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Original Article

Management of thrombocytopenia-associated multiple organ failure: plasma infusion vs plasma exchange

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ABSTRACT

Background. Thrombocytopenia-associated multiple organ failure (TAMOF) causes a high ratio of mortality in pediatric patients. Only anticoagulants and profibrinolytic molecules can be replaced with plasma infusion (PI), while therapeutic plasma exchange (TPE) eliminates antifibrinolytic and thrombogenic molecules and charges inadequate anticoagulants and profibrinolytic molecules. This study aims to compare the efficacy of plasma exchange to plasma infusion in pediatric TAMOF patients.

Methods. Twenty-seven patients with TAMOF were included and the efficacy of PI and TPE was compared. The demographic data, admission laboratory values, Pediatric Logistic Organ Dysfunction (PELOD) scores before the beginning of treatment and PELOD at the end of treatment, and outcomes of groups were compared.

Results. Sixteen children were in the plasma infusion group, eleven children were in the plasma exchange group. The total mortality rate of all patients was 37%. The PELOD scores were significantly reduced on the 5th day of treatment in both groups and also PELOD scores were significantly higher on the 5th day of study in the non-survivor group (p: <0.001). The fifth day of PELOD scores and ferritin had a significant effect on mortality (OR: 1.85, 95% CI: 1.02-2.69; p: 0.04, OR: 1.43, 95% CI: 0.97-2.03; p: 0.05). The overall mortality ratio was not different between TPE and PI groups (p: 0.12).

Conclusions. Although there was no difference in mortality rates in children who received plasma exchange compared to children who received plasma infusion, mechanical ventilation and length of pediatric intensive care unit (PICU) day were shorter in the TPE group. The small patient population may be the major cause for the lack of significant statistical difference.

Key words: thrombocytopenia-associated multiple organ failure, plasma exchange, plasma infusion, pediatric logistic organ dysfunction, pediatric.

Thrombocytopenia-associated multiple organ failure (TAMOF) is a spectrum of microangiopathic disorders related to disseminated microvascular thrombosis such as disseminated intravascular coagulopathy, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS).[1] Exposure to infection, autoimmune diseases, cardiopulmonary bypass, chemotherapy, radiation, and transplantation are the reason for hyper-inflammation that can cause microangiopathic endothelial damage.[2-4] Antifibrinolytic and prothrombotic reactions can occur in the setting of systemic endothelial damage and may cause thrombocytopenia, systemic thrombosis, and multiple organ failure.[5] After the endothelial injury, ultra-large von Willebrand factor (ULVWF) protein clusters are released, under normal conditions, ULVWF is cleaved into smaller and less thrombogenic forms by ADAMTS-13.[6-9] Sepsis-induced many inflammatory mediators inhibit or inactivate a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS-13), and a deficiency of ADAMTS-13 may cause disseminated platelet-/VWF-rich microthrombi

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that are associated with TAMOF.[10] Therapeutic plasma exchange (TPE) restores ADAMTS-13 and eliminates ULVWF and ADAMTS-13 inhibitors for the reason that it becomes a classic treatment option for patients with TAMOF.[5]

Straat et al.[11] found that plasma infusion increased levels of ADAMTS-13 and was associated with decreased levels of von Willebrand factor in critically ill patients. As a result, increased ADAMTS-13 preserved endothelial condition by increasing the ability to cleave ULVWF.[11] Some patients with atypical HUS or TTP may benefit from plasma infusion therapy.[12] The purpose of plasma infusion is to replace ADAMTS-13 that are inadequate in the affected patient. We preferred plasma infusion (PI) therapy for patients with TAMOF when could not be able to reach central venous access or plasma exchange could not be performed due to some technical limits of exchange equipment. This research aimed to compare the efficacy of plasma exchange to plasma infusion in pediatric patients with TAMOF. We know that a comparison of plasma exchange and plasma infusion efficacy has not been studied previously in patients with TAMOF.

Material and Methods

Patient population

This retrospective study was conducted in the tertiary level institution to assess the clinical process, laboratory values, and patients' outcomes meeting the criteria of TAMOF. The period of study was from February 2020 to March 2022.

This study was approved by the Afyonkarahisar Health Science University Faculty Ethics Committee (date: 03.12.2021, no: 2021/13).

Patients 1 month to 18 years old were included for record if patients met the following criteria within 30 hours of screening: 1) New onset thrombocytopenia as defined by a thrombocyte number less than or equal to 100,000/μL or a minimum 50% reduction in initial thrombocyte number if the initial platelet count was less than or equal to 100,000/μL; 2) new-onset organ failure in at least 2 failing organs of five organ systems defined as an Organ Failure Index score greater than or equal to 3 for less than or equal to 30 hours, histologic and biochemical evidence of a thrombotic microangiopathic pathology; 3) organ failure etiology was due to systemic infection, shock, and chemotherapy.

Exclusion criteria

Children were excluded if they had treatment with any form of plasma exchange procedure or plasma infusion within 30 days before research entry or if a terminal disease was being considered. Informed consent was obtained from the parents of patients before TPE or plasma infusion initiation.

Collection of blood samples

Children were divided into two groups; the plasma infusion group and the plasma exchange group. The selection of therapy between PI and TPE was mainly based on the preference of the physician and the possibility of vascular access. The following data were collected; demographic and clinical data, admitting diagnosis resulting in TAMOF, PICU and hospital length of stay, pediatric risk of mortality score III (PRISM III score), need for mechanical ventilation duration, and renal replacement therapy. Pediatric logistic organ dysfunction (PELOD) scores, vasoactive-inotropic score (VIS), and count of failing organ systems were calculated at the beginning of the research entry and consecutively for 5 days. Laboratory values of hemoglobin, thrombocyte count, creatinine, alanine aminotransferase (ALT), fibrinogen, ferritin, D-dimer, international normalized ratio (INR), lactate dehydrogenase (LDH), and outcome of patients were extracted from files of the patient.

Plasma exchange was performed with a centrifugal cell separator (As-Tec 204, COM TEC, Fresenius, Bad Oeynhausen, Germany). The inlet blood flow rate set ranged between 10–

80 mL/min (minimum rate of 10 mL/min). The total blood/anticoagulant ratio was adjusted according to the patient's weight and total plasma volume. The predicted whole plasma volume was calculated as 80 × kg × (1 − Htc)/100 and 1.5 volume plasma was exchanged for the first day of therapy, continued with one volume each day until × 5 days or thrombocyte count over 100,000/μL whichever was shorter in duration. Before the beginning of TPE, the target thrombocyte count kept to greater than 50,000/mm^3. Patients' vital signs and ionized calcium levels were closely monitored during the procedure. Citrate was used for anticoagulation so ionized calcium levels were monitored closely. Calcium was routinely applied to prevent hypocalcemia symptoms. Each plasma exchange cycle was performed for approximately 2-3 hours.

The volume of infused plasma was 15 mL per kilogram for the first 24 hours of the procedure, followed by 10 mL per kilogram each day after the first day. Plasma infusion was continued until the platelet count was above 100,000/μL. If the plasma infusion caused symptoms of fluid overload diuretics were used.

Statistical Analysis

All variables were analyzed by SPSS Statistics 22 software (IBM, Armonk, NY, USA). The comparison of baseline properties of the two groups was evaluated by the Mann-Whitney U test for quantitative features and with Fisher's exact test for qualitative variables. A p-value of less than 0.05 was considered statistically significant. Two-way analysis of variance (ANOVA) was applied to understand the effects between and within groups in course of time. Parameters were included in multiple logistic regression analyses to identify the independent risk factors of mortality.

Results

Twenty-seven pediatric patients meeting the criteria of TAMOF were enrolled in this retrospective study. Sixteen children were in the plasma infusion group, eleven children were in the plasma exchange group. Sepsis was the predominant admitting diagnosis, followed by respiratory failure secondary to infections of the respiratory system. The research included other reasons for TAMOF, including malignancy, multi-trauma, gastroenteritis, and an inborn error of metabolism presenting with acute crises. All patients needed mechanical ventilator support. Renal failure and fluid overload were managed by renal replacement therapies. Demographics, clinical characteristics, and laboratory data were shown in Table I. The median age was 108 months (IQR, 35) in the TPE group and 96 months (IQR, 47) in the PI group, the TPE group was nonsignificantly older than the PI group (p: 0.42). The male/female ratio of the two groups was similar (p: 0.57). Although the median platelet number was lower, and the mean PELOD score and VIS were higher in the TPE group at admission, there were no differences between groups (p: 0.65; p: 0.21; p: 0.47). While the mean PRISM III score and the number of failing organ systems were lesser in the PI group, these differentiations were not statistically significant (p: 0.09; p: 0.12). Length of PICU and hospital stay were higher in patients who received plasma infusion (p: 0.01; p: 0.01). Having the chronic disease was nonsignificantly higher in the PI group (p: 0.54). PI group had significantly longer mechanical ventilation days than the TPE group (p: 0.04). Patients receiving TPE had nonsignificantly increased creatinine levels, but requiring renal replacement therapy was greater in PI receiving cases (p: 0.46; p: 0.08). The PELOD scores were significantly decreased on the 5th day of treatment when compared to PELOD scores before the beginning of treatment in each group.

The median levels of hemoglobin, platelet, ALT, INR, ferritin, fibrinogen, LDH, and D-dimer levels were similar in the two groups. No patients in TPE and PI groups had any treatment complications. During plasma exchange procedures, ionized calcium levels were closely monitored, and no symptomatic hypocalcemia occurred.

Table I. Demographics, clinical characteristics, and laboratory data of the TPE group and PI group.

Variables	TPE group (n:11)	PI group (n:16)	p value
Age (months)*	108 (35)	96 (47)	0.42
Sex			0.57
Male	6	9	
Female	5	7	
Admission diagnosis			0.89
Sepsis	5	6	
Respiratory Failure	2	4	
Malignancy	2	2	
Multi-trauma	1	2	
Gastroenteritis	-	1	
Inborn error of metabolism	1	1	
Hgb (gr/dL)*	9.7 (3.1)	10.2 (1.28)	0.28
PLT $\times 10^3$ /μL*	76000 (53000)	82000 (77000)	0.65
ALT (U/L)*	205 (114)	168 (73)	0.35
D-dimer (ng/dL)	25.33 ± 7.69	26.3 ± 9.25	0.78
INR	2.26 ± 0.45	2.44 ± 0.43	0.18
Fibrinogen (mg/dL)	141.25 ± 38.17	146.18 ± 37.21	0.34
Ferritin (ng/mL)	963.21 ± 318.94	924.47 ± 234.21	0.23
LDH (U/L)	1753.64 ± 273.22	1725.70 ± 241.16	0.12
Creatinine (mg/dL)*	0.86 (0.15)	0.83 (0.14)	0.46
PELOD score day 1	30.38 ± 2.65	28.54 ± 4.27	0.21
PELOD score day 5	21.62 ± 4.14	22.46 ± 6.35	0.87
PRISM III score	17.41 ± 2.28	16.2 ± 2.61	0.09
Vasoactive-Inotropic score day 1 *	35 (5)	30 (7)	0.47
Number of failing organ systems*	5 (2)	5 (1)	0.12
Requiring renal replacement therapy	5	6	0.08
Mechanical ventilation day*	9 (4.2)	11 (5)	**0.04**
Length of PICU stay	13.6 ± 3.42	18.52 ± 6.15	**0.01**
Length of hospital stay	19.54 ± 4.38	23.64 ± 5.12	**0.01**
Chronic disease	2	4	0.54
Hematologic-oncologic disease	1	-	
Metabolic disease	-	1	
Neurologic disease	-	1	
Respiratory disease	1	2	
Mortality	4	6	0.12

*Median (IQR)
Hgb: hemoglobin, PLT: platelet, ALT: alanine aminotransferase, INR: international normalized ratio, LDH: lactate dehydrogenase, PICU: pediatric intensive care unit, TPE: therapeutic plasma exchange, PELOD: Pediatric Logistic Organ Dysfunction, PRISM III: Pediatric, Risk of Mortality Score III, SD: standard deviation, IQR: interquartile range

The total mortality rate of all patients was 37%, mortality for patients receiving TPE was 36.3% (4/11), and 37.5% (6/16) for patients with PI (p: 0.12). The survival rate of the two groups was similar. Demographics, laboratory data, and clinical characteristics of each group are shown in Table II. There was no difference between the survivor and non-survivor groups in terms of age and gender. The median PELOD scores and PRISM III scores were similar between groups

Table II. Demographics, clinical and laboratory variables of survivors and non-survivors.

Variables	Survivors (n:17)	Non-survivors (n:10)	p value
Age (months)*	38 (62)	43 (51)	0.85
Sex			0.61
Male	10	6	
Female	7	4	
Hgb (gr/dL)*	9.7 (2.6)	10.1 (0.73)	0.75
PLT $\times 10^3$ /μL*	85000 (72000)	82600 (61500)	0.53
ALT (U/L)*	128 (96)	135 (74)	0.32
D-dimer (ng/dL)	24.53 ± 6.74	23.78 ± 7.24	0.87
INR	2.16 ± 0.6	2.33 ± 0.21	0.34
Fibrinogen (mg/dL)	148.62 ± 37.18	160.63 ± 41.50	0.28
Ferritin (ng/mL)	850.40 ± 154.20	1052.14 ± 262.51	**0.01**
Lactate dehydrogenase (U/L)	1740.62 ± 325.41	1742.24 ± 215.62	0.85
Creatinine (mg/dL)*	0.84 (0.22)	0.86 (0.43)	0.54
PELOD score day 1	27.51 ± 65	29.48 ± 7.34	0.16
PELOD score day 5	18.14 ± 3.42	30.64 ± 5.74	**<0.001**
PRISM III score	15.32 ± 2.71	19.38 ± 2.41	0.09
Vasoactive-Inotropic score day 1*	21.7 (16)	35 (8)	**0.03**
Number of failing organ systems*	7 (2)	5 (1)	0.21
Requiring renal replacement therapy	4	7	0.81
Mechanical ventilation day*	10 (2.8)	7 (6.2)	**<0.001**
Length of PICU stay	15.74 ± 4.38	12.71 ± 6.34	0.19
Length of hospital stay	20.41 ± 2.24	17.6 ± 6.1	0.07
Chronic disease	4	2	0.21
Hematologic-oncologic disease	-	1	
Metabolic disease	1	-	
Neurologic disease	1	-	
Respiratory disease	2	1	

*Median (IQR)
Hgb: hemoglobin, PLT: platelet, ALT: alanine aminotransferase, INR: international normalized ratio, LDH: lactate dehydrogenase, PICU: pediatric intensive care unit, PE: therapeutic plasma exchange, PELOD: Pediatric Logistic Organ Dysfunction, PRISM III score: Pediatric Risk of Mortality Score III, SD: standard deviation, IQR: interquartile range

on admission. Both in the survivor's group and non-survivors group, the PELOD scores were significantly decreased on the fifth day of treatments when compared to admission days of PELOD scores however, PELOD scores were significantly higher on the 5th day of TPE in the non-survivor group (p: <0.001). Day of mechanical ventilation was longer in the survivor group (p: <0.001). The length of PICU and number of hospitalization days were not different between the groups (p: 0.19; p: 0.07). Requiring renal replacement therapy and several failing organ systems were not different between survivor and non-survivor groups (p: 0.81; p: 0.21). Although ferritin level was significantly higher in non-survivors, the mean levels of fibrinogen, LDH, INR, D-dimer and median levels of hemoglobin, platelet, alanine aminotransferase and creatinine were not different between groups (p: 0.01; p: 0.28; p: 0.85; p: 0.34; p: 0.87; p: 0.75; p: 0.53; p: 0.32; p: 0.54, respectively). Non performed plasma exchange, ferritin, VIS, mechanical ventilation day, and fifth day of PELOD score were added

to the multivariate logistic regression model via forwarding stepwise technique in Table III. The fifth day of PELOD score and ferritin had a significant effect on mortality (OR: 1.85, 95% CI: 1.02-2.69; p: 0.04, OR: 1.43, 95% CI: 0.97-2.03; p: 0.05, respectively).

Consecutive measurements of the PELOD score in the first 5 days were shown in Fig. 1. Two-factor ANOVA was used to measure the PELOD score differences over time between the two groups. The test for the primary effect of plasma exchange or plasma infusion on PELOD by the time presented a nonsignificant effect (F: 0.623, p: 0.43).

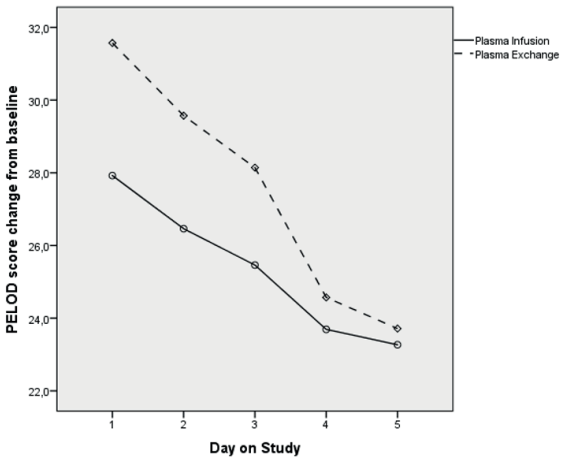

Fig. 1. Pediatric logistic organ dysfunction (PELOD) score comparison of groups who received plasma exchange and receive plasma infusion.

Discussion

TAMOF is a clinical phenotype described by new-onset thrombocytopenia with progression to multiple organ failure. The reason for the decrease in the platelet count is disseminated microvascular thrombosis, which also leads to the deterioration of organ functions.[5] There is currently no standard therapeutic strategy for TAMOF and researchers continue to find efficient medical treatment approaches for clinical phenotype TAMOF. Although plasma exchange is believed to be essential to improve sepsis-induced multi-organ failure syndrome as it restores ADAMTS-13 activity and removes inflammatory mediators, ADAMTS-13 inhibitors, and ULVWF multimers, the American Society of Apheresis guidelines suggests a level C evidence recommendation for the utilization of TPE in sepsis-induced multiple organ failure.[10,13] In addition to TPE, different extracorporeal treatments are used in patients with sepsis or severe sepsis to modulate hyper-inflammation.[14] Some researchers showed that plasma infusion was effective for critically ill patients to increase the ADAMTS-13 activity and decrease the proinflammatory parameters.[11]

The present research is a retrospective clinical study that investigates and compares the effect of TPE and PI on the survival of pediatric patients with TAMOF.

Adult research reported that plasma exchange was superior to plasma infusion for hematological remission and reducing mortality of patients with TTP.[15] The use of TPE was associated with a decreased mortality rate in pediatric patients with TAMOF and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome.[16] Sevketoglu et al.[3] previously reported that plasma exchange was more effective than standard medical treatment of sepsis in Turkish children with thrombocytopenia associated with multiple

Table III. Multivariate Logistic Regression Analysis of Survivors vs Non-survivors.

Variables	Odds Ratio	95% Confidence Interval	p value
PELOD score day 5	1.85	1.02-2.69	**0.04**
Ferritin (ng/mL)	1.43	0.97-2.03	**0.05**
Inotrope score day 1	1.12	0.84-1.41	0.42
Mechanical ventilation day	0.76	0.37-1.52	0.38
Receiving plasma infusion	0.62	0.4-1.24	0.62

PELOD: Pediatric Logistic Organ Dysfunction

organ failure. Fortenberry et al.[17] demonstrated that plasma exchange increases survival and improves organ dysfunction. Church et al.[18] hypothesized that plasma infusion is related to increased nosocomial infections, prolonged length of hospital stay, the occurrence of new-onset organ dysfunction, and mortality in critically ill pediatric patients. The use of fresh frozen plasma may unfavorably influence the survival in severe meningococcemia, which was revealed by Busund et al.[19] In contrast to previous data, we found that PI did not have an unfavorable effect on mortality. There was no difference found in the mortality of patients who received PI compared with children receiving TPE.

Some studies found that the PELOD score was not statistically different between plasma exchange (+) and plasma exchange (-) groups in patients with TAMOF at admission, however plasma exchange significantly decreased the PELOD score and facilitated the resolution of organ failures.[3,17] In our study, the baseline PELOD score was similar between TPE (+) and PI (+) groups and the changes from baseline in PELOD scores in the two therapy groups were not different at the end of the study.

Garcia and colleagues showed that high levels of ferritin were associated with increased mortality in children with severe sepsis.[20] Bennett and colleagues showed that an increase in ferritin levels increases mortality.[21] According to Demirkol and colleagues, serum ferritin levels were significantly higher in non-survivors.[16] Similarly, in this present study, higher ferritin levels were associated with mortality.

The use of TPE did not affect PRISM III scores and PELOD scores in patients with TAMOF and secondary hemophagocytic lymphohistiocytosis / macrophage activation syndrome.[14] In contrast, Sevketoglu et al.[3] showed that the baseline PRISM score, PELOD score, and OFI (Organ Failure Index) score of non-survivors were higher in children with TAMOF. In our present study, non-survivors had a higher PELOD score on the fifth day and this factor was independently associated with mortality, however, there were no difference found in the PRISM III score, baseline PELOD score, and several failing organ systems between the TPE and PI groups.

We also found that the mean length of PICU stays, hospital stays and mechanical ventilation days were longer in the PI (+) group than in TPE (+) group. These conditions can be clarified by the fact that ADAMTS-13 activity was restored more rapidly and antifibrinolytic and thrombogenic molecules eliminated the use of plasma exchange treatment and less time was needed for recovery of organ dysfunction.

Our study has some limitations to consider when evaluating. First, this was a retrospective study done with a small patient population which was the most important limitation, results need to be confirmed in an extensive sample group. Second, some coagulation complexes such as ADAMTS-13 activity and ultra-large Von Willebrand factor multimers could not be measured before and after treatments to evaluate the effect on a net complex level.

In a conclusion, although this retrospective study supports the beneficial effect of PI in patients with TAMOF, TPE is still the more effective treatment option. Even though there was no statistical difference in the effect of both treatments on mortality, the duration of mechanical ventilator, intensive care and hospital stay were longer in the plasma infusion group. The main reason for the lack of statistically significant differences may be the small patient population. Various technical reasons limit us in applying some kind of invasive procedures such as plasma exchange, dialysis, etc. Physicians particularly experience such technical problems in patients with low weight so this research will encourage the use of plasma infusion in children with multiorgan failure.

Ethical approval

Approval was obtained from the Afyonkarahisar Health Science University Faculty Ethics Committee (date: 03.12.2021, no: 2021/13).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KÇ, MÇ; data collection: MÇ; analysis and interpretation of results: KÇ, MÇ; draft manuscript preparation: KÇ, MÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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