic ITP (*n*=22/*n*=67)) with episodes. Patients with a platelet count <30x10^9/L or <50x10^9/L with a clinically significant bleeding were treated either by CDP therapy (1mg/kg/d until response) or HDP (20 mg/kg/d for 3 d) or IVIG (1g/kg/d for 2 d). The patients in all groups continued treatment with oral prednisolone (1 mg/kg/d) until their platelet counts stabilized. After therapy, patients' responses and clinical courses were evaluated.

Results: The initial platelet counts were similar in all groups. HDP was given to 92 patients (65.7%), IVIG to 32 (22.8%), and CDP to 16 (11.4%). Although the HDP group showed a first response sooner than the IVIG and CDP groups, the median platelet count at first response was similar in all groups. Long-term remission was greater in the HDP group (57.6%) than in the IVIG (37.5%) and CDP (25.0%) groups, and their respective recurrence rates were 62.8%, 81.3% and 88.9%.

Conclusion: Our results indicate that HDP's relative effectiveness, low cost, and convenience of use continue to recommend it as a first-line therapy for adult patients with ITP.

Keywords: Immune thrombocytopenia, intravenous immunoglobulin, methylprednisolone, conventional prednisolone, treatment

Öz

Amaç: İmmün trombositopenili (İTP) erişkin hastalarda birinci basamak tedavi olarak yüksek doz metilprednizolon (HDP) ile intravenöz immünoglobulin (İVİG) ve konvansiyonel prednizolonun (CDP) etkinliğini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışma, daha önce tedavi edilmemiş yeni tanı konmuş İTP (*n*=51) veya epizodları olan kalıcı (*n*=22) ya da kronik İTP (*n*=67)'li 140 yetişkin hastayı içermektedir. Trombosit sayısı <30x10^9/L veya <50x10^9/L olan ve klinik olarak anlamlı kanaması olan hastalar ya CDP tedavisi (yanıta kadar 1 mg/kg/gün) ya da HDP (3 gün boyunca 20 mg/kg/gün) ya da İVİG (2 gün boyunca 1g/kg/gün) ile tedavi edilmiştir. Tüm gruplardaki hastalar trombosit sayıları stabilize olana kadar oral prednizolon (1 mg/kg/gün) ile tedaviye devam etti. Tedaviden sonra hastaların yanıtları ve klinik seyirleri değerlendirildi.

Bulgular: Başlangıç trombosit sayıları tüm gruplarda benzerdi. 92'sine (%65.7) HDP, 32'sine (%22.8) İVİG ve 16'sına (%11.4) CDP verildi. HDP grubu, İVİG ve CDP gruplarından daha erken ilk yanıt gösterse de, ilk yanıttaki medyan trombosit sayısı tüm gruplarda benzerdi. HDP grubunda (%57.6), İVİG (%37.5) ve CDP (%25.0) gruplarına göre uzun süreli remisyon daha yüksekti ve bunların nüks oranları sırasıyla %62.8, %81.3 ve %88.9 idi.

Sonuç: Sonuçlar, HDP'nin göreceli etkinliği, düşük maliyeti ve kullanım kolaylığının, onu İTP'li yetişkin hastalar için birinci basamak tedavi olarak önermeye devam ettiğini göstermektedir.

Anahtar kelimeler: İmmün trombositopeni, intravenöz immünoglobulin, metilprednizolon, konvansiyonel prednizolon, tedavi

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INTRODUCTION

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by low platelet counts resulting from platelet destruction and impaired platelet production. The incidence of ITP is 2–5 per 100,000[1–5]. In adults, ITP develops insidiously and becomes chronic, with symptoms and signs mostly reflecting the severity of thrombocytopenia. Among those symptoms and signs, petechiae, purpura, ecchymosis, epistaxis, menorrhagia, and gingival bleeding are common, whereas hematuria, hemoptysis, gastrointestinal bleeding, and cerebral hemorrhaging are rare. Life-threatening hemorrhaging is mostly observed in patients more than 60 years old[6].

ITP has been treated with various pharmacological agents and/or splenectomy[7]. The most important factor affecting which treatment patients diagnosed with ITP should receive is the presence of symptoms of bleeding. Corticosteroids, an economical treatment option, are generally recommended as a first-line therapy. Afterward, thrombopoietin receptor agonists, rituximab–(chimeric anti-CD20 monoclonal antibody), and/or splenectomy are recommended second-line therapies for patients with corticosteroid-refractory or corticosteroid-dependent ITP. The guidelines of the American Society of Hematology recommend administering corticosteroids for adult patients with newly diagnosed ITP and platelet counts $<30\times10^9$/L who have minor mucocutaneous bleeding or are asymptomatic[7]. Platelet response to corticosteroids is slow and usually occurs within 4–14 d. The guidelines also recommend tapering and discontinuing corticosteroids within 6 weeks[7].

Because intravenous immunoglobulin (IVIG) generally provides a rapid response, it is often administered to patients with ITP who need a rapid response and/or are pregnant, and the first response to treatment generally occurs between days 1 and 3 of treatment[8]. Beyond that, guidelines for the emergency management of clinically significant bleeding and for prophylactic prior to invasive procedures in patients with ITP recommend various approaches, including IVIG or high-dose methylprednisolone (HDP), to ensure safe platelet counts[9]. Although studies have shown that IVIG treatment induces a faster response and is more effective than HDP[10–11], its cost is considerably higher. Despite those findings, studies comparing the efficacy of IVIG and HDP in patients with ITP who need emergency treatment have been rare, such that recommendations on their use are usually based on expert opinion or the results of a few controlled studies. In response, considering that HDP may be at least as effective as IVIG in patients with ITP who require emergency treatment as well as more cost-effective, we aimed to determine the effectiveness of HDP compared with IVIG and conventional prednisolone (CDP) therapy in adults with previously untreated, newly diagnosed ITP or with persistent or chronic ITP.

MATERIALS AND METHODS

Design and setting

Our retrospective, single-center, descriptive, observational study received ethical approval from the Non-Interventional Clinical Research Ethics Committee at Çukurova University's Faculty of Medicine (No. 16/18) on February 14, 2013. The study was conducted in Çukurova University's School of Medicine, namely in the Hematology Clinic at Balcalı Hospital, and followed the ethical guidelines stated in the 1964 Declaration of Helsinki and its subsequent amendments.

Sample

The study's sample included 146 adult patients with previously untreated, newly diagnosed ITP (n = 56) or persistent (n = 23) or chronic (n = 67) ITP with episodes and platelet counts $<30\times10^9$/L or $<50\times10^9$/L. During the study, patients received either CDP therapy or HDP or IVIG therapy. The six patients who did not have at least 6 months of follow-up after treatment were excluded from the sample, which thus ultimately included 140 adult patients with previously untreated, newly diagnosed ITP (n = 51) or persistent (n = 22) or chronic (n = 67) ITP. Physicians working in the hematology clinic regularly recorded the anamnesis, physical examination findings, laboratory findings, peripheral blood smear findings, treatment plans, and progress of patients who applied to the hematology clinic in the patients' files kept in the hospital's archive. The treatments were planned by hematologists and administered to patients by nurses working in the hematology clinic.

ITP was diagnosed according to the guidelines of the American Society of Hematology as new, persistent,

or chronic[7], all with a platelet count less than 100 $\times 10^9$/L[8]. New ITP described patients diagnosed within the past 3 months, whereas persistent ITP described patients diagnosed within the past 3–12 months and who were either not in spontaneous remission or could not remain in remission when treatment was stopped. Last, chronic ITP described patients whose ITP had persisted for more than 12 months. Various data were retrospectively recorded from patients' files and clinical observation reports, namely demographic data, physical examination findings during diagnosis, laboratory results, treatments applied, treatment responses, clinical course of the disease, adverse effects, and mortality.

Treatment protocol

Patients were treated with HDP (20 mg/kg/d for 3 d), IVIG (1 g/kg/d for 2 d), or CDP therapy (1 mg/kg/d until response), and all received oral prednisolone (1 mg/kg/d) until their platelet counts stabilized. Corticosteroids were then tapered off for 4–6 weeks. After therapy, we evaluated the patients' response rates and clinical courses.

Response evaluation

We defined the first response as a platelet count $\geq 30\times 10^9$/L and a doubling of the baseline platelet count with the absence of bleeding. Patients' platelet counts were followed daily, then weekly or monthly, depending on the patient's response status. The time to response was defined as the time from the initiation of treatment until first response. We evaluated the response in patients according as complete response (CR), defined as a platelet count $\geq 150\times 10^9$/L; partial response (PR), defined as a platelet count $50–150\times 10^9$/L; minimal response (MR), defined as a platelet count $30–50\times 10^9$/L; and no response (RS), defined as $\leq 30\times 10^9$/L. Permanent CR was defined as continuing for at least 2 months after treatment ended, whereas recurrence was defined as a platelet count $\leq 30\times 10^9$/L or thrombocytopenia causing symptoms of bleeding after a successful initial response. Complete remission was defined as the continuation of CR for 2 months or longer, whereas long-term complete remission was defined as the continuation of CR for at least 6 months.

Symptoms of bleeding

Patients' symptoms of bleeding were classified into five grades: no symptoms of bleeding (i.e., grade 0), petechiae (i.e., grade 1), ecchymosis and/or dripping with moderate loss of blood (i.e., grade 2), major mucous hemorrhage with copious loss of blood without sequelae (i.e., grade 3), and major mucous and/or parenchymal hemorrhage with copious loss of blood with sequelae and/or life-threatening bleeding or death (i.e., grade 4)[12].

Statistical analysis

With a power of 0.75, an effect size of 0.25, and a margin of error of 0.05 ($p = 0.05$), the minimum total sample size required for the proposed study with three groups was determined to be 141. Power analysis was performed with G*Power (version 3.1). For statistical analysis, the patients were divided into three groups: the HDP group, the IVIG group, and the CDP group. The days of events were calculated beginning from the date when first-line treatment was initiated. The variables were investigated using visual and analytical methods (i.e., Kolmogorov–Smirnov test, skewness, and kurtosis) to determine whether their distribution was normal. All parameters were recorded as median ± standard error of the mean (*SEM*) or as percentage. Because age, median platelet count at diagnosis, number of episodes, follow-up time, day of first response, platelet count at first response, and time to response were not normally distributed, Kruskal–Wallis test was performed to compare those parameters. We summarized the categorical variables as numbers and percentages and compared the treatment groups using the chi-square test. The Spearman's rho correlation coefficient was used to assess the relationship between the response rate and long-term complete remission and between the treatment groups and long-term complete remission. Statistical significance was defined as $p < 0.05$. All calculations were performed in the Statistical Package for the Social Sciences version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

We enrolled 140 adult patients with previously untreated, newly diagnosed ITP ($n = 51$) or persistent ($n = 22$) or chronic ($n = 67$) ITP. The median age of the patients was 40 ± 1.5 years, 90 patients were female (64.3%), and the sample's female-to-male ratio was 1.8. Upon admission, the patients' symptoms of bleeding by grade were 17.0%, 5.7%, 33.6%, 35.7%, and 7.9% from grades 0 to 4, respectively. When the demographic data and clinical

features of patients who received HDP, IVIG, and CDP therapy as first-line treatment were compared, a statistically significant difference was observed between the groups' symptoms of bleeding (p=0.003)—namely, grade 2 and 3 symptoms were higher in the HDP group than in the two other groups. Table 1 presents the initial and follow-up parameters of patients according to their treatment groups. A significant difference emerged in terms of patients' age in all groups (p=0.032), and patients in the HDP group were younger than their counterparts in the IVIG group (p=0.008). The number of episodes was higher in the CDP group than in the HDP and IVIG groups (p=0.032; p=0.001), while follow-up time was significant longer in the HDP group than in the CDP group (p=0.008).

Table 2 allows the comparison of the patients' responses, treatment, and follow-up evaluations according to their treatment groups. No statistically significant difference surfaced between the groups when platelet counts were compared in Months 2, 3, 4, 5, 7, 8, 9, 10, and 11 and in first and second year after treatment (p>0.05).

Table 1. Initial and follow-up parameters of patients in treatment groups

	HDP (n=92)	IVIG (n=32)	CDP (n=16)	p
Age	37.5±1.7	50.5±3.5	34.5±5.4	0.032
Gender (Male/Female)	23/69	19/13	8/8	0.001
Median platelet count at diagnosis (x10^9/L)	6.00 ± 0.71	4.62±1.18	10.40 ±2.25	0.06
Number of episode	1±0.14	1±0.10	2±0.13	0.005
Follow-up time (day)	645±131	393±208.5	279.5±102.127	0.012

HDP: high-dose methylprednisolone; IVIG: intravenous immunoglobulin; CDP: conventional prednisolone

Table 2. Comparison of response, treatment and follow-up evaluations of patients in treatment groups

	HDP	IVIG	CDP	p
First response day	3±0.349	6.5±1.15	5.5±1.76	0.001
Platelet count at first response (x10^9/L)	54.5±5.6	60±12.6	52.8±18.35	0.7
Time to response (day)	6±1.28	10±14.8	12±11.4	0.042

HDP: high-dose methylprednisolone; IVIG: intravenous immunoglobulin; CDP: conventional prednisolone

Table 3. Second-line treatments

	HDP, n (%)	IVIG, n (%)	CDP, n (%)
Splenectomy	24 (55.8)	9 (52.9)	4 (44.4)
Rituximab	3 (6.9)	1 (5.8)	1 (11.1)
Eltrombopag	10 (23.2)	3 (17.6)	1 (11.1)
Azathiopyrine	1 (2.3)	-	-
Cyclophosphamide	1 (2.3)	-	-
Vincristine	1 (2.3)	1 (5.8)	-
Danazol	1 (2.3)	-	-
Cyclosporine	2 (4.6)	3 (17.6)	3 (33.3)
Total	43	17	9

HDP: high-dose methylprednisolone; IVIG: intravenous immunoglobulin; CDP: conventional prednisolone

Table 4. Adverse effects of corticosteroid treatment

	n (%)
Signs of Cushing syndrome	10 (9)
Gastrointestinal bleeding	4 (3.7)
Infection	9 (8.3)
Osteoporosis	14 (12.9)
Myopathy	4(3.7)
Sinus tachycardia	6 (5.5)
Hyperglycemia	76 (70.4)

However, a significant difference in platelet counts occurred in Month 1 (p=0.007), when the mean count was higher in the HDP group than in the CDP group (p=0.004), and in Month 6 (p=0.047), when the mean count was higher in the HDP group than in the IVIG group (p=0.013). Another statistically significant difference emerged in the response rate of the treatment groups, which was higher in the HDP group (100%) than in the IVIG group (84%) and CDP group (93%) (p=0.001). However, no significant difference in the type of response occurred between the groups (p=0.138). CR rates were 87.0%, 73.3%, and 71.9%, in the HDP, CDP, and IVIG groups, respectively, while their NR rates were 2.2%, 3.1%, and 6.7%. Remission rates were also significantly different between the groups (p=0.007), with rates of 69.6%, 65.6%, and 31.3% in the HDP, IVIG, and CDP groups, respectively. The between-group difference in long-term complete remission rates was statistically significant as well (p=0.007), with rates of 57.6%, 37.5%, and 25.0% in the HDP, IVIG, and CDP groups, respectively. Last, no significant difference arose in the recurrence rates between the groups, with rates of 88.9%, 81.3%, and 62.8% in the CDP, IVIG, and HDP groups, respectively(p=0.132).

The second-line treatments administered to the patients are shown in Table 3, while Table 4 shows the adverse effects of steroid treatment. Hyperglycemia was the most common adverse effect (70.4 %), and two patients treated with IVIG had an allergic reaction. The overall mortality rate of the sample was 0.7%.We observed a moderate positive correlation between the response rate and long-term complete remission rate in the sample (r=0.3, p=0.020), along with a moderate positive correlation between the treatment groups and long-term complete remission (r=0.33, p<0.05). By group, the rate of long-term complete remission was lowest in the CDP group and highest in the HDP group.

DISCUSSION

In patients with ITP, we determine whether there are any indications for treatment by evaluating the presence of bleeding, the location and severity of bleeding, platelet counts, risk factors of bleeding, previous treatments, and their effectiveness. Advanced age, medications used (e.g., nonsteroidal anti-inflammatory drugs and anticoagulants), and comorbidities (e.g., kidney disease) raise the risk of bleeding. In patients who do have indications for treatment, duration of ITP, response to treatment, and previous treatments are evaluated, and the choice of treatment depends on the risk and severity of bleeding. Life-threatening bleeding (e.g., intracranial or pericardial) should be treated immediately. In such critical situations, although platelet transfusion is the fastest way to increase the platelet count, the increased count is short-lived, and other systemic treatments are necessary. To that end, corticosteroid and IVIG therapies are often applied together, either of which is appropriate in the emergency treatment of severe bleeding that causes decreased hemoglobin levels. If corticosteroid treatment is preferred for adult patients with ITP experiencing severe bleeding, then intravenous dexamethasone 40 mg/d (4 d) or methylprednisolone 1 g/d (3 d) is administered. By contrast, IVIG is usually administered once (1 g/kg), and if no response occurs, then the treatment is repeated. Prednisone (0.5–2.0 mg/kg/d) or dexamethasone (40 mg/d, 4 d) is recommended for patients with ITP with platelet counts less than 30×10^9/L, who are asymptomatic, or who have minor bleeding[7].

In our study, we compared the effectiveness of HDP, IVIG, and CDP therapy in adult patients with ITP. The platelet count before treatment, which was less than 30×10^9/L in all patients, did not affect the choice of treatment. Although the HDP group showed a first response sooner than the IVIG and CDP groups, the median platelet count at first response was similar in all three groups. The response rate in the HDP group was significantly higher than in the IVIG and CDP groups, as was the rate long-term complete remission was higher in the HDP group as well.

In research conducted on corticosteroids, which rank among the most-used drugs in first-line treatments for patients with ITP, Cheng et al. used high-dose dexamethasone (HDD) as an initial treatment for patients with newly diagnosed ITP and observed a response rate and sustained response rate of 85% and 50%, respectively[13]. Borst et al. similarly observed that HDD was effective as a first-line treatment for ITP[14], while Mashhadi et al. found that HDD was more effective than CDP as initial therapy in patients with newly diagnosed ITP[15]. In GIMEMA prospective single-center studies (i.e., dexamethasone 40 mg/d, 4 d, every 28 d, 6 cycles) and multicenter studies (i.e., dexamethasone 40 mg/d, pediatric patients 20 mg/m^2, 4 d, every 14 d, 4 cycles), patients with previously untreated ITP received HDD therapy

as well[12]. The response and long-term response rates of 37 patients with ITP in the single-center study were 89.2% and 67.6%, respectively, while those rates among patients with ITP in the multicenter study were 85.6% and 74.4%, also respectively. Provan et al. have reported response rates to HDP, HDD, CDP therapy, and IVIG of 95%, 90%, 70–80%, and 80%, respectively[16]. In our study, the response rates in the HDP, IVIG, and CDP groups were 100%, 84.4%, and 93.8%, again respectively.

Very few articles in the literature compare the efficacy of corticosteroid and IVIG treatment. In Godeau et al.'s multicenter randomized study, patients with ITP (i.e., platelet count ≤ 20×10^9/L) were treated with IVIG or HDP with or without oral prednisone[10]. Those authors concluded that the sustained response and rapid short-term response were better in the IVIG group that received oral prednisone than in the other groups. In another study comparing HDP and IVIG as initial treatment, Kim et al. did not detect any difference in either the early response rate or long-term outcome but observed rapid complete response only in the IVIG group[11]. Contrary to those studies, we found that treatment with HDP was more effective than the other treatments.

Past studies have shown that corticosteroid therapy is tolerated well by patients with ITP[12–14]. As in our study, all corticosteroid-treated patients should be followed closely for possible adverse effects, the most common of which in our sample were hyperglycemia (70.4%), osteoporosis (12.9%), signs of Cushing's syndrome (9%), and infection (8.3%). At the same time, physicians should evaluate their patients' heath related quality of life (HRQoL). However, no studies in the literature have involved evaluating HRQoL among adult patients with ITP being treated with corticosteroids[7, 17].

One of our study's strengths was that our sample contained more patients than in other studies' samples. Added to that, our results show that, HDP, which is cheaper than IVIG, is also more effective. That result is important in terms of cost-effectiveness. The final guideline of the American Society of Hematology emphasizes the importance of corticosteroids as a first-line treatment but does not mention emergency management or treatment with IVIG[7]. Furthermore, our study has also shed light on the effectiveness of corticosteroids, which should be considered in future creation or amendment of such guidelines. Of course, our study also had limitations, including that it was a single-center, retrospective study and that we did not evaluate HRQoL in the patients treated with corticosteroids.

In conclusion, for adult patients with ITP, whether treatment is necessary needs to be determined first. The general aim of any treatment for ITP is to prevent bleeding that may occur due to thrombocytopenia and deciding whether such treatment is needed should take the patient's age, daily activity, living conditions, comorbidities, platelet count, and symptoms of bleeding into consideration. Our study's results indicate that HDP's relative effectiveness, low cost, and convenience of use continue to recommend it as a first-line therapy for adult patients with ITP. At the same time, too few studies to date have evaluated the effectiveness, HRQoL, and cost-effectiveness of the emergency treatment of ITP among adults[18], and recommendations for such situations have not been renewed in the guidelines for treatment, meaning that decisions and actions in clinically treating ITP are usually based on expert opinion. In light of both trends, multicenter, randomized controlled, prospective studies on best practices for treating ITP in adult patients are needed.

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