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Use of Therapeutic Plasma Exchange in Children With Thrombocytopenia-Associated Multiple Organ Failure in the Turkish Thrombocytopenia-Associated Multiple Organ Failure Network

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Abstract

Objective—Thrombocytopenia-associated multiple organ failure can lead to high mortality in critically ill children, possibly related to consequences of thrombotic microangiopathy. Plasma exchange therapy may improve thrombotic microangiopathy. The purpose of this observational cohort study is to describe whether there is an association between use of plasma exchange therapy and outcome in the Turkish thrombocytopenia-associated multiple organ failure network.

Setting-Interventions—We performed a retrospective cohort analysis in patients with thrombocytopenia-associated multiple organ failure at three different PICUs comparing those who received plasma exchange (+) plus standard therapies with those who did not receive plasma exchange (–) and only received standard therapies.

Results—Among 42 of the enrolled patients with thrombocytopenia-associated multiple organ failure, all had a primary or secondary sepsis diagnosis. Fifteen received plasma exchange therapy (PE [+]) group) and 27 received standard medical treatment without plasma exchange (PE [–] group). The mean age was 17.69 months (8.24–54.22) in the PE (+) group and 13.46 months (6.47–20.55) in the PE (–) group. Age ($p = 0.232$), gender ($p = 0.206$), thrombocyte count ($p = 0.09$), Organ Failure Index score ($p = 0.111$), and pediatric logistic organ dysfunction score ($p = 0.177$) at admission were not statistically different between groups. The overall 28-day mortality

was higher in the PE (–) group (70.37%) compared with the PE (+) group (26.67%) (univariate $p = 0.006$; multivariate controlling for pediatric logistic organ dysfunction, Organ Failure Index, Pediatric Risk of Mortality scores, and neurological failure $p = 0.048$). Length of stay was increased in the PE (+) group ($p = 0.004$).

Conclusions—The positive association found between use of plasma exchange therapy and improved survival supports the potential of this therapy in Turkish children with thrombocytopenia-associated multiple organ failure. The positive, although less so, associated treatment effect observed after controlling for illness severity provides further rationale for performing a randomized controlled trial in the pediatric Turkish thrombocytopenia-associated multiple organ failure network. Sample size calculations call for a 100-patient trial with a pre hoc interim analysis after enrollment of 50 patients with thrombocytopenia-associated multiple organ failure.

Keywords

children; disseminated intravascular coagulation; microangiopathy; sepsis; thrombocytopenia-associated multiple organ failure; thrombotic microangiopathy; thrombotic thrombocytopenic purpura

Critically ill patients develop systemic microangiopathic endothelial injury caused by many types of systemic insults. In the setting of systemic endothelial injury, prothrombotic and antifibrinolytic responses can be injurious and are manifested by thrombocytopenia, systemic thrombosis, and multiple organ failure (1–5). Thrombocytopenia-associated multiple organ failure (TAMOF) is a thrombotic microangiopathic syndrome that has been defined in critically ill patients who develop endothelial damage caused by exposure to infection, transplantation, chemotherapy, radiation, cardiopulmonary bypass, and autoimmune diseases (6). Clinical and laboratory studies have demonstrated that TAMOF represents a spectrum of pathology that includes thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), and secondary thrombotic microangiopathy (TMA) (6–11).

In patients with TAMOF, many cellular components and proteins are elevated and activated in the blood; others are deficient and depleted as a result of TMA. Many studies have shown that there may be a potential role of plasma exchange as a treatment for patients with TMA, which included TTP, DIC and secondary TMA as a spectrum of TAMOF (12–15). The purpose of this study is to describe the use of plasma exchange therapy in critically ill children with TAMOF in three PICUs in Turkey in order to inform planning of a future randomized controlled trial in the pediatric Turkish TAMOF Network.

MATERIALS AND METHODS

This multicenter retrospective study was performed at three different tertiary care PICUs in Turkey (Bakirkoy Dr. Sadi Konuk Research and Training Hospital [BDSK], Cukurova University [CU], and Ankara University [AU]). This study was approved by local ethical committee. Data were collected retrospectively using printed case report forms. Clinical and laboratory data were recorded. An evaluation of organ function was based on a set of

laboratory and clinical variables according to the Organ Failure Index (OFI) score with the most abnormal value for each of the six organ systems being collected at admission (16, 17). Pediatric logistic organ dysfunction (PELOD) score was recorded on days 1, 2, 5, 8, 12, and 16. Hospital length of stay (LOS), PICU LOS, patients' congenital disease or chronic acquired disease, the day of death, and laboratory tests at admission (hemoglobin, prothrombin time [PT], activated partial thromboplastin time [aPTT], thrombocyte count, fibrinogen, ferritin, d-dimer, and lactate dehydrogenase [LDH]) were recorded. Chronic congenital disease is considered to be a condition existing at birth and often before birth, which persisted through admission, whereas chronic acquired disease is considered as disease acquired after birth and persisted through admission.

Patients with platelet counts less than $100,000/\text{mm}^3$ OFI greater than or equal to 3 present for less than 30 hours, and weight greater than 5 kg (minimum weight required due to technical limits of exchange equipment) were included in the study. Etiology of multiple organ failure due to systemic infection, shock, transplantation, chemotherapy, or cardiopulmonary bypass and thrombocytopenia secondary to diagnosed TTP/hemolytic uremic syndrome were included. Patients were excluded from the study if they had treatment prior to study entry with any form of plasma exchange therapy within 30 days or if terminal illness led withdrawal of therapy to be being considered.

Patients were divided into two groups: plasma exchange (+) group (PE [+]) that received plasma exchange and plasma exchange (–) group (PE [–]) that did not receive plasma exchange. Plasma exchange was obtained by plasma filtration (Prismaflex, TPE1000 filter, Gambro Lundia AB, Sweden). The blood removal rate ranged between 10 and 100 mL/min depending on patient weight and tolerance of volume changes. Plasma exchange was performed over 2–3 hours. Plasma exchange volume was calculated as $0.065 \times \text{kg} \times (1 - \text{hematocrit})$. During plasma exchange, heparin was used for anticoagulation and titrated to maintain the activated clotting time between 180 and 220 seconds. Fresh frozen plasma was used as replacement fluid in all patients. The plasma exchange (+) group received a 1.5 plasma volume exchange on day 1 followed by either 1 volume exchange daily $\times$ 14 days or until resolution to an OFI less than 3 for 48 hours, whichever was shorter in duration. Plasma exchange therapy was used as a therapy according to the Guidelines on the Use of Therapeutic Apheresis in Clinical Practice by the American Society for Apheresis.

Statistical calculations were performed with Number Cruncher Statistical System 2007 program for Windows (NCSS, LLC, Kaysville, UT). Mann-Whitney *U* test was used in the comparison of groups. Chi-square test and Fisher exact test were performed during the evaluation qualitative data. Multiple logistic regression analysis was used for the correlation of variables to mortality and survival. Two-way analysis of variance (ANOVA) was used to evaluate the effects within and between groups over time.

RESULTS

This retrospective study was performed between 2010 and 2013. A total of 42 patients (22 from BDSK, 13 from CU, and 7 from AU) with TAMOF were enrolled with the following principal diagnosis: previously healthy with sepsis ($n = 8$), DIC ($n = 27$), TTP ($n = 4$),

malignancy ($n = 6$), end-stage liver failure ($n = 2$), end-stage heart failure ($n = 2$), and miscellaneous (multitrauma, aspiration pneumonia, and congenital megacolon [$n = 3$]). All patients including the eight patients with a principal diagnosis of sepsis met the clinical definition of sepsis (eight as a primary diagnosis and 34 as a secondary diagnosis). Fifteen of 42 patients (nine from BDSK, three from AU, and three from CU) received standard treatment with plasma exchange (PE [+]) group), and the remaining 27 patients received standard treatment without plasma exchange (PE [-]) group). Standard treatment included the following: all patients with sepsis and septic shock received culture sensitivity-directed antibiotic therapy and American College of Critical Care Medicine-recommended Hemodynamic Support Guideline therapies (18). Continuous renal replacement therapy was used for renal failure and fluid overload, mechanical ventilation for respiratory failure, and general supportive care for liver failure included correction of any fluid and electrolyte imbalances and management of hypoglycemia. The decision to initiate plasma exchange was made by each centers' clinician discretion.

We did not experience any life-threatening side effects directly related with plasma exchange therapy (such as infection, thrombosis, hypothermia, massive bleeding, electrolyte imbalances, and hypothermia). There was minimal blood leakage around the intravascular catheter in two patients.

Table 1 demonstrates the mean age was 37.76 ± 46.28 months in the PE (+) group and 15.96 ± 14.59 months in the PE (-) group. Age and sex were not different between groups ($p = 0.232$ and $p = 0.206$) (Table 1). While the mean thrombocyte count tended to be higher, and the mean OFI and PELOD score at admission tended to be lower in the PE (-) group, the differences were not statistically different between groups ($p = 0.09$, $p = 0.111$, and $p = 0.177$) (Table 1). Having chronic congenital disease or chronic acquired disease were also not different between groups ($p = 0.235$ and $p = 0.654$) (Table 1). All patients in both groups were mechanically ventilated. Mechanical ventilation days tended to be longer in the PE (+) group ($p = 0.086$) but again was not statistically significant.

Figure 1 shows serial calculations of the PELOD score over the days 1, 2, 5, 8, 12, and 16. PELOD score differences over time between groups were measured using two-factor ANOVA. The test for the main effect of plasma exchange ($F = 25.62$, $p < 0.0001$) shows a significant PE effect. Also, the test for the main effect of time ($F = 8.10$, $p = 0.0001$) tells us that there is a significant time effect. Finally, there was a significant interaction between plasma exchange and time ($F = 0.063$, $p = 0.001$, two-way ANOVA).

The overall mortality rate was 54.76% (14 male, 9 female). Nineteen of 27 patients (70.37%) in the PE (-) group (13 DIC, four sepsis, two cancer patients) and four of 15 patients (26.67%) in the PE (+) group (two TTP, two DIC patients) died (Table 1). Mortality was significantly lower in the PE (+) group ($p = 0.006$) (Table 1). Comparing survivors versus nonsurvivors (Table 2), mean age was 33.12 ± 44.15 months in survivors and 16 ± 9.47 months in nonsurvivors. Mean age and sex were not different between survivors and nonsurvivors ($p = 0.791$ and $p = 0.845$, respectively) (Table 2). The OFI score on day 1, PELOD score on day 1, Pediatric Risk of Mortality (PRISM) score, and OFI neurologic score were significantly different in nonsurvivors ($p = 0.049$, $p = 0.01$, $p = 0.0001$, and $p =$

0.005, respectively). Not receiving plasma exchange was also associated with mortality ($p = 0.006$) (Table 2). Requiring continuous renal replacement therapy, having chronic congenital disease, having chronic acquired disease, and having cardiovascular, respiratory, renal, and hepatic involvement as defined by the OFI score were not different between survivors and nonsurvivors ($p = 0.154$, $p = 0.703$, $p = 0.936$, $p = 0.096$, $p = 0.281$, $p = 0.516$, and $p = 0.255$, respectively). Although fibrinogen levels and OFI cardiovascular score suggested trends, the mean levels of fibrinogen, hemoglobin, LDH, PT, aPTT, ferritin, and d-dimer levels were not different between survivors and nonsurvivors ($p = 0.051$, $p = 0.318$, $p = 0.356$, $p = 0.330$, $p = 0.221$, $p = 0.998$, and $p = 0.496$, respectively) (Table 2). PELOD score on day 1, PRISM score on day 1, OFI score on day 1, neurologic involvement as defined by the OFI score, and not receiving plasma exchange were included in logistic regression model. In multivariate analysis, not receiving plasma exchange was independently associated with mortality-adjusted odds ratio 1.81 (95% CI, 0.20–16.29; $p = 0.048$) (Table 3). PRISM score was also associated with mortality-adjusted odds ratio 1.74 (95% CI, 1.13–2.69; $p = 0.013$) (Table 3).

DISCUSSION

New onset thrombocytopenia is a major determinant of TAMOF, which has been established as an independent risk factor for mortality in intensive care patients (19, 20). At this time, evidence from many separate studies supports the use of plasma exchange for TTP and possibly secondary TMA in reversal of disease (21, 22). In addition, plasma exchange has been associated with less than expected mortality in patients with severe sepsis, septic shock, and meningococemia (23, 24). The goals of plasma exchange in TAMOF are to remove excessively thrombogenic and antifibrinolytic molecules and to replenish the deficient anticoagulants and profibrinolytic molecules in order to regain a normal homeostatic milieu (17).

Rock et al (21) reported that in adult patients with TTP, receiving plasma exchange had a higher rate of response as defined by an increase in the platelet count and a reduced mortality than those who received plasma infusion. In another adult study, Stegmayr et al (13) reported that in patients with DIC and MOF as part of TAMOF, plasma exchange therapy is associated with improved survival (82%) compared with observed survival (< 20%) in historical controls. In pediatric patients, Churchwell et al (24) demonstrated that plasma exchange reversed coagulopathy and resulted in survival in seven out of nine children with meningococcus-associated purpura fulminans. Our present study of a larger group of children with TAMOF included DIC and other TMA; we have found that children who received plasma exchange had a 26.67% mortality rate compared with 70.37% mortality rate in children who did not receive plasma exchange (Table 1). Pene et al (25) reported that plasma exchange in adults with TMA was independently associated with lower mortality, regardless of disease severity—adjusted odds ratio 0.234 (95% CI, 0.095–0.573; $p = 0.001$). In our study, nonsurvivors had higher PRISM score, PELOD score, and OFI score at admission which is not surprising and logistic regression model controlling for these factors we found that in our cohort of children with TAMOF, treating without plasma exchange was independently associated with death, adjusted odds ratio 1.81 (95% CI, 0.20–16.29; $p = 0.048$) (Table 3).

In several studies, in patients with primary and secondary thrombotic microangiopathies, intensive plasma exchange was associated with resolution of organ dysfunction (15, 21, 23, 26). In our study, between PE (+) and PE (–) groups, disease severity and organ dysfunction score values (PELOD score and OFI score) and thrombocyte count were not statistically different between two groups at admission. We found that there was a significant interaction between plasma exchange and time ($F = 0.063$, $p = 0.001$, two-way ANOVA). This means that the plasma exchange therapy was associated with facilitated resolution of multiple organ failure. Although children with TAMOF have been reported to have reduced a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) levels with plasma exchange restored ADAMTS-13 activity, it is still unknown whether decreased ADAMTS-13 is an innocent marker or the pathogenic cause of organ dysfunction. Ono et al (27) reported in adult patients with sepsisinduced DIC that the degree of ADAMTS-13 deficiency was associated with the degree of renal failure and the likelihood of resolution of renal failure. Similarly, Nguyen et al (12) demonstrated that intensive plasma exchange therapy restored ADAMTS-13 activity and was associated with resolution of organ dysfunction in children with thrombocytopenia-associated MOF. A major limitation of our study is that we could not measure ADAMTS-13 activity due to the lack of availability in our country. Nevertheless, we found that plasma exchange therapy was associated with facilitated resolution of multiple organ failure in children with TAMOF.

Another finding in our study is that the mean PICU LOS and hospital LOS were longer in PE (+) group than in PE (–) group. This may have been explained by the fact that the PE (–) group included 71% (19 of 27) of nonsurviving patients who had a shorter PICU LOS.

There are important limitations to consider in our study. We did not perform more complex measures of coagulation such as ADAMTS-13, ultralarge Von Willebrand factor multimers, tissue factor, or plasminogen activator inhibitor-1 reducing our ability to examine mechanism of disease related to coagulopathy. We also did not perform a randomized trial. Our study has a cohort design which shows that receiving plasma exchange therapy was associated with improved organ failure resolution and improved survival in children with TAMOF. Because we cannot determine led clinicians to choose to treat some TAMOF patients with plasma exchange, and other TAMOF patients with standard therapy, it will be necessary to perform a randomized trial in order to evaluate any beneficial effect of plasma exchange therapy in children implied by our cohort design.

Our findings give support to future randomized evaluation of plasma exchange as a promising therapeutic approach in critically ill children with devastating systemic TMA and ensuing multiple organ failure.

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Figure 1. Pediatric logistic organ dysfunction (PELOD) score comparison of groups who received plasma exchange and those who did not receive plasma exchange.

Table 1

Comparison of Patients Treated With and Without Plasma Exchange

Descriptions	Plasma Exchange (<i>n</i> = 27) (–) (%)	Plasma Exchange (<i>n</i> = 15) (+) (%)	<i>p</i>
Age (mo) ^a	15.96 ± 14.59	37.76 ± 46.28	0.232
Sex (female/male) ^b	9/18	8/7	0.206
Pediatric Risk of Mortality score	22.19 ± 5.16	19.07 ± 5.23	0.066
Thrombocyte count on day 1 ^a	55,852 ± 27,873	41,200 ± 25,752	0.09
Total OFI score on day 1 ^a	4 ± 0.78	3.6 ± 0.83	0.111
Pediatric logistic organ dysfunction day 1 ^a	24.33 ± 7.24	18.4 ± 6.08	0.177
OFI Cardiovascular	25 (92.59)	12 (80)	0.227
OFI Respiratory	22 (81.48)	8 (53.33)	0.053
OFI Renal	12 (44.44)	8 (53.33)	0.580
OFI Hematologic	24 (88.89)	14 (93.33)	0.638
OFI Hepatic	3 (11.11)	3 (20)	0.430
OFI Neurologic	22 (81.48)	9 (60)	0.129
Inotrope use	25 (92.59)	12 (80)	0.227
Receiving renal replacement therapy	12 (44.44)	8 (53.33)	0.580
Chronic acquired disease ^b	9 (33.33)	4 (26.67)	0.654
Chronic congenital disease ^b	8 (29.63)	2 (13.33)	0.235
PICU length of stay (d) ^a	10.26 ± 9.33	23.60 ± 19.09	0.003
Hospital length of stay (d) ^a	12.48 ± 10.93	26.27 ± 18.31	0.004
Mechanical ventilation day ^a	8.52 ± 7.80	13.2 ± 10.23	0.086
Nonsurvivor ^b	19 (70.37)	4 (26.67)	0.006

OFI = Organ Failure Index.

^aMean ± SD, Mann-Whitney *U* test.^bChi-square test.

Table 2

Comparison of Survivors and Nonsurvivors

Descriptions	Survivors (<i>n</i> = 19) (%)	Survivors (<i>n</i> = 19) (%) Nonsurvivors (<i>n</i> = 23) (%)	<i>p</i>
Age ^a	33.12 ± 44.15	16 ± 9.47	0.791
Sex (female/male) ^b	8/11	9/14	0.845
Total OFI score on day 1 ^a	3.58 ± 0.69	4.09 ± 0.85	0.049
Pediatric logistic organ dysfunction on day 1 ^a	14.68 ± 10.19	23.91 ± 12.97	0.01
Pediatric Risk of Mortality score ^a	17.05 ± 5.07	26.48 ± 6.15	0.0001
Thrombocyte count ^a	53,052.63 ± 26,922.67	48,608.7 ± 28,842.42	0.695
Hemoglobin ^a	9.62 ± 2.79	8.63 ± 1.56	0.318
Lactate dehydrogenase ^a	1,918.63 ± 3,299.14	1,810.57 ± 2,031.01	0.356
Prothrombin time ^a	29.86 ± 8.37	30.93 ± 15.54	0.330
Activated partial thromboplastin time ^a	57.94 ± 19.92	71.96 ± 33.01	0.211
Fibrinogen ^a	114.95 ± 70.25	199.36 ± 150.21	0.051
Ferritin ^a	1,841.09 ± 2,508.19	580 ± 94.75	0.998
D-dimer ^a	25,169.82 ± 31,749.09	10,340 ± 8,890.56	0.496
Having chronic acquired disease ^b	6 (31.58)	7 (30.43)	0.936
Having chronic congenital disease ^b	4 (21.05)	6 (26.09)	0.703
Receiving continuous renal replacement therapy ^b	7 (36.84)	4 (17.39)	0.154
OFI Cardiovascular ^b	15 (78.95)	22 (95.65)	0.096
OFI Respiratory ^b	12 (63.16)	18 (78.26)	0.281
OFI Renal ^b	8 (42.11)	12 (52.17)	0.516
OFI Hepatic ^b	4 (21.05)	2 (8.70)	0.255
OFI Neurologic ^b	10 (52.63)	21 (91.30)	0.005
Not receiving plasma exchange ^b	8 (42.11)	19 (82.67)	0.006

OFI = Organ Failure Index.

^aMean, Mann-Whitney *U* test.^bChi-square test.

Table 3

Multivariate Analysis of Survivors Versus Nonsurvivors

Descriptions	<i>P</i>	OR	95% CI	
			Lower	Upper
Not receiving plasma exchange	0.048	1.81	0.20	16.29
Pediatric logistic organ dysfunction day 1	0.684	0.97	0.86	1.11
Pediatric Risk of Mortality 24	0.013	1.74	1.13	2.69
Total OFI score	0.168	0.30	0.06	1.66
OFI Neurologic involvement ^a	0.599	0.03	0.001	1.12

OFI = Organ Failure Index.

^aNeurologic involvement according to OFI scoring.