RESEARCH PAPER

Therapeutic Plasma Exchange in Children – Experience From a Tertiary Care Center

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Objective: To assess the safety, efficacy and outcomes of therapeutic plasma exchange (TPE) in children. **Methods**: Data were retrieved from hospital records for all children ≤18 years who underwent TPE between August, 2011 and July, 2018. **Results**: 46 children [median (range) age 96 (8-204) months] underwent 293 sessions of TPE by membrane plasma separation technique. Renal disease was the commonest indication (24, 52.2%) followed by neurological illnesses (17; 36.9%). 36 (78.2%) patients belonged to American Society for Apheresis category I. Overall, the most common indication was atypical hemolytic uremic syndrome (aHUS) (16; 34.8%). Fresh frozen plasma plus albumin was used as replacement fluid in aHUS, while albumin was used in others. 40 (86.9%) patients had complete/partial recovery while six did not show any sign of recovery. Complications were seen in 21 (7.1%) sessions; majority of which were minor in the form of blood pressure fluctuations. **Conclusion**: TPE can be performed safely and effectively for renal and non-renal indications, even in small children.

Keywords: *Atypical hemolytic uremic syndrome, Neurological indications, Plasmapheresis*

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Therapeutic plasma exchange (TPE) has become increasingly popular and effective therapy for many renal and immunological diseases and has proved to be life-saving in certain conditions [1-3]. TPE is a procedure where a part of the plasma of an individual is removed by an extracorporeal procedure and replaced with either fresh frozen plasma (FFP) or albumin, retaining the cellular component of the blood while removing pathogenic circulating antibodies, immune complexes, cytokines and toxins [4]. In addition, it can replace a deficient molecule such as complement factor H (CFH) in atypical hemolytic uremic syndrome (aHUS) [5]. Although the principles of TPE are the same in adults and children, there are technical differences unique to children such as poor vascular access and high volume of distribution [4,6].

The American Society for Apheresis (ASFA) has assigned disease conditions to one of four categories based on the quality of published evidence and strength of recommendation for TPE. The recommendations are mainly based on adult studies and do not distinguish between childhood and adult-onset diseases [7]. The literature on TPE for children is mostly limited to single-center, retrospective studies, hence, the recommendations for TPE are usually extrapolated from adult studies [1-2,4].

The primary objective of this study was to review the indications and technical details of cohort of children treated with TPE at our center. The efficacy of the treatment was also studied for individual diseases and different ASFA categories along with the complications related to the procedure.

METHODS

We conducted a review of hospital records of children ≤18 years, who underwent TPE at our institution between August, 2011 and July, 2018. The study was approved by the institutional ethics committee and informed consent was waived. Data were collected from the hospital medical records, which included indications, technical details of procedure and complications. Indications were catego-rized into renal, neurological and others, and also as per ASFA guidelines [8].

Decision for TPE was taken by the pediatric nephrologist based on the indications. All procedures were performed according to the hospital protocol by pediatric renal nurses and technicians, along with pediatric nephrologist in the pediatric intensive care unit (PICU). Appropriate site for venous access was selected as per the age of the patient. Size of the membrane filter was selected and exchange volumes were calculated. Procedure was performed by membrane filtration technique using Fresenius 4008S dialysis machine (Fresenius Kabi). Anticoagulation was done with heparin.

The outcome was measured at the time of discharge as complete response, partial response and absent response. Efficacy of the treatment was defined according to the

underlying pathology and assessed using the criteria published by Paglialonga, et al. [9]. Complications encountered related to the treatment were evaluated and categorized as access-related complications and proce-dure-related complications.

RESULTS

During the study period, 293 procedures were performed in 46 patients [30 males; median (range) 96 (8-204) months]. The demographic characteristics and technical details of the procedure are presented in **Table I**. Three children were younger than two years and weighed <10 kg. Most common access used was femoral vein (25; 54.3%). The median (range) TPE sessions per patient was 5 (1-21).

Renal disease was the commonest indication for TPE (24; 52.2%) followed by neurological illness (17; 36.9%). Also, majority of the sessions were performed for renal indications (197; 67.2%). The most common diagnosis was aHUS (16; 34.8%) accounting for 153 sessions. The indications for TPE and ASFA categories are shown in **Table II**. Maximum indications belonged to ASFA category I (36; 78.2%), while none to category IV. Median (range) duration of initiation of TPE from onset of symptoms was 12 (1-60) days.

Amongst 36 patients in ASFA category I, 22 (61.1%) had complete recovery, 12 (33.3%) had partial recovery and 2 (5.6%) showed no sign of recovery (**Table II**). ASFA category I was found to have significantly better recovery than category III (P=0.004). No significant difference was found between other groups.

Complications were seen in 21 (7.1%) sessions. Two cases of catheter-related bloodstream infection along with access thrombosis were seen. They recovered following relocation of the venous access and intravenous antibiotics. Among the procedure-related complications, hypertension (n=3) was self-resolving and required no additional treatment. For hypotension (n=4), transient stopping of diuretic and fluid resuscitation was required in one case. Among serious complications, one patient developed pulmonary edema, which resolved with diuretics but required discontinuation of the procedure. The second patient had seizures, likely due to clearance of anti-epileptic drugs, requiring an extra dose. There were no deaths or chronic sequelae directly related to TPE; however, two patients died due to the underlying disease.

DISCUSSION

In the current study, the commonest indication for TPE were renal (52%) and neurological (37%), which is consistent with previous reports [5,9]. However, the most common indications in the World apheresis registry were neurological disorders [10]. The difference in indications of TPE is likely due to difference in each centers' specific subspecialties, center-specific patient selection criteria and classifications [5].

The number of patients classified in ASFA category I or II was higher than other reported studies. Two recent analyses from developed countries reported 56.7% and 61% of the patients in category I or II [9,5]. A large analysis performed in US reported under-utilization of TPE with only 13.4% patients with ASFA category I receiving TPE [3]. This difference could be due to better adherence to the ASFA guidelines at our center and early referral for TPE. Moreover, due to non-availability of eculizumab in India, aHUS patients are primarily being managed with TPE.

Majority of adult centers in India prefer centrifugal methods [11], while pediatric centers use membrane filtration methods [12]. In contrast, centrifugal method is the most common apheretic procedure both in pediatrics and adults in the USA [3]. For the substitution fluid used, similar findings were reported by Paglialonga, et al. [9] with indication being the deciding factor for type of replacement fluid. However, Sinha, et al. [12] reported FFP alone to be the most common replacement fluid. For anticoagulation, heparin was used solely by us, while citrate was the most common documented anticoagulant in the World Apheresis Registry [10].

Overall, 86.9% patients showed either complete/partial recovery. The highest recovery rates were seen for renal (91.6%) disorders in our cohort. On the contrary, only 64% patients with renal disorders recovered in a previous study [5]. Our response rate in neurological disorders is also better than in the European survey, where only 55.5% had a full/partial recovery [9]. Higher overall response in our study may be due to the larger proportion of aHUS patients, majority

Table I Demographic Profile of Patients and Details of Therapeutic Plasma Exchange

Characteristics	*Value*
Weight (kg)[a]	23.2 (17.8-35)
Duration of hospital stay (d)[a]	33.5 (18-51)
Vascular access	
Femoral vein	25 (54.3)
Internal jugular vein	16 (34.8)
Both	5 (10.9)
Sessions per patient	5 (4- 6)
Exchange volume 60 mL/kg[b]	25 (54.3)
Filter membrane surface area 0.6 sq.m[c]	35 (76.1)
Replacement fluid	
Albumin + normal saline	30 (65.2)
Albumin + fresh frozen plasma	16 (34.8)

Data presented as no. (%) or [a]median (IQR). [b]40 mL/kg exchange volume was used in the rest; [c]0.3 sq.m membrane used in the rest.

Table II Indications and Outcomes of Therapeutic Plasma Exchange in Children as per ASFA category (*N*=46)

Clinical diagnosis	*N (%)*	*No. of sessions, n=293*	*ASFA category*	*Recovery*		
				CR n=25	*PR n=15*	*NR n=6*
Renal	24 (52.2)	197 (67.2)		16 (66.7)	6 (25)	2 (8.3)
Atypical HUS						
Anti CFH +ve	11	117	1	10 (90.9)	1 (9.1)	0
Anti CFH –ve[a]	5	36	1	3 (60)	2 (40)	0
FSGS						
Steroid resistant (native kidney)	1 (2.2)	5	III	0	0	1 (33.3)
Post renal transplant recurrence	1 (2.2)	4	I	0	1 (33.3)	0
Pre renal transplant FSGS	1 (2.2)	5	NC	1 (33.3)	0	0
Antibody mediated rejection	1 (2.2)	6	I	0	1 (100)	0
ANCA associated vasculitis	2 (4.4)	11	I	1 (50)	0	1 (50)
ABOi renal pre-transplant desensitization	1 (2.2)	2	I	1 (100)	0	0
Anti GBM antibody nephritis	1 (2.2)	11	III	0	1 (100)	0
Neurological	17 (36.9)	85 (29)		7 (41.2)	8 (47)	2 (11.8)
Autoimmune encephalitis	13 (28.3)	65	I	7 (53.8)	6 (46.2)	0
Guillain-Barre syndrome	2 (4.4)	10	I	0	1 (50)	1 (50)
Fulminant SSPE	1 (2.2)	3	NC	0	0	1 (100)
ADEM	1 (2.2)	7	II	0	1 (100)	0
Others	5 (10.9)	11 (3.8)		2 (40)	1 (20)	2 (40)
Methemoglobinemia	2 (4.4)	7	III	1 (50)	0	1 (50)
Hepatic encephalopathy	1 (2.2)	1	III	0	1 (100)	0
Autoimmune hemolytic anemia	1 (2.2)	2	III	1 (100)	0	0
Sepsis MODS	1 (2.2)	1	III	0	0	1 (100)

Data in no. (%). [a]Considered in category I as mutation analysis not done. CR, complete recovery; PR, partial recovery; NR, no recovery; HUS, hemolytic uremic syndrome; CFH, complement factor H; FSGS, focal segmental glomerulosclerosis; ANCA, anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; SSPE, subacute sclerosing pan encephalitis; ADEM, Acute disseminated encephalomyelitis; MODS, multi organ dysfunction syndrome; NC, not classified; TPE, therapeutic plasma exchange; ABOi, ABO incompatible

having anti-CFH antibody, who showed good response to TPE. Other pediatric studies from India have shown a variable response in aHUS ranging from 27-87.5% [12-15]. We found significantly better response of ASFA category I patients to TPE than category III patients. But others have reported no such association [9]. However, the recovery in these patients could not be attributed solely to TPE as 63% of our patients received concomitant immunosuppression also. We observed complications in 7.1% of TPE sessions, which is comparable to previously published reports from India and abroad [5,9,12,15]. Previously reported adverse event rate is 4-10% [10,16]. Despite the presence of many young children in our cohort, no increase in complication was noted in this group. This finding further confirms the safety of TPE in small children.

The major limitations of the study are its retrospective design, relatively small number of patients per indication, and the fact that it is a single-center analysis. Moreover, there was a lack of genetic testing in children with aHUS without anti-CFH antibodies. Nevertheless, this work adds to the limited data available on TPE use in Indian children.

In conclusion, TPE is an effective therapeutic modality with minimal complications in pediatric renal and non-renal disorders. It is safe, even in small children, in well-equipped settings.

Ethical clearance: Ethics committee, Sir Ganga Ram Hospital; No. EC/08/18/1415 dated August 30, 2018.
Contributors: RM: designing of study, data collection, analysis, drafting the manuscript, approval of the final version; KA, PKP: conception and designing of study, analysis, revision of manuscript, approval of the final version. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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