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

Pediatrik Nefroloji Hastalarında Plazma Değişimi Endikasyonları ve Sonuçlarının Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

OBJECTIVE: Therapeutic plasma exchange (TPE) has been used in many diseases as primary or adjunctive therapy. We present our TPE experience in a pediatric nephrology practice setting.

MATERIAL and METHODS: We retrospectively evaluated the indications and outcomes of TPE performed between 2008-2013 on the basis of the 2013 American Society for Apheresis Guidelines.

RESULTS: One hundred and sixteen TPEs were performed in 15 patients (6 male / 9 female, mean age 12.9±3.5 years). The indications were hemolytic uremic syndrome (HUS) in 7 (four atypical) patients, pre-transplant TPE in 3 patients with focal segmental glomerulosclerosis (FSGS), treatment-resistant membranoproliferative glomerulonephritis (MPGN) in 1 patient, antibody mediated rejection (AMR) in 3 patients, and thrombotic microangiopathy (TMA) in 1 renal transplantation patient. Six months after TPE, hypertension persisted in two of seven and proteinuria in three of seven HUS patients, although all HUS patients had normal creatinine levels. Similarly, serum creatinine and urinary protein excretion were within the normal range in all FSGS patients and in one patient with AMR. Thrombocytopenia and anemia resolved and the blood creatinine level decreased in a patient with TMA.

CONCLUSION: Although adherence to adult TPE guideline indications is around 50%, treatment results of TPE are satisfactory in 2/3 of our pediatric nephrology patients. Pediatric TPE Guidelines based on pediatric evidence-based data will help achieve better clinical outcomes in children.

KEY WORDS: Plasmapheresis, Nephrology, Pediatric

ÖZ

AMAÇ: Tedavi amaçlı plazma değişimi (TPD) birçok hastalıkta, primer veya destek tedavisi olarak uygulanmaktadır. Çalışmada, merkezimizde izlenen çocuk nefroloji hastalarında TPD tedavisinin sonuçlarının değerlendirilmesi amaçlanmıştır.

GEREÇ ve YÖNTEMLER: Merkezimizde 2008-2013 yılları arasında TPD uygulanan 15 pediatrik nefroloji hastasında endikasyonlar ve tedavi sonuçları, 2013-Amerika Aferez Derneği (ASFA) kılavuzu eşliğinde değerlendirildi.

BULGULAR: Hastaların (K/E: 9/6) yaş ortalaması 12,9±3,5 (6-17) yıl idi. Yedi hastaya hemolitik üremik sendrom (HÜS), fokal segmental glomuloskleroz (FSGS) tanısı olan üç hastaya böbrek nakli öncesi, bir hastaya membranoproliferatif glomerulonefrit (MPGN), üç böbrek nakil hastasına antikor aracılı rejeksiyon(AAR) ve bir nakil hastasına ise trombotik mikroanjiopati (TMA) endikasyonuyla 116 seans TPD uygulandı. HÜS tanılı hastaların dördü atipik HÜS olarak değerlendirildi. İzlemde HÜS tanılı hastalarının 2/7'sinde hipertansiyon ve 3/7'sinde proteinüri sebat ederken, 6 ay sonraki değerlendirmede, kan kreatinin düzeyleri normaldi. Benzer şekilde, tüm FSGS hastalarında serum kreatinin ve idrarda protein atılımı normal sınırlarda idi. AAR tanısı olan bir hastada TPD'e yanıt alındı. Trombotik mikroanjiopatili hastada TPE sonrası trombositopeni ve anemide düzelme, kreatinin değerinde azalma sağlandı.

SONUÇ: Erişkin kılavuzlarındaki TPD endikasyonları pediatrik hastalarımıza uyarlandığında, yarısında uygun endikasyonla TPD yapıldığı görülmekle birlikte, hastalarımızın 2/3'ünde TPD ile tedavide başarı sağlanmıştır. Pediatrik kanıta dayalı veriler temel alınarak hazırlanacak pediatrik kılavuzlarla daha iyi klinik sonuçlara ulaşılacağı düşünülmektedir.

ANAHTAR SÖZCÜKLER: Plazmaferez, Nefroloji, Pediatrik

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INTRODUCTION

Therapeutic plasma exchange (TPE) can be applied as a treatment option in many conditions such as hematological, neurological, nephrological and autoimmune/rheumatic disorders (1,2). Therapeutic plasma exchange is capable of removing toxins, pathological antibodies, toxic medications, and beneficial clotting factors. The removed plasma is replaced by 5% albumin and/or 0.9% saline, fresh-frozen plasma (FFP) (3). The American Society for Apheresis (ASFA) guidelines published in 2013 re-defined the indications for TPE in four categories (4). Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary stand alone treatment or in conjunction with other modes of treatment. Example: Guillain-Barre syndrome, focal segmental glomerulosclerosis (FSGS) recurrent in transplanted kidney, atypical Hemolytic Uremic Syndrome (HUS) with factor H antibodies, Anti-glomerular basement membrane disease (Goodpasture's syndrome), Anti-neutrophil cytoplasmic antibodies (ANCA)-associated rapidly progressive glomerulonephritis and antibody mediated rejection. Catogory II: Disorders for which apheresis is accepted as second-line therapy, either as a stand alone treatment or in conjunction with other modes of treatment. Example: Acute disseminated encephalomyelitis, atypical HUS with complement mutations. Category III: Optimum role of apheresis therapy is not established. Decision making should be individualized. Example: Extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multi-organ failure. Category IV: Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. Example: membrane co-factor protein (MCP) mutations.

Hemolytic uremic syndrome is a leading clinical indication for plasmapheresis in pediatric nephrological diseases. HUS has various forms including the Streptococcus pneumoniae-associated HUS, Shiga toxin (Stx) producing Escherichia coli (STEC)-associated HUS, cobalamin C (cblC) defect-associated HUS, and atypical HUS. In patients who enjoy full remission and normal renal function under TPE there is no reason to change the TPE therapy. In children who have commenced TPE as first-line therapy during the acute phase, it was proposed to switch to complement blockade when the diagnosis of HUS is established (5). Therapeutic plasma exchange does not have any demonstrable therapeutic effect in patients with STEC-associated HUS or Thrombotic thrombocytopenic purpura (TTP)/HUS secondary to malignancy, mitomycin C, allogeneic bone marrow transplantation, or malignant hypertension (6).

Certain renal diseases can be successfully managed by TPE. It is particularly of use in primary AMR in renal transplantation (RTx) and to prevent FSGS recurrence after RTx by removing putative circulating serum factors. Post-transplant nephrotic syndrome and/or FSGS relapse lead to graft loss at a rate of 15-44%, and TPE appears to be an important treatment option (6,7).

In this article, we aimed to evaluate certain TPE characteristics including its therapeutic indications, complications, and the outcome of patients in a pediatric nephrology setting.

PATIENTS and METHODS

We retrospectively evaluated the records of pediatric nephrology patients who underwent TPE between 2008 and 2013 at our center. Demographic features, clinical indications, and disease outcomes were investigated. All TPE procedures were performed at the bedside throughout which all patients were monitored. All adverse events (AE) and complications were recorded. Procedures were conducted by trained apheresis technicians and assisted by hematology and nephrology fellows. Therapeutic plasma exchange was performed with Fresenius Com-Tec instrument in seven patients and with Fresenius Astec204 instrument in eight patients. Central venous catheters were used for vascular access. Clinical data, complications, and procedures details were retrospectively gathered. In all HUS patients, whole blood cell count, serum creatinine level, urinary protein excretion, and Lactate dehydrogenase (LDH) level were monitored where necessary and 6 months after the last session of TPE. Gazi University Ethics Committee approval was obtained.

RESULTS

A total of 116 TPE sessions were performed in 15 patients (6 male,9 female; mean age 12.9±3.5 (6-17) years). The indications were HUS in seven patients (four of whom had atypical HUS), preemptive pre-transplant TPE in three patients with FSGS, treatment-resistant membranoproliferative glomerulonephritis (MPGN) in one patient, AMR in three patients, and thrombotic microangiopathy (TMA) in one renal transplantation recipient (Table I). Therapeutic plasma exchange was committed with 1.5 x plasma volume in 12 patients, with 1x plasma volume in three patients. Fresh-frozen plasma was used in seven HUS patients, one TMA patient, and one MPGN patient. 5-20% albumin solutions were used in the remaining 6 patients.

Daily FFP treatment did not lead to remission in any of the HUS patients, and they underwent TPE. Two HUS patients had high anti-Factor H antibody levels, and these patients were considered in category I according to 2013 ASFA guideline (4) (Table I,II). Another one had heterozygous D263H mutation in the gene of membrane cofactor protein (CD46) , a surface-bound complement regulator protein that degrades both C3b and C4b on host cells (8). This mutation was considered polymorphisms; and therefore she was included in category IVA (4). One patient who had recurrent HUS was accepted as atypical HUS. However, neither genetic nor immunological defect was detected in her complement system. Three patients were treated with Eculizumab (complement C5 inhibitor) and two with Rituximab (anti-CD20 monoclonal antibody) after their TPE sessions, which were ineffective to sustain remission. TPE was stopped earlier in patients treated with Eculizumab (Table II). Creatinine levels were high, ranging from 1.4 to 20 mg/dl, in all HUS

patients at presentation, five of whom required hemodialysis. After a 6-month period of appropriate treatment with biologic agents and/or TPE, creatinine levels returned to normal range in all HUS patients (Table II). However, hypertension persisted in two of seven HUS patients and proteinuria in three of seven HUS patients.

Three FSGS patients taken to PE to prevent- post-RTx FSGS recurrence. These patients had no mutation on podocin or Wilms'Tumor 1 (WT1) gene exon 8 and 9. Serum creatinine and urinary protein excretion of these three patients remained normal 6 months after the terminations of the sessions (Table III).

Renal transplant patients with AMR episodes were treated with TPE and intravenous immunoglobulin (IVIG). They were included in category I according to ASFA 2013 guideline (4). One patient had proteinuria without renal dysfunction, which was dissolved after TPE. The other two patients developed chronic allograft nephropathy (CAN), and they have been undergoing hemodialysis since then (Table III).

Thrombocytopenia and anemia resolved and creatinine level decreased just after TPE in a patient with TMA. However CAN developed after 6 months due to different pathological conditions such as infection, drug toxicity, and chronic disorders (e.g lymphoma) (Table II).

Table I: Application of therapeutic apheresis other than therapeutic plasma exchange.

Diseases	No. patients	No. procedures	Indication Category	Patient number with ESRD after 6 months
Hemolytic Uremic Syndrome (HUS)	3	14	Not defined	
Atypical HUS	4	19	I (two patient) IV (one patient)	
FSGS	3	51	Not defined	
MPGN	1	4	Not defined	
AMR in kidney transplanted patients	3	23	I (three patient)	2
TMA in kidney transplanted patients	1	5	Not defined	1*
Total	15	116		

* Because of other pathological conditions. **ESRD:** End stage renal disease, **FSGS:** Focal segmental glomerulosclerosis, **MPGN:** Membranoproliferative glomerulonephritis, **AMR:** Antibody-mediated rejection, **TMA:** Thrombotic Microangiopathy

Table II: Characteristics of the patients with HUS and TMA.

No	Age (years)	Diagnosis	Mutation / Pathology	ASFA category	TPE session	Pre -cr (mg/dl)	Post cr (>6 month) (mg/dl)	Pre/Post (>6month) Urine protein (mg/m²/hour)	Specific treatments
1	6.0	aHUS	Heterozygous D263H	IV	5	4.40	0.57	35 / 3.5	Eculizumab
2	17.0	HUS			5	20.00	0.60	96 / 13.9	
3	15.0	HUS			5	5.90	0.95	81 / 3.2	Eculizumab
4	11.0	HUS			4	3.30	0.60	42 / 22	
5	6.0	aHUS	Anti-Factor H antibody	I	2	1.40	0.41	28 / 3.2	Eculizumab
6	11.0	aHUS	No mutation, no antibody		8	1.40	0.7	74.5 / 31	Rituximab
7	13.0	aHUS	Anti-Factor H antibody	I	4	3.70	0.70	47 / 3.9	Rituximab
8	14.0	TMA			5	1.60	1.10	20.2 / 15.1	

ASFA: American Society for Apheresis guideline, **TPE:** Therapeutic plasma exchange

Table III: Characteristics of the patients with AMR and glomerulopathy.

No	Age (years)	Diagnosis	Mutation / Pathology	ASFA category	TPE session	Pre -cr (mg/dl)	Post cr (>6 month) (mg/dl)	Pre/Post (>6month) Urine protein (mg/m²/hour)	Specific treatments
1	16.0	AMR	Banf g1,i1,t1-2 v0, ci0,cv0,ptc2 c4d3	I	10	2.00	0.96	57 / 3.8	IVIG
2	14.0	AMR	Banf g0,i2,t0 ah0 ci3,cv0,ptc0 cdd0	I	5	2.70	4.00	167 / 23	IVIG
3	12.0	AMR	Banf t2-3,io,go,vo c4d1	I	8	4.30	6.00	61 / 30	
4	17.0	FSGS	No podocin, WT1 gene (exon 8/9) mutation		16	0.81	0.85	72.9 /3.7	
5	12.0	FSGS	No podocin, WT1 gene (exon 8/9) mutation		8	6.10	0.60	21 / 2.8	
6	12.0	FSGS	No podocin, WT1 gene (exon 8/9) mutation		27	10.80	0.63	270 / 3.9	
7	17.0	MPGN	Type 2		4	2.50	0.57	330 / 110	Immuno-suppressive treatment

IVIG: Intravenous Immunoglubulin, **WT1:** Wilms'Tumor 1

Finally, TPE procedure was discontinued due to side effects in a patient with MPGN. Adverse events including hypertension, tachycardia, pruritus, palpitation, and shivering were seen in two additional patients. None of the patients died from any complication. Enhanced premedication was performed in those individuals to prevent these AEs.

DISCUSSION

Available data on TPE in the pediatric population is not as extensive as that in adults. Lack of clear indications and a definitive treatment regimen as well as the perceived technical difficulty are the main limiting factors for TPE in children. Several clinical studies have been conducted to prove the efficacy of TPE in pediatric patients. Witt (9) and colleagues collected data of 136 children between 2003 and 2007, which showed that the most frequent apheresis modalities were leukopheresis, plasma exchange, and lipid apheresis. De Palo (10) et al. investigated complications and treatment outcomes in 51 patients, while Michon (11) et al. evaluated complications in 186 pediatric patients. A national survey of hemapheresis in Turkey was reported more than 10 years ago (12). It reported data of 869 TPE sessions performed in 21 centers (172 patients). Neurological disorders and TTP/HUS were the most common indications.

We evaluated the indications, efficacy, and complications of TPE in a group of pediatric nephrology patients. Adherence to ASFA guideline was also determined. Hemolytic uremic syndrome is the most common indication for TPE. Atypical HUS has a poor prognosis and it leads to end stage renal disease (ESRD) in approximately 50% of patients. Factor H mutations are the most common causes of atypical HUS (13). Although FFP replacement can be provided in atypical HUS, TPE has been found superior to plasma infusion in terms of survival (14,15). According to ASFA 2013 guideline (4) there is no indication of TPE in Shiga toxin induced HUS (Category IV). However when the etiology is unknown, the justification for urgent TPE can only be made by evaluating the risk of early death, irreversible kidney damage, or risks associated with prolonged disease activity (dialysis, blood transfusion, etc.) (16,17). ASFA 2013 guideline (4) suggests TPE as a first-line

therapy (Category I) in the presence of Factor H antibodies and as a second-line therapy (Category II) in cases with complement gene mutations. However, atypical HUS requires additional medical treatments options like Eculizumab (5), as the case of our patients. Eculizumab should be considered in the presence of any sign of subclinical hemolytic activity or renal TMA (18).

Therapeutic plasma exchange has been increasingly used in AMR in renal transplant recipients, which may cause graft loss due to its hypo- or non-responsiveness to conventional drug therapy in most of the cases (19). Therapeutic plasma exchange can markedly lower the plasma donor-specific antibodies which cause AMR (20). Hence, ASFA 2013 (4) recommends TPE as a first-line therapy for this indication (Category I). Although we chose this treatment modality in biopsy proven AMR in our cases, two of our patients lost their allografts, and both of these patients had serious accompanying viral nephropathy (BK and EBV), which could have been the reason for poor outcomes in these cases. Brown et al (21) showed a graft survival rate of 78% in adult cases with long term (5 year) use of TPE in AMR. Little information is available in the literature regarding the long-term outcome of TPE as a rescue therapy for AMR in the pediatric age group. Also, it is impossible to make a recommendation for TPE in our AMR patients as their number was low.

Focal segmental glomerulosclerosis is more likely to be diagnosed in children and young adults than in adults. Several studies have suggested that preemptive TPE has a beneficial effect for preventing recurrences of FSGS in kidney allografts. The risk of recurrence in a first graft varies between 20% and 50%, with a risk of graft loss of 30-50% (22). A circulating permeability factor is the most commonly suggested pathogenic mechanism, which is probably a non-immunoglobulin low molecular weight protein (23) that can be removed by TPE (24); therefore, TPE may prevent disease recurrence in the pre-transplant or perioperative period in high-risk individuals (25). In a retrospective analysis of 20 patients, a decrease from 67% to 33% in the recurrence rate was reported with preemptive TPE (24). Gohh et al. (26) observed that eight sessions of preemptive TPE decreases the rate of recurrence. TPE appears to be effective in treating recurrent FSGS after kidney transplantation and should be started as soon as possible. Although ASFA 2013 guideline (4) recommended that TPE be indicated only in recurrence after transplantation (Category I), we performed preemptive TPE based on successful results in non-controlled trials (24,26). Podocyte genes should be examined to define genetic causes. In our patients, there were no mutations in podocin (NPHS2) and WT1 gene (exon 8 and 9), Thus, these patients were considered to have a very high risk for developing FSGS recurrence, making preemptive TPE essential, although the absence of the mutation analysis in highly expressed podocyte genes in patients presenting with FSGS limited the rationale of this approach. There is still no recurrence in our cases at two years follow-up.

A retrospective study (27) including 67 children undergoing TPE in 12 European pediatric nephrology units during 2012 showed that 56.7% of the patients in this cohort had an ASFA 2013 guideline category I or II disease. We observed exactly the same rate in our cohort, so that 53% of our patients were in ASFA 2013 guideline category I or II. Although there was no indication (ASFA 2013), we performed the procedure in patients with typical HUS, MPGN, thrombotic microangiopathy, and MCP mutation (n=6; 47%). After a 6-month period of appropriate treatment with/without biologic agents, creatinine levels returned to normal range in four patients with HUS.

The relatively low number of patients and the absence of a control group may have limited the reliability of our results. The analysis of Podocin and WT1 mutation in our patients with FSGS was not enough to exclude genetic variants, that is another limitation in our study.

In conclusion, TPE may be considered a life-saving or organ-saving treatment strategy in certain indications in children. However, these indications are not well defined. When the etiology of HUS is unknown, a decision for an urgent TPE can only be made by evaluating the risks associated with prolonged disease activity. Adherence to adult guideline recommendations for TPE is observed in 50% of pediatric patients with appropriate indications such as aHUS due to anti Factor H antibody positivity, FSGS recurrence, and AMR. Therefore, determining universally acceptable clinical indications and treatment schedules of TPE for children is an absolute necessity.

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