FNG & Demiroğlu Bilim Tıp Dergisi 2019;5(3):119-123
doi: 10.5606/fng.btd.2019.022

Original Article / *Özgün Makale*

Evaluation of thrombotic thrombocytopenic purpura cases: A single-center experience

Trombotik trombositopenik purpura olgularının değerlendirmesi: Tek merkez deneyimi

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ABSTRACT

Objectives: In this study, we aimed to analyze the laboratory data of patients with idiopathic thrombotic thrombocytopenic purpura (TTP).

Patients and methods: A total of 20 patients (7 males, 13 females; median age 42.5 years, range 20 to 75 years) diagnosed with idiopathic TTP were retrospectively evaluated. Age, sex, median plasmapheresis count, LDH, platelet count, hemoglobin, hematocrit, indirect bilirubin levels, and treatment responses of the patients were assessed. Groups were formed according to plasmic score.

Results: Lactate dehydrogenase (LDH) levels before and after plasmapheresis, on day 1, 3, and 7, total and indirect bilirubin levels, creatinine, AST/ALT, hemoglobin, leukocyte values, and platelet counts were compared. The median LDH levels of patients regressed to normal in an average of three days (range: 1-19). Mean platelet count was 47,100/μL at admission. Platelet count returned to normal in a median of 7 (3-32) days. The median number of plasmapheresis procedures was 8.5 (5-58). All patients underwent prednisolone treatment. Three patients died, in which one had severe neurological involvement. Mortality rate was 15%.

Conclusion: In the treatment of TTP, monitoring of LDH, platelet count and bilurubin values is important in evaluating the treatment response of plasmapheresis process. Further studies involving patient data are needed for the plasmic score used to assess severe idiopathic ADAMTS13 deficiency.

Keywords: Idiopathic thrombotic thrombocytopenic purpura, plasmapheresis, plasmic score.

ÖZ

Amaç: Bu çalışmada idiyopatik trombotik trombositopenik purpura (TTP) hastalarının laboratuvar verileri değerlendirildi.

Hastalar ve yöntemler: İdiyopatik TTP tanısı konulan 20 hasta (7 erkek, 13 kadın; ortanca yaş 42,5 yıl; dağılım 20-75 yıl) retrospektif olarak değerlendirildi. Hastaların yaş, cinsiyet, ortanca plazmaferez sayısı, laktat dehidrogenaz (LDH), trombosit sayısı, hemoglobin, hematokrit, indirekt bilirubin düzeyleri ve tedavi yanıtları değerlendirildi. Gruplar plasmic skora göre oluşturuldu.

Bulgular: Hastaların plazmaferez işlemi öncesi ve sonrası 1. gün, 3. gün ve 7. gün LDH, total ve indirekt bilirubin düzeyi, kreatinin, AST/ALT, hemoglobin, lökosit değerleri ve trombosit sayıları karşılaştırıldı. Hastaların işlem öncesi yüksek olan ortanca LDH değeri, ortalama üç günde (1-19 gün) normale geriledi. Hastaların başvuru anında trombosit değerleri ortalama 47100/μL idi. Hastaların tedavi sonrası trombosit değerleri ortanca yedi günde (3-32 gün) normale döndü. Plazmaferez işlemi sayısı ortanca 8.5 (5-58) idi. Tüm hastalara prednizolon tedavisi verildi. Nörolojik tutulum ağır olan bir hastanın yanı sıra, toplamda üç hasta kaybedildi. Mortalite oranı %15 idi.

Sonuç: Trombotik trombositopenik purpura tedavisinde plazmaferez işleminin tedavi yanıtını değerlendirmede erken dönemde LDH, trombosit sayısı ve bilurubin değerlerinin takibi önemli olmaktadır. Ciddi idyopatik ADAMTS13 eksikliğini değerlendirmek için kullanılan plasmic skor için daha çok hasta verilerini içeren çalışmalara gereksinim mevcuttur.

Anahtar sözcükler: İdiyopatik trombotik trombositopenik purpura, plazmaferez, plasmic skor.

Thrombotic microangiopathic hemolytic anemia was first described under thrombotic thrombocytopenic purpura by Symmers in 1952.[1] Thrombotic microangiopathies are characterized by thrombosis in microvasculature involving various organs.

Received: July 16, 2019 ***Accepted:*** August 08, 2019 **Published online:** October 31, 2019

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Cite this article as:
Ceylan C, Hızarcı Ş, Keskin G, Çağla Patır D, Olgun A. Evaluation of thrombotic thrombocytopenic purpura cases: A single-center experience. FNG & Demiroğlu Bilim Tıp Dergisi 2019;5(3):119-123.

Thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) are classic examples. Microangiopathic changes may also be caused by disseminated intravascular coagulation, autoimmune diseases, neoplasms, and infections.[2] With accumulation of thrombosis in microvasculature, these diseases are characterized by thrombocytopenia, neurologic symptoms, impaired renal functions, and direct Coombs negative microangiopathic hemolytic anemia as a result of erythrocyte damage in microcirculation.[3]

Thrombotic thrombocytopenic purpura incidence is reportedly 2-4 cases per million per year.[4] Despite ADAMTS13 enzyme deficiency of <10% as a requirement for TTP diagnosis, this may be impossible to test in emergency conditions. In fact, commercial kits may show inconsistency in up to 12% of patients.[5,6] The disease may be congenital or acquired depending on ADAMTS13 activity and inhibitor levels.

Thrombotic thrombocytopenic purpura primarily affects the central nervous system and gastrointestinal system. Although renal involvement is shown in renal biopsies, clinical acute renal failure is limited. While acute renal failure is forefront in hemolytic uremic syndrome, classic TTP mainly manifests neurological symptoms. Because mortality rate is 95% when untreated, most cases should be immediately assessed to initiate plasmapheresis. Intense plasma exchange in recent years has lowered acute mortality of TTP to less than 25%.[7]

This retrospective study investigates the effect of demographics and plasmapheresis on biochemical parameters in patients diagnosed with idiopathic TTP.

PATIENTS AND METHODS

In this study, patients admitted to the İzmir Tepecik Training and Research Hospital Hematology Clinic diagnosed with microangiopathic hemolytic anemia between 2014-2017 and who had hemolysis parameters tested, underwent treatment and follow-up, had ADAMTS13 activity tested at initial diagnosis, and underwent immediate plasmapheresis (PEX) were included in the study. All patients with drug-associated microangiopathic hemolytic anemia, rheumatic disease, solid tumor, and infection were excluded from the study. Twenty patients (7 males, 13 females; median age 42.5 years; range, 20 to 75 years) followed up with diagnosis of TTP were retrospectively evaluated. Patients with ADAMTS-13 activity of less than 10% were followed up with TTP diagnosis. ADAMTS-13 activity could not be assessed in some patients due to urgent plasmapheresis, but were considered TTP since plasmapheresis achieved clinical recovery. Recommended replacement dosage (1-1.5× plasma volume) was administered in every plasmapheresis procedure. Standard prednisolone treatment was also initiated. Patients with platelet count >150,000 for two consecutive days and normal lactate dehydrogenase (LDH) levels were considered responsive to treatment and plasmapheresis treatment was discontinued.

The study protocol was approved by the İzmir Tepecik Training and Research Hospital Ethics Committee. Informed written consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 20.0 software (IBM Corp., Armonk, NY, USA). The non-parametric test Wilcoxon test was used to assess LDH and platelet analyses for assessment of data without normal distribution. Descriptive statistics were expressed as frequency and median (minimum-maximum). The value of $p<0.05$ was considered statistically significant.

RESULTS

Lactate dehydrogenase, total and indirect bilirubin, creatinine, AST/ALT, hemoglobin, hematocrit, leukocyte and platelet values of before plasmapheresis, and one, three, and seven days after plasmapheresis were compared (Table 1). Three patients died during the treatment period. Median plasmapheresis count was 8.5 (5-85); while LDH returned to normal in median three days (range: 1-19); platelet count regressed to normal in median seven days (range, 3-32) and indirect bilirubin similarly regressed to normal in median of three days (range, 1-8) (Table 2). Median LDH value was 702.5 U/L on day one which decreased to median of 244 U/L on day seven. Hemoglobin was median

Table 1. Median values of data before and during plasmapheresis

	Before plasmapheresis		Day 1		Day 3		Day 7	
	Median	Min-Max	Median	Min-Max	Median	Min-Max	Median	Min-Max
Lactate dehydrogenase (U/L)	702.5	200-2,570	464	208-1,300	267	162-1,604	244	100-633
Hemoglobin (g/dL)	9.65	5.8-14.9	8.75	6.0-15.1	8.15	6.3-10.2	9.6	6.6-11.3
Platelet (/µL)	33	7-183	30	6-149	68.5	8-352	151	7-495
Hematocrit (%)	27.5	17-44	25.9	18-45	26.8	20-31	28.7	18-34
Creatinine (mg/dL)	1.00	0.6-11.5	1.00	0.6-11	0.9	0.7-7.5	0.9	0.6-5.9
Indirect bilirubin (g/dL)	1.26	0.09-3.44	0.87	0.08-3.63	0.48	0.03-2.22	0.95	0.32-2.39

Table 2. Patient data

	n	%	Median	Min-Max
Age (year)			42.5	20-75
Number of exitus patients	3	15		
Gender				
Male	7			
Female	13			
Median plasmapheresis count	8.5			5-85
Number of days until normal lactate dehydrogenase	3			1-19
Number of days until normal platelet count	7			3-32
Number of days until normal bilirubin	3			1-8

Min: Minimum; Max: Maximum.

9.65 g/dL on day one and 9.6 (range, 6.6-11.3) on day seven, while initial median platelet count was 33,000/µL, 68,000/µL on day three, and 151,000/ µL on day seven. Median platelet count was not statistically significant on day one, but there was significant increase between day three and day seven (Figure 1). Plasmic score evaluation was performed for 20 patients.[8] Seven patients (35%) had low score, 10 patients (50%) moderate score, and three patients had high plasmic score (Table 3). Of the three patients who died, one had plasmic score of seven, the other two patients had plasmic scores of 5 and 4. The plasmic scores of the 20 patients are presented in Table 3.

DISCUSSION

Thrombotic thrombocytopenic purpura has an incidence of 2-6 per million and results in 100% mortality if left untreated. The basic treatment approach of TTP is 1-1.5× plasma volume/day plasmapheresis, 1 mg/kg/day prednisolone, and if there is more than 12 hours delay to initiation of plasma exchange, plasma infusion (20-40 mL/kg/day), and 80 mg/day aspirin in select patients with platelet count over 50,000. Some studies report mortality of 10-20% despite plasmapheresis.[9,10] In this study, mortality was 15% and consistent with the literature. According to data from England, France, and the United States, TTP mostly affects

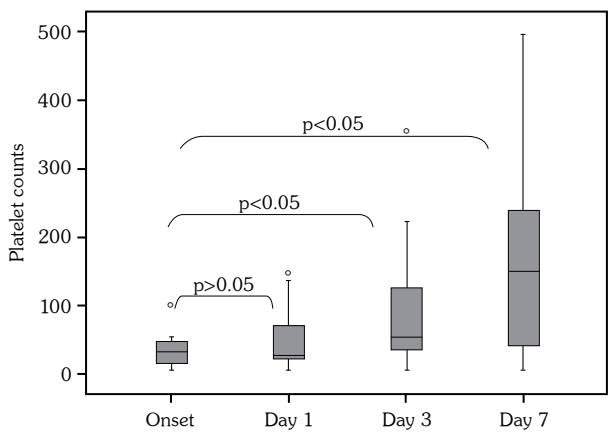

Figure 1. Platelet counts before and during plasmapheresis.

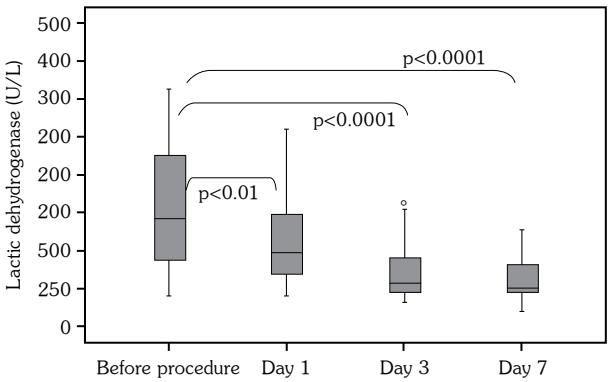

Figure 2. Lactate dehydrogenase levels before and during plasmapheresis.

Table 3. Plasmic score distribution of 20 patients

Plasmic score	n	%
Low (0-4)	7	35
Moderate (5)	10	50
High (6-7)	3	15

women between age 40-50,[9,11] consistent with our findings. Median age of male patients was 59 years (range, 31-75). Old data reported renal involvement in TTP was 18%, although newer research reports this rate ranges from 10-76%.[12] In our study, 10 of the 20 patients (50%) had initial renal involvement. Four patients had creatinine level above 2.5 mg/dL. Thrombocytopenia and microangiopathic hemolytic anemia are initial findings of TTP. Platelet count $<20\times10^9$/L, Hemoglobin <9 g/dL, Bilirubin >2 mg/dL, and LDH may be elevated by up to four times. In our patient group, median platelet count was 33×10^9/L. Five patients (25%) had platelet count below 20×10^9/L. Median platelet count was 30×10^9/L on day one, 68.2×10^9/L on day three, and returned to normal in median of seven days. Platelet count, hemoglobin, LDH, and schistocytes in peripheral smear were considered reliable parameters in monitoring response of patients who underwent plasmapheresis. Platelet count began to increase on day three of plasmapheresis and was consistent with treatment response. Patients were reassessed with peripheral smear, although we could not obtain this data from records. Not all studies consider LDH level a helpful parameter,[13] while red cell distribution width (RDW) may be an important parameter for monitoring schistocytes.[14] In our study, LDH values were prone to decrease on day one, which was inconsistent with the literature, and appeared helpful in monitoring plasmapheresis treatment (Figure 2). Time until LDH regressed to normal was relatively shorter compared to platelet count and occurred in a median of three days. We believe LDH value is an important indicator of plasmapheresis response in the early term. Median plasmapheresis time was 8.5 days (range, 5-85); Swart et al.[15] reported median plasmapheresis time of 10.0.

Seven separate parameters including plasmic score,[8] platelet count, degree of hemolysis, presence of cancer, lack of transplantation, Mean corpuscular volume (MCV) value, international normalized ratio (INR), and creatinine allow evaluation of prognosis in patients with severe ADAMTS13 deficiency. In this study, one of the three patients with plasmic score of 6-7 died, with mortality rate as 33% (Table 3). The other two exitus patients had plasmic score of 5. The low number of patients was a limitation on evaluation of plasmic score.

Thrombotic thrombocytopenic purpura is a rare disease that causes thrombotic microangiopathy. Early diagnosis and effective treatment of thrombotic thrombocytopenic purpura significantly reduces mortality rates. The common outcome of ours and other studies suggest that plasmapheresis should be initiated as soon as possible in suspected TTP or when TTP cannot be ruled out. Furthermore, various scoring systems may be early predictors of prognosis. Without waiting for ADAMTS13 results, evaluating patients according to clinical and laboratory data is important. We also determined that decreased LDH in the early term is also a finding that can be used to assess response to treatment in patients undergoing plasmapheresis. As plasmic score was unevaluated in our patients due to low patient sample, further research should be conducted on a broader scale.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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