Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(2):762-5

Etiological evaluation and the role of plasma exchange treatment in trombotic microangiopathies: A retrospective analysis from Eastern Anatolia

Emine Hidayet[1], Mehmet Ali Erkurt[1], Ahmet Sarici[1], Soykan Bicim[1], Irfan Kuku[1], Ilhami Berber[1], Emin Kaya[1], Ahmet Kaya[1], Mustafa Ozgul[1], Ayse Uysal[2]

[1]Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
[2]Fırat University Facolty of Medicine, Department of Hematology, Elazıg, Turkey

Received 24 November 2021; Accepted 10 January 2022
Available online 28.03.2022 with doi: 10.5455/medscience.2021.11.379

Abstract

The aim is this study was to make the etiological classification of patients diagnosed with TMA in our region and to statistically evaluate the effect of therapeutic plasma exchange, which we use in treatment, on laboratory recovery and mortality. In our study, between 2009-2017, 85 patients diagnosed with TMA in our center evaluated retrospectively. Thirty- one (36.5%) of our patients were followed up with HELLP, 23 with thrombotic thrombocytopenic purpura (TTP) (27.1%), 20 (23.5%) snake bites, and 11 (12.9%) with atypical hemolytic uremic syndrome (aHUS). TPE treatment was performed in all patients. TPE treatment was found effective in patients with HELLP syndrome, TTP and snake bite and statistically significant improvement was obtained in laboratory parameters ($p<0.05$). However, TPE treatment was not found to be effective in the treatment of atipical HUS ($p>0.05$). Mortality rates were found 9.7%, 21.7%, 27.3%, and 0% in patients with HELLP Syndrome, TTP, aHUS, and snake bite, respectively. The primary treatment in HELLP syndrome was termination of pregnancy, it was observed in our study that TPE was effective in TTP, HELLP syndrome and snake bites and treatment should be started without delay.

Keywords: Thrombotic microangiopathy, therapeutic plasma exchange, HELLP syndrome, thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome

Introduction

Thrombotic microangiopathy (TMA) is characterized by ischemic tissue damage caused by microangiopathic hemolytic anemia, thrombocytopenia and microthrombi in various tissues. The presence of fragmented erythrocyte (schistocyte) in peripheral smear, laboratory findings due to mechanical hemolysis (non-immune hemolytic anemia, lactate dehydrogenase increase, indirect bilirubin increase, haptoglobin decrease and reticulocytosis) and normal routine coagulation parameters strongly supports the diagnosis of TMA [1]. In peripheral smear, more than 1% of schistocytes are considered pathological and suggest TMA [2,3].

TMA can be divided as primary and secondary [4,5]. Primary TMA causes are TTP and aHUS, occur spontaneously, regardless of an underlying condition. Secondary TMA causes include pregnancy (HELLP syndrome), autoimmune diseases, malignancy, bone marrow transplantation or the use of certain medications [6,7]. The differentiation of the etiology is of utmost importance as the pathophysiological basis will dictate the choice of appropriate treatment [8].

Therapeutic plasma exchange (TPE) is the replacement process where mostly allogenic plasma is used as a replacement fluid for therapeutic purposes [9]. This method makes possible the removal of pathological substances, such as antibodies, immune complexes, cryoglobulins, immunoglobulin light chains, cytokines, adhesion molecules, and endotoxins, while also allowing the replacement of missing plasma components. This treatment achieves dramatic responses in various conditions, especially some forms of thrombotic microangiopathies [10].

In our single center study, we aimed to evaluate the etiological classification of patients with TMA and emphasize the benefits of TPE treatment.

Materials and Methods

Eighty-five patients who were diagnosed with TMA and TPE performed between 2009-2017 were included in the study. This

***Corresponding Author:** Mehmet Ali Erkurt, Inonu University, Turgut Ozal Medical Center, Department of Hematology, Malatya, Turkey
E-mail: erkurtali@hotmail.com

study was approved by ınonu University Ethics Committee (approved number: 2017/3-9).

As a prerequisite for diagnosing TMA, thrombocytopenia in hemogram and fragmented erythrocytes (schistocytes) in peripheral smear are mandatory. ADAMTS13 level could not be studied at the time of diagnosis due to technical insufficiency. Patients were diagnosed as TMA clinically and laboratory. In our study, the control group could not be included because TPE was applied to all our patients followed up with a preliminary diagnosis of TTP.

Temporary dual-lumen dialysis catheters were inserted into the patients before TPE. The latest generation cell separator apheresis device [Spectra Optia apheresis system (Terumo BCT)] was used in performingthe procedure. Daily clinical, laboratory and peripheral smear findings were followed and decided for continuation of TPE. Plasma volume to be used in one session was calculated with the formula: Estimated plasma volume =0.07x(kg) x(1- hemotocrit). One ampoule of calcium gluconate and one ampoule of dexamethasone were injected before the procedure to prevent hypocalcemia and allergic reactions. Daily TPE was performed until the platelet count exceeded 100.000/μL and LDH was normalized. Fresh frozen plasma was used as the replacement fluid in all procedures.

In all patients, age, hemoglobin (Hgb) values, leukocyte, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB), blood urea nitrogen (BUN), creatinine, prothrombin time (PT), partial thromboplastin time (aPTT), international normalized ratio (INR), lactate dehydrogenase (LDH) levels were evaluated both before and after plasma exchange. Patients' complete blood counting (CBC) was performed with the impedance method on Beckman Coulter Immage (Beckman Coulter, California, USA) device; Hgb photometric method, leukocyte subgroups by laser method; serum BUN, and creatinine by Aeroset Abbott (AbbottLaboratories, Minnesota, USA) spectrophotometric method.

Statistical Analysis

Values recorded to SPSS 17.0. Data on quantitative variables were presented as mean ± standard deviation and median (min-max), and data on qualitative variables were presented as numbers and percentages (%). Statistical evaluation was determined by the ShapiroWilk normality test that quantitative variables did not show normal distribution ($p<0.05$). Wilcoxon test was used to test the change of before and after plasma exchange. Longrank test were used to evaluate the effect of plasma exchange on overall survival among groups and in the general patient population. Statistical evaluation of qualitative variables was done by Monte Carlo Chi Square method. A p value <0.05 was considered statistically significant.

Results

In our study, HELLP syndrome was the most common type of TMA (36.5%). The frequency of TTP, snake bites, and aHUS was 27.1%, 23.5%, and 12.9%, respectively. In totally, 85 patients were included in the study. Group 1 included 31 patients with a diagnosis of HELLP syndrome (31 female, 0 male), group 2 included 23 patients with TTP (14 women, 9 men), group 3 included 20 patients with the diagnosis of snake bites (3 females, 17 males), and finally group 4 included 11 patients with aHUS (6 females, 5 males). (Table 1).

Table 1. Distribution of TMA patients by etiology

	HELLP syndrome n, (%)	TTP	aHUS	Snake Bites
Female	31	14	6	3
Male	0	9	5	17
Total	31	23	11	20
Age, Median (Range)	31.0	40.7	39.5	49.5

Since laboratory values including platelet, AST, ALT, LDH, TB and DB were examined in patients with HELLP syndrome, the values before and after TPE was found statistically significant ($p<0.05$) (Table 2).

Table 2. Laboratory values of TMA patients before and after TPE

Parameters, Median (Range)	HELLP Syndrome (Before)	HELLP Syndrome (After)	TTP (Before)	TTP (After)	Atypical HUS (Before)	Atypical HUS (After)	Snake Bite (Before)	Snake Bite (After)
WBC (Median)	13.5(7.7-34.0)	11(4-25)	11.8(3.8-73)	9.4(3-29.9)	10.3 (1.40-20.9)	10.3 (1.4-20.9)	14.1 (3.6–25)	12.4(1.4-738)
HGB (Median)	10.4(7.7–34.0)	10(5-15)	8.9(5-12.8)	10.2(6.9–13.5)	8.6(6.1–11.6)	8.6 (6.1–11.6)	12.4 (6.6–18.8)	9.4 (4–18.8)
Platelet (Median)	64(10–279)	168(26-463)	23(5-103)	187(7-629)	72 (9-338)	72 (9-338)	78 (9-276)	58 (5-336)
INR(Median)	1.0(0.8–2.30)	1.0 (0.8-1.6)	1.1(1–2.9)	1.1(0.9-1.6)	1.1(0.78–1.6)	1.1 (0.78-1.6)	1.2(0.9–2.1)	1.1(0.78-2.9)
aPTT (Median)	30.4(23.4-200)	29.4(16.6–91.6)	26.6(11.6-41)	25.1(20-67)	31.7(24-45)	31.7(24.7-45)	28.45(12.6-300)	29(11.6-300)
PT (Median)	12.1(9.1–26.2)	11.9(8.8–104.7)	13.5(11-31)	13(9.9-19.3)	12.3(8.9-15.6)	12.3(8.9–15.6)	14.15(10.4-22.8)	14.1(10.4–22.8)
AST(Median)	198 (19-6235)	31 (11-327)	79(21–2052)	21(10-1575)	26(17-122)	26(17-122)	19 (33-13)	33 13-95)
ALT (Median)	122 (11-2927)	35 (6-111)	33(13-1086)	82.8(11-405)	26 (7-122)	26 (7-62)	21.5(11-59)	21.5(11-59)
LDH (Median)	1061(254-12235)	285(190-1086)	1682(455-4589)	290 (163-1984)	548(315-1995)	548(315-1995)	309(152-637)	309(152-637)
TB (total bilirubin) (Median)	1.42(0.2-46)	0.86 (0.12–5)	3.24(0.63–7.15)	0.6(0.1-14.5)	1.25(0.52–4.84)	1.25(0.52–4.84)	0.56(0.33–5.02)	0.56(0.33–5.02)
DB (direct bilirubin) (Median)	0.56(0.1-30)	0.34 (0.1-4)	0.58(0.24–3.10)	0.26(0.05–8.16)	0.48(0.10–1.11)	0.48(0.1–1.11)	0.22(0.1-30)	0.22(0.1–0.7)
Creatinine (Median)	1.0(0.4–6.0)	0.7(0.5-6.92)	1.45(0.5-8)	0.88(0.64-4.96)	1.46(0.64-16)	1.46(0.64-16)	0.76(0.42–2.26)	0.76(0.42–2.26)
BUN (Median)	17(5-100)	19 (7-125)	36 (6-93)	21(4.1-89)	48(6.8-125)	48(6.8-125)	18 (10-32)	18 (10-31)

When laboratory values including platelet, AST, TB, DB, LDH and creatinine were examined in TTP patients, the values before and after TPE was statistically significant ($p<0.05$). When platelet, INR, PT and ALT laboratory values were examined in patients followed by snake bites, the change before and after TPE treatment was found statistically significant. ($p<0.05$). None of the laboratory values compared before and after TPE in aHUS patients were found statistically significant ($p<0.05$) (Table 3). The most common complications associated with the procedure were chills and tremors. There was no serious complication related to the procedure.

Of the patients, 11 patients (12.94%) died dur to underlying process. Mortality rates are displayed in table 4. We had no mortality in patients with snake bites.

Table 3. P values of laboratory findings of TMA patients before and after TPE

	HELLP Syndrome	TTP	Atypical HUS	Snake Bite
WBC	0.007	0.330	0.790	0.191
HGB	0.778	0.163	0.533	0.52
Platelet	0.001	0.001	0.075	0.002
INR	0.965	0.175	0.865	0.011
aPTT	0.336	0.773	0.386	0.668
PT	0.530	0.093	0.128	0.008
AST	0.001	0.002	0.657	0.925
ALT	0.001	0.394	0.306	0.001
LDH	0.001	0.001	0.155	0.324
TB (total bilirubin)	0.004	0.001	0.534	0.15
DB (direct bilirubin)	0.001	0.004	0.894	0.19
Creatinine	0.344	0.016	0.286	0.387
BUN	0.018	0.555	0.477	0.640

Table 4. Mortality rates of the groups

	HELLP syndrome n, (%)	TTP	Atypical HUS	Snake Bite
Death Toll	3	5	3	0
%	9.7	21.7	27.3	0
Survivors	28	18	8	20
%	90.3	78.3	72.7	100
Total	31	23	11	20
%	100	100	100	100

Discussion

Barbour et al. stated that the etiological classification of TMA should be improved and this development would provide a good guide for prognosis and treatment. We think that etiological evaluation will accelerate the diagnosis and decrease the mortality rate. Although it is reported in the literature that there are more primary TMAs, secondary TMA is more observed (60%) in our study. There are two studies in the literature on the etiological classification of TMA [4,5].These studies evaluated the pediatric age groups in contrary to our study. The most common cause of TMA in the pediatric age group has been reported as TTP, and Shiga toxin-related hemolytic uremic syndrome (STEC-HUS) In our study, the most common causes of TMA was HELLP syndrome, and TTP. HELLP syndrome is a disease of adult age group, so may have an impact on the different etiological ranking. In our study, snake bite was the third most common reason for TMA.

The findings of our study were compatible with the literature. In the study conducted by Martin et al. mortality rate in HELLP syndrome was 3.2%, in another study conducted by Sibai et al, mortality rate in HELLP syndrome was 1.1%. Mortality rates are reported as 1-25% in the literature [11,12]. Eser et al. reported that TPE in HELLP syndrome is an important treatment step because it shortens the duration in intensive care unit and reduces mortality [13]. Erkurt et al. reported that TPE significantly improved mortality in HELLP syndrome patients with a platelet count below 50.000/mL as classfifed Mississippi score class I. TPE was proposed as Category III in the treatment of class I HELLP syndrome [14].

TTP is defined by a severe deficiency of ADAMTS13. ADAMTS13 is the protease that cleaves large von Willebrand factor multimers in the vasculature, and its deficiency promotes formation of platelet microthrombi [15]. Since the results of ADAMTS 13 can take several days and have different results, the diagnosis of TTP is primarily made clinically [16]. If the concern for the diagnosis of TTP is strong, then TPE may need to be initiated while the diagnostic evaluation continues. However, if the patient is not critically ill and the suspicion for the disorders discussed below is greater than the suspicion for TTP, then it may be appropriate to defer TPE while the evaluation continues. Scull-M et al. stated that TPE is the main basis of TTP treatment and reduced the mortality from 90% to 10-20%, Pereira et al. also stated that the delay in the onset of TPE caused preventable early mortality [6.17]. In

our study, the mortality rate in patients with TTP was 9.1%. The American Association of Blood Banks (AABB), American Society for Apheresis (ASFA) and the British Society for Haematology recommend to perform TPE by changing the plasma volume 1-1.5 times as the standard initial treatment in TTP and add steroids to all patients in the treatment [18,19]. Again, according to the English guidelines, it is recommended to continue the process until 2 days after the platelet count is >150.000/mm³. In our study, we performed TPE in all patients with a volume of 1:1 and started the glucocorticoid as 1 mg/kg per day and discontinued TPE gradually when >150.000/mm³ was achieved.

Snake bites were detected as the third most common cause of TMA in our study. TPE is a technique that removes toxins due to proteins that cannot be fully removed by dialysis or hemoperfusion In snake poisoning, since toxins bind to many different proteins in the hemostatic system, TPE treatment provides benefit in eliminating poisons [20,21]. In our study, 20 patients with snake bites were successfully treated with TPE. No mortality was observed in patients who received TPE. In brief, we think that TPE provides laboratory and clinical improvement in patients who don't improve with antivenom and aggressive supportive care, especially in cases of snake bites who applied witin the first 6 hours.

Atypical HUS were detected as the fourth most common cause of TMA in our study. Recent studies have shown that eculizumab treatment has changed the approach to atypical HUS treatment [22]. If eculizumab treatment is not started as soon as possible, End-Stage Renal Disease (ESRD) and mortality are inevitable. Therefore, eculizumab is now considered as the first line option in the treatment of aHUS. Campistol et al. reported that early onset of eculizumab will stop and improve the TMA process in patients with aHUS, and also it will prevent their progression to ESRD [23]. We performed TPE and glucocorticoid treatment before eculizumab started who were diagnosed as aHUS. We think that the treatment of aHUS is eculizumab, which is effective on morbidity and mortality. Since TPE does not prevent the development of ESRD and only delays mortality, it should be used as a supportive treatment next to eculizumab treatment.

Conclusion

In conclusion, the etiological causes of TMA may show regional differences. In patients presenting with thrombocytopenia and microangiopathic hemolytic anemia, TMA should be considered and its etiology should be determined as soon as possible. It is known that the primary treatment in HELLP syndrome is termination of pregnancy. In our study, it was concluded that TPE may be effective as a bridge therapy in the HELLP syndrome until termination. It was also found to be effective in TTP and snake bites, and it was concluded that treatment should be started without delay.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by ınonu University Ethics Committee (2017/3-9).

References

1. Tsai HM. Untying the knot of thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome. Am J Med 2013;126:200-9.
2. George JN. How I treat Patients With Thrombotic Thrombocytopenic purpura: Blood 2010;116:4060-9.
3. Burns ER, Lou Y, Pathak A. Morphologic diagnosis of thrombotic thrombocytopenic purpura. Am J Hematol 2004;75:18-21.
4. Copelovitch L, Kaplan BS. The thrombotic microangiopathies. Pediatr Nephrol 2008;23:1761-7
5. Arnold DM, Patriquin CJ, Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. CMAJ 2017;189:153-9
6. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 2012; 158: 323-35.
7. Moake JL. Thrombotic microangiopathies. N Engl J Med 2002;347:589-600.
8. Tekgündüz E, Yılmaz E, Erkurt MA et all. A multicenter experience of thrombotic microangiopathies in Turkey: The Turkish Hematology Research and Education Group (ThREG)-TMA01 study. Transfus Apher Sci 2018:57;27-30.
9. Huestis DW, Bove JR, Busch S. Practical Blood Transfusion. 3rd ed. Boston: Little, Brown and Company. 1981:315-72.
10. Korkmaz S, Medeni SS, Demirkan F et all. The Turkish Experience With Therapeutic Plasma Exchange: A National Survey. Transfus Apher Sci 2019:58;287-92.
11. Martin JN Jr, Blake PG, Lowy SL, et al. Pregnancy complicated by preeclampsiaeclampsia with syndrome of hemolysis, elevated liver enzymes and low platelet count: How rapid is postpartum recovery? Obstet Gynecol 1990;76:737.
12. Sibai BM, Ramadan MK, Usta I, et al. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLPsyndrome). Am J Obstet Gynecol 1993;169:1000-6.
13. Eser B, Guven M, UnalA et all. The Role of Plasma Exchange in HELLP Syndrome. Clin Appl Thromb Hemost 2005;11:211–17.
14. Erkurt MA, Berber I, Berktas HB. A life-saving therapy in Class I HELLP syndrome: Therapeutic plasma exchange. Transfus Apher Sci. 2015;52:194-8.
15. Zheng X,Chung D,Takayama TK, et al. Structure of von Willenrand factor cleaving protease (ADAMTS 13), a metalloprotelnase involved in trombotic thrombocytopenic purpura. J Biol Chem 2001;276:41059-63.
16. Page EE, Kremer Hovinga JA, Terrell DR, et al. Thrombotic thrombocytopenic purpura: diagnostic criteria, clinical features, and long-term outcomes from 1995 through 2015. Blood Adv 2017;1:590-600.
17. Pereira A, Mazzara R, Monteagudo J, et al. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: a multivariate analysis of factors predicting the response to plasma exchange. Anna Hematol 1995;70:319–23.
18. Smith JW, Weinstein R. Therapeutic apheresis: a summary of current indication categories endorsed by the AABB and American Society for Apheresis. Transfusion 2003;43:820-2.
19. Allford SL, Hunt BJ, Rose P, et al. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. Br J Haematol 2003;120:556-73.
20. Yildirim C, Bayraktaroğlu Z, Gunay N, et al. The use of therapeutic plasmapheresis in the treatment of poisoned and snake bite victims: an academic emergency department's experiences. J Clin Apher. 2006;21:219-23.
21. Szczepiorkowski M, Winters JL, Bandarenko N, et al. Guidelines on the use of therapeutic apheresis in clinical practice evidence based approach from the apheresis applications committee of the American society for apheresis J Clin Apher 2010;25:83-177.
22. Verhave JC, Wetzels JFM, van de Kar NCAJ. Novel aspects of atypical haemolytic uraemic syndrome and the role of eculizumab. Nephrol Dial Transplant 2014;29:131-41.
23. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. Nefrologia 2013;33:27-45.