Therapeutic Plasma Exchange in Pediatric Patients: Results from a Single Center

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Abstract

Therapeutic plasma exchange (TPE) can be applied as an effective therapeutic option in children with hematological, neurological, nephrological, and autoimmune/rheumatic disorders. We aimed to report our TPE experience in pediatric patients. In this article, we retrospectively reviewed the records of pediatric patients who underwent TPE between 2019 and 2021. A total of 128 TPE sessions were performed in 25 patients (13 males,12 females; mean age 59.6 ± 11.7 [3–198] months). The TPE indications were sepsis with/without multiorgan dysfunction syndrome in five patients, acute liver failure, hemolytic uremic syndrome caused by Shiga toxin, and autoimmune hemolytic anemia in three patients, respectively, multiple sclerosis, autoimmune encephalitis, and multisystem inflammatory syndrome in children (MIS-C) in two patients each, and myasthenia gravis crisis, meningococcemia, hemolytic uremic syndrome caused by coronavirus disease 2019, hemophagocytic lymphohistiocytosis, autoimmune encephalitis, and metabolic disease (fatty acid oxidation defect, liver failure) in one patient each. Based on our findings, we proposed that the American Society for Apheresis criteria should be updated according to newly described clinical conditions such as MIS-C.

Keywords
- therapeutic plasma exchange
- American Society for Apheresis guidelines
- multisystem inflammatory syndrome in children

Introduction

Therapeutic plasma exchange (TPE) can be applied as an effective therapeutic option in children with hematological, neurological, nephrological, and autoimmune/rheumatic disorders.[1,2] TPE separates blood cellular components by centrifugation-based techniques to replace large molecules, pathological antibodies, toxic medications, and nonbeneficial clotting factors by filtration devices with albumin or fresh frozen plasma (FFP).[3] Four categories of TPE indications were defined by the American Society for Apheresis (ASFA) guidelines published recently in 2019.[4] These are: Category I:

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Disorders for which apheresis is accepted as first-line therapy. Category II: Disorders for which apheresis is accepted as a second-line therapy, either as a stand-alone treatment or in conjunction with other treatment modalities. Category III: Optimum role of apheresis therapy is not established. Decision-making should be individualized. Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful.[5] The indications in children, however, have been derived from small retrospective analyses.[6,7] In our retrospective study, we aimed to report the TPE experience in pediatric patients who underwent the procedure in the intensive care unit and to evaluate its outcomes aiming to add our experience to the limited body of data on pediatric TPE.

Materials and Methods

We retrospectively reviewed the records of pediatric patients who underwent TPE between 2019 and 2021 in our intensive care unit. The demographic characteristics, medical history, laboratory findings, complications, and procedural details were collected from the patients' medical records. All TPE procedures were performed at the bedside throughout which all patients were monitored. All adverse events (AEs) and complications were recorded. All procedures were performed by trained apheresis technicians assisted by hematology and intensive care fellows. TPE was performed with the Gambro Prismaflex instrument. Central venous catheters were used for vascular access. Standard heparin (10 U/kg/h) was used as anticoagulant. The ethics committee approval of the study was obtained from the Kahramanmaraş Sütçü İmam University Clinical Research Ethics Committee (date: June 15, 2021, No:06).

Results

A total of 130 TPE sessions were performed in 25 patients (13 males,12 females; median (interquartile range) age 33 months (13.5–114). The TPE indications were sepsis with/without multiorgan dysfunction syndrome in five patients, acute liver failure (ALF), hemolytic uremic syndrome caused by Shiga toxin, and autoimmune hemolytic anemia (AHA; two cold type and one warm type) in three patients, respectively, multiple sclerosis (MS), autoimmune encephalitis, and multisystem inflammatory syndrome in children (MIS-C)[8] in two patients each, and myasthenia gravis crisis, meningococcemia associated with coagulopathy, hemolytic uremic syndrome (HUS) caused by coronavirus disease 2019 (COVID-19), hemophagocytic lymphohistiocytosis, autoimmune encephalitis, and metabolic disease (fatty acid oxidation defect, liver failure) in one patient each (►**Table 1**). Albumin (5–20%) solution was used in 5 patients with neurologic disorders (MS, autoimmune encephalitis, myasthenia gravis) and FFP was used in the remaining 20 patients, who have also risk of active bleeding or a coagulopathy. The diagnosis of COVID-19 of the patients with MIS-C was made by polymerase chain reaction tested 1 month ago. They presented with fever, rash, abdominal pain, and elevated acute phase reactants.

None of the septic patients showed satisfactory response to the antimicrobial therapy; since they met the criteria of thrombocytopenia-associated multiple organ failure,[5] they underwent TPE. These patients were considered as Category III according to the ASFA guidelines.[4] Daily FFP treatment did not lead to remission in any of the HUS patients, and they underwent TPE. These patients were considered as Category IV according to the ASFA guidelines, and none of them

Table 1 Application of therapeutic apheresis other than therapeutic plasma exchange

Diseases	Number of patient	Number of procedures	Replacement solution	Indication category	Result
HUS	3	15	FFP	IV	1 died, 2 remission
HUS (COVID-19)	1	5	FFP	Undefined	Remission
Sepsis (MODS)	5	25	FFP	III	1 died, 4 remission
Acute liver failure	3	15	FFP	III	1 died, 2 remission
MS (chronic progressive)	2	10	Albumin	III	2 remission
Autoimmune hemolytic anemia	3	16	FFP	II, III	3 remission
Autoimmune encephalitis	2	12	Albumin	II	2 remission
Multisystem inflammatory syndrome in children	2	10	FFP	Undefined	Remission
Myasthenia gravis (myasthenic crisis)	1	5	Albumin	I	Remission
Meningococcemia	1	5	FFP	Undefined	Died
Hemophagocytic lymphohistiocytosis (secondary)	1	5	FFP	I	Died
Metabolic disease (6-carbon medium-chain fatty acid oxidation defect)	1	5	FFP	Undefined	Transferred to another hospital
Total	25	128			5 died, 19 remission

Abbreviations: COVID-19, coronavirus disease 2019; FFP, fresh frozen plasma; HUS, hemolytic uremic syndrome; MODS, multiple organ dysfunction syndrome; MS, multiple sclerosis.

developed chronic kidney disease. ALF was considered as Category III disease according to the revised ASFA guideline. Acute MS attack was considered as Category II disease according to ASFA guidelines. AHA was considered as either Category II or III. Direct Coombs' test turned from positive to negative in all patients with AHA, and they improved dramatically. The rest of the indication categories are shown in ►**Table 1**.

Five of our patients died; others achieved remission, except for the one patient with inborn error of metabolism who experienced multiorgan failure and was transferred to a tertiary-level care center after five sessions.

Finally, the TPE procedure was not needed to be discontinued in any patient for a procedure-related complication. AEs including tachycardia, pruritus, and shivering were seen in two patients. None of the patients died from TPE complications. None of them needed premedication to prevent these AEs.

Discussion

TPE indications in the pediatric population are not as clear as in adults. Several clinical studies[9,10] have reported the efficacy of TPE in pediatric patients. A national survey from Turkey[11] reported the data of 172 pediatric patients who underwent 869 TPE sessions in 21 centers. Neurological disorders and TTP/HUS were the most common TPE indications. We evaluated the indications, efficacy, and complications of TPE in a group of patients who were treated in a pediatric intensive care unit. We also examined the adherence to ASFA guidelines.

TPE is suggested to be ineffective in Shiga toxin-induced HUS (Category IV) according to the ASFA guidelines.[4] However, when the etiology is unknown, an urgent TPE can be performed according to a patient's mortality and prolonged morbidity risks such as end-stage kidney disease.[12,13]

TPE in sepsis has been reported as a potential adjunctive therapy[14–16] and it was graded by the ASFA guidelines as a Category III indication.[4,15] A study with 106 septic patients showed an improved survival (33.3 vs. 53.8%) with TPE.[17] We suggest that both the TPE timing and disease severity might be crucial for achieving a beneficial effect of TPE in sepsis since TPE is able to provide rapid hemodynamic improvement and favorable changes in the cytokine profile.[18] One of our patients with sepsis who was 18 years old died. He developed hypoalbuminemia, and TPE was performed on day 12. In the other septic patients, TPE was started on days 4 to 6. We propose that sepsis progressing to multiple organ dysfunction syndrome may be included in Category II instead of Category III.

Plasma exchange (PE) is an effective treatment of cold antibody AHA through the elimination of circulating antibodies in the plasma[19]; it is also suggested as a third-line treatment in relapsing patients who underwent splenectomy and are unresponsive to immunosuppressive treatment.[19,20] Cold antibody autoimmune hemolytic is included in Category II.[4] It has been shown that cold antibody AHA develops subsequently in approximately half of the patients who have infection initially.[21] Three of our patients with AHA responded to TPE dramatically. This experience emphasizes that plasmapheresis is an efficient treatment method in patients with cold antibody AHA. The only patient with warm AHA who had not responded to steroids and intravenous immunoglobulin (IVIG) had benefited from TPE. It is recommended to use high-dose steroid IVIG in patients with warm antibody hemolytic anemia, and TPE is recommended for those who do not respond.[5,22] In conclusion, after TPE, there was no need for transfusion and hemolysis findings regressed (hemoglobin did not decrease, reticulocyte and bilirubin values decreased) in all of the patients with AHA.

COVID-19-associated MIS-C is characterized by hyperinflammation.[23,24] A previous report[25] with 27 cases suggested MIS-C is a life-threatening clinical condition. Therefore, aggressive management of hyperinflammation is mandatory. Keith et al[26] have shown that TPE is a potential therapeutic alternative for critically ill patients with COVID-19, targeting the effects of high levels of cytokines, inflammation, endothelial dysfunction, and coagulopathy. Two patients with MIS-C responded well to TPE. We think that the MIS-C may be added to the ASFA criteria either as Category II or Category III. Besides if TPE is to be performed after immunomodulatory treatment, this needs to be at least 24 hours later in order not to interfere with the treatment efficiency.

In the case series of Churchwell et al,[27] on eight pediatric patients with fulminant meningococcemia who underwent intensive plasma and whole blood exchange, the procedure proved to be safe in patients with meningococcemia and associated disseminated intravascular coagulation, although it was not defined by ASFA. We cannot, however, comment on this, as we had only one patient with such condition included in our study who died during the fifth session of plasmapheresis, due to meningitis and cerebral edema.

Liver transplantation is the accepted treatment for patients with ALF. However, donor organ shortage may have resulted in lower transplantation rates and longer waiting times in these patients, and, therefore, TPE can be performed in the interim till a donation is available. ALF is defined as a Category III indication according to ASFA. However, there are concerns regarding the overuse of PE in this condition, and this treatment strategy must be individualized. Studies have shown that the number of TPE sessions widely varies, and there is no standard recommendation in this regard.[28–30] High-volume PE (2–3 × plasma volume) is considered as a first-line therapy in the setting of liver failure, either as primary treatment or in conjunction with other modes of treatment such as continuous renal replacement therapy.[4] Although we performed TPE with upper limit (1.5 × plasma volume) of the standard volume,[5] which is not a "high plasma volume," two of our patients with ALF recovered after five TPE sessions. However, the third patient died during the follow-up period.

The study design, having been a cohort one, with a relatively low number of patients, and lack of a control group may have actually limited the reliability of our results.

Conclusion

Our center experience with TPE has been reviewed. We conclude that TPE is a life-saving treatment option in certain pediatric conditions, needs to be standardized in this population of patients in terms of indications and treatment scheduling. Based on our findings, we propose that the ASFA criteria should be updated according to newly described clinical conditions such as MIS-C.

Authors' Contributions
T.D. and Y.K. contributed to analysis and drafted the manuscript. M.M., S.I., U.U.G., C.A., and C.D. helped evaluate subjects. Y.K. designed and critically revised the manuscript. All authors read and approved the manuscript.

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Conflict of Interest
None declared.

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