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Therapeutic plasma exchange for pediatric nonrenal disease indications and outcomes: A single-center experience

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Abstract:

INTRODUCTION: Outcome data in pediatric plasma exchange, especially in nonrenal indications are scarce. We aimed to evaluate its role and outcome in our patients.

SUBJECTS AND METHODS: A retrospective study of children admitted in the year 2016 to the Pediatric Intensive Care Unit requiring plasma exchange for nonrenal indications was undertaken. Plasma exchange was given as adjunctive therapy along with primary treatment for the disease concerned. Demographic and clinical data were studied, and descriptive statistical analysis was carried out.

RESULTS: Ten children underwent plasma exchange during this 1-year period with a male: female ratio of 3:2 and a mean age of 10 years (range 3–16 years). The indications were acute disseminated encephalomyelitis (n = 2), acute neuromyelitis optica (n = 1), catastrophic antiphospholipid antibody syndrome secondary to systemic lupus erythematosus (SLE) (n = 1), severe SLE with cerebritis/hemophagocytic lymphohistiocytosis (HLH) (n = 2), severe dengue sepsis with HLH/multi-organ dysfunction syndrome (n = 2), and thrombotic microangiopathy secondary to snake bite envenomation (n = 2). All received either 1.5 or 2 times plasma volume exchange (mean sessions – 4, range = 1–6). The mean duration of stay in hospital was 17.2 days (range = 3–40 days), and follow-up was 78 days (range = 3–180 days), with the majority of children (8/10, 80%) survived from the catastrophic illness at the time of discharge. Two children (2/10, 20%) succumbed due to the disease *per se* in severe dengue sepsis in one and enterobacteriaceae sepsis (hospital-acquired pneumonia) in another.

CONCLUSION: Plasma exchange was found to be beneficial as complementary therapy in a critical care setting, especially for nonrenal indications.

Keywords:

Children, hemophagocytic lymphohistiocytosis, multi-organ dysfunction syndrome, plasma exchange, thrombotic microangiopathy

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Introduction

Therapeutic plasma exchange (TPE) is an extracorporeal procedure where plasma is separated from the cellular component of patient's blood, which is retained. Then, plasma is discarded and replaced with either fresh frozen plasma (FFP) or albumin.[1] TPE is commonly employed in various neurologic, immunologic, renal, and hematological conditions where it removes pathogenic circulating autoantibodies, immune complexes, cytokines, and

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toxins from the blood.[1] The American Society for Apheresis (ASFA) assigns conditions to 1 of 4 categories and 1 of 2 grades based on the quality of published evidence and strength of recommendations.[2] The majority of evidence used in the ASFA guidelines is from adult studies and the recommendations do not distinguish between childhood and adult-onset diseases. There is a scarcity of paediatric data worldwide in the form of case reports and case series, and hence, the recommendations for TPE are extrapolated from adult studies. Although the indications and principles are the same as in adults, pediatric TPE is technically challenging in view of difficult in vascular access, small intravascular and extracorporeal volume and psychosocial issues.[1] TPE shows an additive survival benefit in many critically ill conditions that a nephrologist should be aware of such usage in nonrenal diseases.[3,4] There are only a few reports of pediatric plasma exchange from India so far[5,6] that too most of the indications were atypical hemolytic uremic syndrome (aHUS). The present study aimed to explore the use of TPE for nonrenal indications apart from aHUS in a critical care unit, especially in the pediatric population.

Subjects and Methods

A retrospective chart review of children admitted between November 2015 and October 2016 (1 year) to the Pediatric Intensive Care Unit (ICU), Apollo Children Hospitals at Chennai, India requiring plasma exchange for nonrenal indications was undertaken. Institutional Ethics Committee approval was obtained. Plasma exchange was given as adjunctive therapy along with primary treatment for the disease concerned. Demographic data, clinical data, details of treatment for primary diseases, plasma exchange procedure details, complications of procedure, outcome, and follow-up details were collected. The descriptive statistical analysis was carried out.

A double-lumen internal jugular or femoral vascular catheter (size 8/10 French as per age and weight of the child) was used considering the child's coagulopathic and hemodynamic status. TPE was carried out by membrane filtration technique. A Fresenius 4008-S hemodialysis machine with Fresenius plamaFlux PSu 1S or 2S (effective surface area –0.3 m or 0.6 m^2, respectively) plasma exchange filter was used. Fresenius plamaFlux PSu 1S and 2S was used in children aged <4 and ≥4 years, respectively. The procedure was performed as per our standard protocols under strict aseptic ways by a senior hemodialysis technician with adequate training in handling pediatric patients. Blood flow was kept at 3–5 ml/kg/min (100–125 mL/min). The appropriate tubing was used to maintain the extracorporeal volume according to age and weight of the patient. Blood priming of the tubing was not done as all the patients were >2 years of age and weighed >10 kg. The time for the procedure was 80–120 min. As most of the study patients were very sick and in disseminated intravascular coagulation (DIC), saline flushing was done during the procedure to prevent extracorporeal clotting, but in some heparin was used as indicated. The dose of heparin used was 50 IU/kg stat followed by 1000 IU/h. All patients received promethazine injection and paracetamol tablet as premedications. Our institute protocol was to deliver once daily TPE for 2–3 days initially followed by alternative days as per the requirement until achieving the treatment goal. However, this regimen was tailored to individual need. Estimated plasma volume (EPV) was calculated from Kaplan formula as EPV in liter = (0.065 × weight) × (1 – hematocrit).[7] The volume of the patient's plasma exchanged was 1.5–2.0 times the calculated EPV depends on the need. Patient's plasma was replaced with 100% colloid (combined FFP and albumin). The proportion of FFP and albumin varied depending on the treating disease condition. FFP proportion was kept equal or more than albumin if the patient had coagulopathy abnormality. Prophylactic calcium gluconate injection was given (to prevent hypocalcemia associated with the use of colloid replacement fluids) during the procedure as an infusion (10 mL mixed in 1:1 dilution 5% dextrose) at half-hourly interval with strict cardiac monitoring. Vitamin K (5 mg) and water-soluble vitamins (1 vial = 5 ml as an infusion) were replaced post-TPE as per our unit policy based on the fact that coagulation factors and vitamins were depleted after TPE.[8,9]

Results

Ten children underwent plasma exchange during this 1-year period with a male:female ratio of 3:2 and a mean age of 10 years (range 3–16 years). The indications for plasma exchange are mentioned in Table 1 and were categorized and graded as per recent the ASFA 2016 guidelines[2] on the use of therapeutic apheresis in clinical practice. All treatment details and outcome of all ten patients are mentioned in Table 1. Necessary investigations were carried out to make a diagnosis of acute disseminated encephalomyelitis (ADEM), antiphospholipid antibody (APLA) syndrome, hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), thrombotic microangiopathy (TMA), and others. HLH was diagnosed based on HLH 2004 revised diagnostic criteria.[10] All children received either 1.5 or 2 times plasma volume exchange (mean sessions – 4, range 1–6). Patient's plasma was replaced with 100% colloid (both FFP and 5% human albumin). Primary treatment were given (like sepsis treatment as per intensive care sepsis protocol, continuous veno-venous haemodiafiltration (CVVHDF)

Table 1: Clinical profile of study patients

Age (years)/ gender	Diagnosis	Other comorbidities	Indication for TPE (ASFA 2016 category and grading)	Volume of plasma exchanged	Number of TPE done	Replacement fluid	Treatment given	Duration of stay in hospital	Outcome and follow-up
8/male	ADEM	Respiratory failure	ADEM (II, 2C)	1.5×	5=3 daily followed by 2 AD	50/50 - FFP/5% albumin	MP 30 mg/kg/day - 3 days, oral steroid 0.5 mg/kg/day for 1 month, IVIg - 0.4 mg/kg/day - 5 days	16 days	Improved At 6 months - CR
7/ female	ADEM	Nil	ADEM (II, 2C)	1.5×	5=3 daily followed by 2 AD	50/50 - FFP/5% albumin	MP 30 mg/kg/day - 3 days, oral steroid 0.5 mg/kg/day for 1 month, IVIg - 0.4 mg/kg/day - 5 days	15 days	Improved At 2 months - CR
7/male	Acute neuromyelitis optica (Devic's disease)	Brainstem involvement/ autonomic instability	Severe demyelinating illness (II, IB)	1.5×	6=3 daily followed by 3 AD	75/25-5% albumin/FFP	MP 30 mg/kg/day - 5 days, oral steroid 0.5 mg/kg/day for 15 days, IVIg - 0.4 mg/kg/day - 2 cycles	40 days	Expired Cause: Enterobacter sepsis (hospital acquired pneumonia)
13/ female	Systemic lupus erythematosus	Secondary APLA-renal infarct and mesenteric ischemia and deep vein thrombosis of leg and Class IV LN	Catastrophic APLA (II, 2C)	2×	4=2 daily followed by 2 AD	75/25 - FFP/5% albumin	MP 30 mg/kg/day - 3 days followed by oral steroid and pulse cyclophosphamide once in 15 days and anti-coagulants	8 days	Improved At 3 months - CR
16/ female	Systemic lupus erythematosus	Cerebral lupus - optic neuritis/ PRES and HLH	Severe lupus (CNS) and HLH/MAS (II, 2C and III, 2C respectively)	2×	3=3 daily	50/50 - FFP/5% albumin	MP 30 mg/kg/day - 3 days followed by oral steroid and Rituximab 600 mg - 2 doses and MMF 1.5 g a day	21 days	Improved At 2 months - PR, HLH - disappeared, vision difficulty plus
13/male	Systemic lupus erythematosus	Class IV LN and HLH	HLH/MAS (III, 2C)	2×	5=3 daily followed by 2 AD	50/50 - FFP/5% albumin	MP 30 mg/kg/day - 5 days followed by oral steroid and IV cyclosporine 8 mg/kg/day - 3 days and pulse cyclophosphamide once in 15 days	14 days	Improved At 2 months HLH-CR, renal-PR
3/male	Dengue shock syndrome/ MODS (AKI/ALI)/HLH	Secondary bacterial sepsis (Klebsiella)/ fungal peritonitis (Aspergillus) (as he is on IPD initially)	HLH and MODS (III, 2C or 2B in severe sepsis)	1.5×	4=4 AD	50/50 - FFP/5% albumin	IPD initially for 4 days then CVVHDF 30 ml/kg/h given for 72 h then SLED on AD - 4 sessions and antibiotics/ antifungals	35 days	Improved At 6 months - CR
15/male	Dengue encephalitis/ MODS (AKI/ALI/ fulminant liver failure)		MODS (III, 2B)	2×	1	75/25 - FFP/5% albumin	CVVHDF 30 ml/kg/h given for 46 h and other supportives	3 days	Expired

Contd...

Table 1: Contd...

Age (years)/ gender	Diagnosis	Other comorbidities	Indication for TPE (ASFA 2016 category and grading)	Volume of plasma exchanged	Number of TPE done	Replacement fluid	Treatment given	Duration of stay in hospital	Outcome and follow-up
3/male	Snake envenomation	TMA and AKI	TMA (III, 2C)	1.5×	5=3 daily followed by 2 AD	75/25 - FFP/5% albumin	Anti-venom and 3 session of IHD done	12 days	Improved At 2 months - normal renal function, no peripheral MAHA
15/ female	Snake envenomation	TMA and AKI	TMA (III, 2C)	1.5×	2=2 daily	75/25 - FFP/5% albumin	Anti-venom and 2 session of IHD done	8 days	Improved At 1 month - normal renal function, no peripheral MAHA

ADEM = Acute disseminated encephalomyelitis, TPE = Therapeutic plasma exchange, ASFA = American Society for Apheresis, AD = Alternative day, FFP = Fresh frozen plasma, MP = Methyl prednisolone, IVIg = Intravenous immunoglobulin, CR = Completely recovered, APLA = Antiphospholipid antibody, LN = Lupus nephritis, PRES = Posterior reversible encephalopathy syndrome, HLH = Hemophagocytic lymphohistiocytosis, CNS = Central nervous system, MAS = Macrophage activation syndrome, MMF = Mycophenolate mofetil, PR = Partially recovered, MODS = Multi organ dysfunction syndrome, AKI = Acute kidney injury, ALI = Acute lung injury, IPD = Intermittent peritoneal dialysis, CVVHDF = Continuous veno-venous hemodiafiltration, SLED = Slow and low efficiency dialysis, IHD = Intermittent hemodialysis, MAHA = Microangiopathic hemolytic anemia, TMA = Thrombotic microangiopathy

or intermittent hemodialysis or intermittent peritoneal dialysis (IPD) for acute kidney injury (AKI), anti-snake venom for snake bite envenomation, and immunosuppression/immunomodulatory agents for immunological and neurological disease) along with plasma exchange for the diseases mentioned. Plasma exchange was given as adjunctive treatment in view of the very sick status of our patients in ICU.

Acute disseminated encephalomyelitis and acute neuromyelitis optica

Three patients (ADEM, n = 2 and acute neuromyelitis optica [NMO], n = 1) [Case no. 1–3 in Table 1] were treated with intravenous (IV) methylprednisolone 30 mg/kg/day for 3–5 days followed by oral steroid for 1 month then tapering and a course of IV immunoglobulin (IvIg) 0.4 mg/kg/day for 5 doses. The second course of IvIg was given in NMO patient in view of poor response to the first course. Plasma exchange 5–6 cycles [Table 1] was done as adjunctive therapy as these patients did not show much improvement with steroid and IvIg. After TPE, both ADEM patients improved, but patient with NMO expired in view of enterobacteriaceae sepsis secondary to hospital-acquired pneumonia though he showed neurological improvement with treatment. The oral steroid was stopped after 15 days of treatment in the later in view of sepsis.

Severe systemic lupus erythematosus

Catastrophic antiphospholipid antibody syndrome (APLA) secondary to systemic lupus erythematosus

The child with systemic lupus erythematosus (SLE) had features of catastrophic APLA (life-threatening bilateral renal infarcts, mesenteric ischemia, deep vein thrombosis (DVT) of legs and laboratory evidence of positive lupus anticoagulant and anti-cardiolipin IgG and IgM) and renal biopsy-proven class IV lupus nephritis [Case no. 4 in Table 1]. She was treated with pulse IV steroid 15 mg/kg/day for 3 days followed by oral steroid 1 mg/kg/day for a month and further tapering along with pulse IV cyclophosphamide 15 mg/kg once every 15 days for 3 months. Oral anti-coagulant was given. She received 4 plasma exchanges in view of catastrophic APLA along with above treatment; further, TPE was not continued as she showed symptomatic improvement and resolution of DVT on Doppler ultrasonography. After 3 months of follow-up, she showed clinical and laboratory remission (anti-cardiolipin and lupus anticoagulant became negative, bland urine, normal serum creatinine, and albumin).

Central nervous system lupus and hemophagocytic lymphohistiocytosis

A 16-year-old girl had features of renal and extrarenal features of lupus [Case no. 5 in Table 1]. She had optic neuritis and features of posterior reversible encephalopathy, also had features of HLH or MAS (fever, splenomegaly, pancytopenia, high ferritin, high triglyceride, and bone marrow evidence of hemophagocytosis). She was given standard treatment with steroid and mycophenolate mofetil (MMF) 1.5 g/day. Furthermore, she received rituximab 600 mg 2 doses 2 weeks apart for the severe nature of the illness along with three daily plasma exchanges. TPE was not continued further as she was not affordable, but she showed clinical improvement with above treatment. Renal biopsy was not done for the same reason. After 2 months of treatment, her neurological status showed

some improvement (higher mental functions improved, but vision difficulty was there) and there was complete resolution of HLH. Renal wise, she was in partial remission.

Severe hemophagocytic lymphohistiocytosis or macrophage activation syndrome

A 13-year-old boy had renal biopsy-proven class IV lupus nephritis with severe HLH [Case no. 6 in Table 1]. He was treated with IV cyclosporine 8 mg/kg/day for 3 days in view of severe HLH, also with plasma exchange. With five TPE, he showed improvement in HLH, further standard treatment with steroid and cyclophosphamide was given. At 2 months follow-up, he showed complete resolution from HLH with partial remission status in lupus nephritis.

Severe sepsis with hemophagocytic lymphohistiocytosis and multi-organ dysfunction syndrome

A 3-year-boy had severe dengue with multi-organ dysfunction syndrome (MODS) – AKI stage III, acute respiratory distress syndrome [Case no. 7 in Table 1]. He was given IPD for 4 days initially for AKI and other supportive treatment were carried out. As he did not improve with that modality, he was changed to CVVHDF, effluent dose 30 ml/kg/h, which was continued for 3 more days. Furthermore, he had secondary klebsiella pneumoniae blood infection, Aspergillus peritonitis (secondary to IPD catheter) for which appropriate antibacterial and antifungal was added. CVVHDF was changed to intermittent slow and low-efficiency dialysis (SLED) for 4 alternative days then. He received 4 alternative days TPE post SLED for the picture of HLH and severe sepsis. He showed improvement and discharged after all above multi-disciplinary care.

With the above experience, we tried plasma exchange for other 15-year-old boy with severe dengue sepsis with encephalitis and MODS (renal, liver, and lung injury) [Case no. 8 in Table 1]. He received one session of plasma exchange along with CVVHDF. He succumbed to his illness within 72 h of admission as his PRISM[11] (Pediatric RISk of Mortality score = 35) at admission was high.

Snake envenomation with thrombotic microangiopathy

Two children with snake bite envenomation had AKI for which dialysis was given and also had TMA picture (low hemoglobin, low platelet, high lactate dehydrogenase, numerous schistocytes on peripheral blood smear and normal coagulative parameters) for which TPE was administered [Case no. 9 and 10 in Table 1]. Anti-venom was given along with supportive care. Renal biopsy was not carried out in view of low platelet counts in these two patients, and they showed tremendous improvement after plasma exchange, dialysis, and anti-venom within 7–10 days period.

Complication and outcome

The mean duration of stay in hospital was 17.2 days (range 3–40 days), and follow-up was 78 days (range 3–180 days) with the majority of children (8/10, 80%) survived from the catastrophic illness at the time of discharge. Two children (2/10, 20%) (MODS secondary to severe dengue sepsis/encephalitis [n = 1] and acute NMO [n = 1]) succumbed due to the disease *per se* in earlier (high PRISM score at admission) and enterobacteriaceae sepsis (hospital-acquired pneumonia) in later.

One patient (n = 1, 10%) had an allergic reaction, and one (n = 1, 10%) had hypokalemia during or after the procedure whom were managed appropriately. Two patients (Case no. 3 and 7) had secondary infection during illness, these could not be ascertained only to TPE usage as other risk factors such as prolonged stay in ICU, treatment with immunosuppressive agents, the source of infection such as ventilator, P.D catheter, and others were present. None of our children had hypocalcemia (as prophylactic calcium was given to all as part of our protocol), coagulopathy worsening, and hypotension secondary to the procedure.

Discussion

The clinical utility of plasma exchange has been increasing recently for various renal and nonrenal diseases. The ASFA classifies the indications of plasma exchange in to four categories (Category I: standard and accepted as first-line therapy; Category II: Generally accepted, supportive to other therapies; Category III: optimum role is not established, individualized usage; Category IV: available controlled trials have shown the lack of therapeutic efficacy) and two grades (Grade 1: strong recommendation; Grade 2: week recommendation; A, B, and C in each: high, moderate and low quality evidence, respectively) based on the level of evidence available.[2] 14 new diseases are included in the indications for TPE in ASFA 2016 guidelines[2] when compared to 2013 issue.[12] This clearly shows the increased utility of TPE in clinical practice that a nephrologist should be aware of as TPE is exclusively offered by department of nephrology in most of the centers in India. Especially in ICU, TPE has gained its role as complementary to other treatment. We have provided TPE for 3 pediatric patients with aHUS, a common indication for TPE in that age group (Category I in Factor H antibodies and III in complement gene mutations as per ASFA 2016 guidelines[2]) during the 1-year study period as like in few earlier Indian reports.[5,6] However, interestingly, we came across TPE usage in

paediatric ICU for category II and III non renal diseases (as per ASFA) within this short 1 year period; hence, we intend to describe our experience for enlightening the usage of TPE in various nonrenal settings.

Acute disseminated encephalomyelitis and acute neuromyelitis optica

TPE therapy in both ADEM (Case No. 1 and 2) and NMO (Case No. 3) is described as category II indication and graded as 2C in the former, 1B in the later.[2] In our case series, two patients with ADEM (Case no. 1 and 2) did not show much improvement with standard therapy (steroid and IvIg); hence, TPE was offered and they showed tremendous improvement after TPE. ADEM is an acute inflammatory demyelinating central nervous system (CNS) illness which generally occurs after a viral or bacterial infection, or vaccination.[13] The pathogenesis is believed to be the activation of an autoimmune response against myelin oligodendrocyte glycoprotein secondary to infection where viral or bacterial epitopes resembling neuronal antigens have the capacity to activate myelin-reactive T-cell clones through molecular mimicry.[13] There have been no randomized control trials (RCTs) available for treatment of ADEM, evidences so far is based on case series and reports. TPE is offered after standard steroid therapy in most of the case series. There are only few case reports in regarding the usage of TPE in ADEM from India.[14] The therapeutic aim is to abbreviate the CNS inflammatory reaction by anti-inflammatory agents such as steroid and IvIg. TPE works by removing pathogenic autoantibodies against myelin oligodendrocyte glycoprotein in ADEM.[15]

Like ADEM, NMO is also an acute inflammatory demyelinating CNS illness predominately involving optical nerve. Autoantibody (NMO-IgG) against aquaporin-4, the principal water channel on astrocyte foot processes at blood-brain barrier, is pathogenic in NMO.[16] Hence TPE has a role in the treatment by removing the offending antibody. A number of case series and reports have shown TPE benefits in corticosteroid-refractory NMO which are given in details in ASFA 2016 update.[2] TPE added to pulsed IV corticosteroids was more effective than pulsed IV corticosteroids in NMO patients having predominant optic neuritis in a nonrandomized control study by Merle *et al*.[17] TPE was planned after sluggish response with initial treatment such as steroid and two cycles of IvIg in our patient (Case no. 3). Although our patient showed the signs of neurological improvement from TPE in acute NMO, he expired unfortunately secondary to hospital-acquired infection.

Severe systemic lupus erythematosus

In Catastrophic APLA (Case No. 4), indication to start TPE is categorized as II, 2C.[2] It is a hypercoagulable state, defined as the acute onset of multiple thromboses in at least three organ systems (our patient had bilateral renal infarcts, mesenteric ischemia, and DVT of legs) in patients with antiphospholipid antibodies.[18] In addition, systemic inflammatory response syndrome is commonly found.[18] Furthermore, our patient had features of SLE along with renal biopsy-proven Class IV lupus nephritis. This patient could be having catastrophic APLA secondary to SLE. Hence, she was treated with the standard protocol (steroid plus cyclophosphamide pulse) for SLE along with TPE and anticoagulation for catastrophic APLA. Steroid and cyclophosphamide were aimed to control inflammation and lupus activity; TPE was planned in view of renal infarcts and mesenteric ischemia. The patient showed improvement in 3 months follow up visit. The benefit of TPE in Catastrophic APLA is not clear, but it has a role in removing antiphospholipid antibodies and inflammatory milieu (cytokines, tumor necrosis factor-α, complement).[19,20] Furthermore, TPE is helpful in removing pathogenic autoantibodies and immune complexes of SLE[20] (which could have triggered catastrophic APLA in our case).

In another patient with CNS lupus and HLH/MAS (Case No. 5), TPE was found to be beneficial apart from standard lupus treatment (steroid, MMF, and rituximab). TPE usage is categorized and graded as II, 2C for CNS lupus[2] and III, 2C for HLH/MAS secondary to SLE.[2] Rationale for TPE in severe lupus cerebritis is to remove pathogenic autoantibodies (such as anti-neuronal, anti-ribosomal-P and others), and inflammatory cytokines.[21] A review of 26 patients with CNS lupus by Neuwelt who were treated with TPE or TPE/cyclophosphamide revealed that 74% of patients improved, 13% of patients stabilized, and 13% of patients progressed.[21] This result highlighted a potential benefit for TPE in refractory or critically ill SLE patients. HLH or MAS is an immune-mediated life-threatening disease that causes acute cytokine storm which damages vital organs.[22] The basis of treatment of HLH is to eliminate the trigger (treatment of SLE with steroid, MMF and Rituximab in Case no. 5 and steroid and cyclophosphamide in Case no. 6) and the suppression of inflammatory response with immunosuppressive and cytotoxic drugs[22] (steroids in Case no. 5 and 6, cyclosporine in Case no. 6). The role of TPE in HLH is to supress the hyper inflammatory state or cytokine storm to facilitate recovery from organ damage apart from standard therapy.[22,23] There are no large controlled trials to support TPE usage in HLH. There is only one controlled trial in children by Demirkol *et al*. where 23 patients with hyperferritinemia and secondary HLH/sepsis/MODS/MAS treated with TPE and methylprednisolone or IVIG therapy (n = 17, survival 100%) was associated with improved survival compared to TPE and dexamethasone and/or

cyclosporine and/or etoposide (n = 6, survival 50%) (P = 0.002).[24] In case series and case reports of adult patients with secondary HLH to cancer, autoimmune disease and infection by Ramos-Casals *et al*., TPE had a survival rate of nearly 77% (20/26; survival of patients with cancer 9/10, autoimmune disease 6/8, infection 5/7, and idiopathic 0/1).[23] These reports clearly demonstrate the potential benefit of TPE in dreadful disease HLH. In our patients (Case no. 5 and 6), TPE was considered along with standard treatment of SLE in view of critical nature of the disease at presentation, and they showed improvement with above treatment.

Severe sepsis with hemophagocytic lymphohistiocytosis and multi-organ dysfunction syndrome

In severe sepsis with MODS, indication for TPE is categorized as III, 2B and in HLH as Category III, Grade 2C.[2] We all know that sepsis is the most common cause of death in noncoronary ICU. Hence, sepsis requires multidisciplinary treatment including source control, effective antimicrobials, hemodynamic support, and ventilatory care. TPE is postulated to improve organ function by removing inflammatory and antifibrinolytic mediators and to restore hemostasis by replenishing anticoagulant proteins and ADAMTS13.[25,26] Observational studies such as case series, retrospective cohorts showed a beneficial effect of TPE in improving survival in sepsis whereas reports from prospective randomized studies have been conflicting. One RCT of septic paediatric patients by Nguyen *et al*. showed significant improved 28-day survival in TPE group compared to standard treatment.[26] Other RCT by Reeves *et al*. involving both adult and children with sepsis did not show the difference in mortality between TPE and standard treatment for sepsis.[27] The largest RCT in 106 adult septic patients by Busund *et al*. impressed to have a 28-day mortality rate of 33% in TPE group and 53.8% in control ($P < 0.05$).[28] In a meta-analysis by Rimmer *et al*., there was no association with significant reduction of overall mortality in TPE, but on sub group analysis, adult patients (not pediatric) was found to have associated with decreased mortality, suggesting a relatively high likelihood of bias in terms of enrolment criteria.[29] Another meta-analysis by Zhou *et al*. that encompassed all of blood purification techniques, including hemofiltration, hemoperfusion, and TPE found decreased mortality making it difficult to draw conclusions for the benefit of TPE alone.[30] There are conflicting results for the benefit of TPE in sepsis from the evidence so far available. In one of our patient (Case no. 7), TPE was administered as a complementary treatment along with standard care in view of HLH/MODS secondary to severe sepsis as the child was very sick on the course of hospital stay and finally he improved with the treatment given. However, unfortunately, the other patient (Case no. 8) with severe sepsis and MODS expired within 72 h of treatment in view of critical nature of his illness at presentation itself.

Snake envenomation with thrombotic microangiopathy

Although there is no consensus opinion of snake bite causing TMA and TPE is helpful in the situation, we observe such association and also TPE is found to be useful. Hence, we intend to mention the disputed TMA picture caused by snake bite and role of TPE in snake envenomation elaborately.

Snakebite causes venom-induced consumption coagulopathy (VICC) by the activation of coagulation cascade.[31] Proposed mechanism of snakebite leading in to TMA like picture (microangiopathic hemolytic anemia (MAHA) and thrombocytopenia without related to VICC or DIC) is by direct venom-induced endothelial injury by activation of von-Willebrand factor (vWF) and vascular endothelial growth factor;[32] and enhanced polymerization of vWF secondary to depletion of ADAMTS-13.[33] In 2007 ASFA guidelines, there was no mention of TPE role in snake envenomation, but in later 2010 update and further guidelines (2013, 2016 updates) described its usage and categorized as III, 2C[2,12] based on the evidences published in 2006 and later on. Rationale for TPE usage is like any other toxin removal, it has the capacity to eliminate protein-bound toxins (snake venom in our scenario) after redistribution in to blood compartment, to remove inflammatory and coagulopathic storms and able to replace depleting factors such as ADAMTS 13 thus improves in microangiopathy and coagulopathy caused by snake venom.[34] There is no controlled trial showing the benefit of TPE in snake envenomation and evidence obtained so far is from case reports and case series. There are numerous reports of snake bite causing AKI and TMA from Sri Lanka[35-37] and Australia,[38-40] and successfully treated with hemodialysis and TPE as like in our two patients (Case no. 9 and 10). Pantanowitz and Andrzejewski in his review explored the possible role of TPE in snake envenomation from various case reports published earlier.[34] Two largest case series published in 2006[41] and 2013[42] from Turkey showed the complementary effect of early TPE in the management of hematologic problems and in limb preservation/salvage strategies secondary to snake bite among 16 and 37 patients, respectively. There are two reports of snake bite induced TMA from India in early 1986[43] and recently in 2017.[44] In the later report from India, TPE was tried for one patient with TMA who showed improvement with the treatment.[44] In our two patients (Case no. 9 and 10), there was no evidence of DIC. They had AKI and TMA for which

hemodialysis and TPE was given, respectively and showed accelerated clinical recovery from renal and hematological issues. Hence, the possibility of TMA should be considered in snakebite patients presenting with AKI, thrombocytopenia, MAHA, and normal coagulation. Prompt diagnosis and early treatment with plasmapheresis may improve the clinical outcome in snake envenomation.

The study was retrospective in nature, carried out in a single center. It was not controlled to show the effectiveness of complementary TPE therapy along with standard treatment. However, all our pediatric patients were very sick which forced us to administer TPE in those conditions. We did not observe any major side effects of TPE as prophylactic strategies like calcium infusion and others had been carried out as part of our protocol and were done with strict monitoring under the care of a trained paramedics and doctors in ICU. There is the lack of RCTs in most of the indications mentioned in our study; hence, it requires more evidence-based approaches to standardize care and also to provide a platform for innovation to move the field forward.

Conclusion

This is a small comprehensive study of pediatric TPE in an intensive care setting in 1 year period describing clinical outcomes, especially in nonrenal indications that a nephrologist should be aware of. Nonetheless, plasma exchange therapies are becoming increasingly essential in critical care settings, with a wide and widening spectrum of indications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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