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ORIGINAL RESEARCH

Renal and Patient Outcomes of Therapeutic Plasma Exchange in Nephrology Practice: A Single-Center Experience

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ABSTRACT

Therapeutic plasma exchange (TPE) is an alternative treatment approach for specific conditions in the nephrology field. TPE is utilized for the treatment of ANCA-associated vasculitis, anti-GBM disease, thrombotic microangiopathy syndromes, and acute kidney transplant rejection and as part of desensitization protocols in kidney transplant recipients. However, TPE indications are limited, efficacy remains a topic of debate. With this regard, we aimed to evaluate our clinical outcomes of TPE experience among non-transplant kidney diseases. Data from 36 patients (age 44.19±18.66 years; 20 females) underwent TPE were evaluated retrospectively. The number of TPE sessions, diagnosis, pre- and post-procedure laboratory results, vascular access routes, complications, and treatment responses were recorded retrospectively from the electronic file system. Overall, patients underwent an average of 7.42±3.77 TPE sessions. Vascular access was a central venous catheter for all. TPE indications were vasculitis (n: 10), thrombotic microangiopathy (n: 20), glomerulonephritis unresponsive to treatment (n: 4), and anti-phospholipid syndrome (n: 2). 25 patients required hemodialysis, and the dialysis requirement was resolved in 11 patients at the end of treatment. There were no reported serious adverse events. Regarding renal outcome, 10 had normal renal function, 9 had chronic kidney disease, and 10 were on chronic dialysis. Seven people died, 5 of whom required dialysis at the time of diagnosis. It has been observed that the TPE, which is used as an initial, complementary, or salvage treatment option depending on the underlying disease, gives a positive response in terms of kidney and patient survival in patients with favourable initial renal functions.

Keywords: Renal dysfunction. Therapeutic plasma exchange. Vasculitis. Thrombotic microangiopathy syndrome. Outcomes.

Nefroloji Uygulamasında Terapötik Plazma Değişimi ile Böbrek ve Hasta Sonuçları: Tek Merkez Deneyimi

ÖZET

Terapötik plazma değişimi (TPE), nefroloji alanında belirli koşullar için alternatif bir tedavi yaklaşımıdır. TPE, ANCA ile ilişkili vaskülit, anti-GBM hastalığı, trombotik mikroanjiyopati sendromları ve böbrek nakli akut reddinin tedavisinde ve böbrek nakli alıcılarında desensitizasyon protokollerinin bir parçası olarak kullanılabilir. Ancak, TPE endikasyonları sınırlıdır ve etkinliği tartışmalıdır. Bu bağlamda, nakil dışı böbrek hastalıkları arasında TPE deneyimimizin klinik sonuçlarını değerlendirmeyi amaçladık. TPE geçiren 36 hastanın (yaş 44,19±18,66 yıl; 20 kadın) verileri retrospektif olarak değerlendirildi. TPE seanslarının sayısı, tanı, işlem öncesi ve sonrası laboratuvar sonuçları, vasküler erişim yolları, komplikasyonlar ve tedavi yanıtları elektronik dosya sisteminden retrospektif olarak kaydedildi. Genel olarak, hastalar ortalama 7,42±3,77 TPE seansına girdi. Vasküler erişim hepsinde santral venöz kateterdi. TPE endikasyonları vaskülit (n: 10), trombotik mikroanjiyopati (n: 20), tedaviye yanıt vermeyen glomerülonefrit (n: 4) ve anti-fosfolipid sendromu (n: 2) idi. 25 hasta hemodiyalize ihtiyaç duydu ve 11 hastada tedavi sonunda diyaliz gereksinimi sona erdi. Ciddi bir yan etki bildirilmedi. Tedavi sonunda 10'unun böbrek fonksiyonu düzeldi, 9'unda böbrek disfonksiyonu gelişti ve 10'u kronik diyaliz hastası oldu. Yedi kişi öldü, bunlardan 5'i tanı anında diyalize ihtiyaç duymuştu. Altta yatan hastalığa bağlı olarak ilk, tamamlayıcı veya kurtarma tedavisi seçeneği olarak kullanılan TPE'nin, başlangıçta böbrek fonksiyonları daha iyi olan hastalarda böbrek ve hasta sağkalımı açısından olumlu yanıt verdiği gözlemlendi.

Anahtar Kelimeler: Böbrek disfonksiyonu. Terapötik plazma değişimi. Vaskülit. Trombotik mikroanjiyopati sendromu. Sonuç.

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Therapeutic plasma exchange (TPE) has long been used for certain kidney disorders considered to be associated with circulatory causal factors. TPE procedure relies on removing plasma substances from circulation in exchange for replacement fluid which is usually fresh frozen plasma (FFP). The removed substances usually have a large molecular weight of >15,000 Da[1,2]. It is an extracorporeal therapy and according to the technique, vascular access can be required to provide adequate blood volume. There are some important points about this featured procedure that practitioners are responsible for, such as indications, replacement fluid type and amount, anticoagulation, duration, and monitoring for and treating procedural complications[1].

Evidence-based data support using TPE for some specific kidney disorders. Anti–glomerular basement membrane (GBM) disease is the one that evidence of benefit is marked. Besides, in the modern era of advanced drugs, TPE usually finds a place as an additive or a salvage therapy in the nephrology field. Updated guidelines recommend TPE in patients with troublesome conditions like severe renal disease, alveolar haemorrhage, and treatment unresponsiveness[3-6]. In this context of the aforementioned challenging issues, patient and renal outcomes with TPE are considerable. With this regard, we aimed to evaluate our clinical outcomes of TPE experience among non-transplant kidney diseases.

Material and Method

Study population

We performed a retrospective study involving patients who underwent TPE therapy in a university hospital between January 2013 and December 2019.

Data were obtained by review of electronic patient files and apheresis unit records. The data of 63 kidney transplant patients and 36 patients who underwent TPE for other nephrological reasons were obtained. Kidney transplant patients were not included in the evaluation.

The number of TPE sessions, diagnosis, pre- and post-procedure laboratory results, vascular access routes, complications, and end-of-treatment responses were recorded retrospectively.

All procedures performed in the study involve human participants in accordance with the ethical standards of the institutional research committee at which the studies were conducted (approval number 2019-14/41) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

TPE procedure

At our center, a centrifugation-based procedure was performed for the TPE. Fresh frozen plasma was used as replacement fluid. Plasma volume was calculated with the formula [0.07x kg x (1 – hematocrit)]. Pretreatment with diphenhydramine and 20 mg intravenous methylprednisolone was administered. At least 5 sessions with a daily or every other day schedule were performed. During the sessions, adverse events (AEs) and vital signs were recorded.

Outcomes

All the patients were hospitalized during TPE therapy. On discharge, patient status and renal outcome were determined as treatment outcomes. Renal outcome was classified as dialysis dependence, normal renal function, and renal dysfunction. Renal dysfunction is defined as serum creatinine under 1.5 mg/dL.

Statistical analysis

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 23.0, IBM Corporation, Armonk, NY). The numerical and categorical variables were expressed as the mean ± standard deviation and ratios, respectively.

The Wilcoxon signed rank test was used for comparisons within the group. A p value <0.05 was considered statistically significant.

Results

A total of 36 patients' data were evaluated. The mean age was 44.19±18.66 years, and 20 patients were female. Vascular access was obtained by a central venous catheter for all. And there was no reported complication associated with vascular access.

Overall, patients underwent an average of 7.42±3.77 TPE sessions. TPE indications were vasculitis (n: 10), thrombotic microangiopathy (n: 20), glomerulonephritis unresponsive to treatment (n: 4), and anti-phospholipid syndrome (n: 2). Distribution of vasculitis was ANCA associated (n: 5), anti-GBM disease (n: 3), lupus associated (n: 1), and non-classified (n: 1). Glomerulonephritis were distributed as focal segmental glomerulosclerosis (n: 2), acute post-infectious glomerulonephritis (n: 1), and membranoproliferative glomerulonephritis (n: 1). Mean laboratory values at the time of diagnosis revealed serum creatinine 4.79±2.58 mg/dL, eGFR 33.34±5.1 mL/min, haemoglobin 8.7±0.23 g/dL, platelet 142,908.58±20,866.56/mm^3, LDH 620.80±99.9 IU/L. Serum creatinine and urea levels significantly desreased, and eGFR levels significantly increased at the end of TPE therapy (Table I). During the follow-ups, 25 patients required hemodialysis, and at the end of treatment, 11 patients were free of the dialysis.

Table I. The comparison of changes in laboratory parameters after TPE.

Variables	Pre-TPE	Post-TPE	p value
Serum creatinine (mg/dL)	4.79±2.58	3,52±2,87	**,046**
Serum urea (mg/dL)	138.5±15.8	66,60±39,38	**,002**
eGFR (mL/min/1.73 m^2)	33.34±5.1	51,07±45,832	**,007**
Calcium (mg/dL)	8.70±0.17	9,01±0,69	,053
LDH (U/L)	620.80±99.9	222,71±35,07	,080
Leucocyte (/mm^3)	11,979.74±1,017.33	9406,09±4876,53	,100
Haemoglobin (g/dL)	8.7±0.23	9,36±4,58	,098
Platelet (/mm^3)	142,908.58±20,866.56	217650,0±79134,11	,015

TPE: therapeutic plasma exchange; eGFR: estimated glomerular filtration rate; LDH: lactate dehydrogenase.

There were no reported serious AEs. During the TPE therapy, only mild hypocalcemia and anaemia occurred. In addition to TPE, immunosuppressive treatment consisting of systemic corticosteroids and cyclophosphamide was used for all the patients with vasculitis. Seven patients died, and 5 of 7 required dialysis at the time of diagnosis. Regarding renal outcome, 10 had normal renal function, 9 had renal dysfunction, and 10 were on chronic hemodialysis at discharge (Table II).

Table II. Renal and patient outcomes at the end of TPE therapy.

Variables	Vasculitis (n: 10)	TMA (n: 20)	Glomerular disease (n: 4)	Anti-fosfolipid Syndrome (n: 2)	Total (n: 36)
SCr <1.5 mg/dL	2 (20%)	8 (40%)	1 (25%)	-	10 (27.8%)
SCr >1.5 mg/dL	4 (40%)	3 (15%)	1 (25%)	-	9 (25%)
Haemodialysis	2 (20%)	6 (30%)	2(50%)	-	10 (27.8%)
Mortality rate	2 (20%)	3 (15%)	0	2 (100%)	7 (19.4%)

Values were given as n (%). TPE: therapeutic plasma exchange; TMA: thrombotic microangiopathy; SCr: serum creatinine.

Discussion

TPE is a specialized treatment option for frequently severe conditions with advanced renal involvement, alveolar haemorrhage, and TMA syndromes that could be life-threatening. Our study used TPE as a primary or salvage therapy for critical patients. Renal impairment was a frequent accompanying organ dysfunction, and TPE had a favourable impact on renal functions with a rate of 44% dialysis independence. However, dialysis requirement at the time of diagnosis was associated with mortality.

Several AEs can occur during the TPE procedure. These AE can be classified as vascular access-associated, anticoagulation-associated, and replacement fluid-associated. Vascular access is an important component of the procedure. The filtration-based TPE procedure is based on convection and requires a blood flow rate of 150-200 mL/min. Whereas in the centrifugation-based procedure, centrifugal force is the mechanistic factor, and a blood flow rate of 10-150 mL/min is adequate. Relevant to the aforementioned factors usually vascular access is needed for adequate blood flow. A central venous catheter, ports, or arteriovenous fistulas or grafts are the options for vascular access[1]. In practice, the leading route is a central venous catheter. In our study, a central venous catheter was placed for this purpose to all the patients and there were no reported catheter-associated AE. Additionally, 25 of 36 patients required hemodialysis, and their placed central venous catheter was also used for hemodialysis.

Because the TPE is an extracorporeal therapy, adequate anticoagulation is essential to prevent clotting in the extracorporeal circuit. Citrate and heparin are the 2 standard agents for anticoagulation. Citrate is infused in the extracorporeal circuit, and it chelates ionized calcium to prevent activation of the coagulation cascade. A total of 80% citrate is removed in the centrifugation-based procedure with the discarded plasma centrifugation TPE, whereas only 20%-30% is cleared in the filtration-based TPE. Although citrate has a safety profile, the prominent is hypocalcemia. Compared with citrate, heparin is almost entirely cleared during TPE and is the preferred anticoagulant in filtration-based TPE. Furthermore, instead of citrate, heparin has to be preferred in patients with liver failure[1]. In our cohort, a centrifugation-based procedure was used, and citrate was the preferred agent for anticoagulation. Mild hypocalcemia was the only reported AE among our patients.

The replacement fluid type depends on the indication for apheresis, as well as infection and bleeding risks. Human albumin and FFP are the 2 choices for replacement fluid. Compared with FFP, albumin has a lower risk of hypersensitivity reactions, transfusion-related acute lung injury, and transmission of infection but is more expensive. Plasma is convenient for replenishing ADAMTS13 in thrombotic thrombocytopenic purpura (TTP) and clotting factors in patients with bleeding. Allergic reactions are prominent AEs of FFP, and to prevent this, patients can be pretreated with diphenhydramine and steroids[1,5]. In our practice, pretreatment with diphenhydramine and 20 mg intravenous

methylprednisolone is a standard procedure, and there were no reported severe allergic reactions in our cohort.

Prescription of TPE therapy is essential to manage the disease successfully. Beyond indication, the clinician has to assign the parameters of the exchange volume, duration, and number of TPE sessions. TPE sessions typically exchange 1 to a maximum of 1.5 plasma volume. Larger plasma exchange volumes can lead to hypotension. Duration and number of the sessions can differ according to the primary disease, the result obtained, and the targeted substance. We estimated the plasma exchange volume with the formula of (0.07 x kg x (1 – hematocrit)). We aimed not to exceed 1.5 plasma volume for exchange and with this regard, there was no reported hypotension episode among our patients.

Most immune complex (IC) diseases are related to the production of immunoglobulin G (IgG). IgG has an extravascular distribution of 45%, a long half-life of 22 days, and a low turnover rate of 7% a day. Therefore, every other day's schedule of TPE is usually adequate to achieve meaningful clearance, and IgG levels can decrease to 16%-20% of the baseline with 6 sessions. Additionally, like anti-GBM disease, for diseases with a high autoantibody production rate, a daily session schedule is more proper with concomitant immunosuppression. To achieve amelioration, knowing the properties of the targeted substance is essential for the prescription. In our study population, 16 of 36 patients had an IC-mediated disease. Therefore, a daily/every other day schedule was performed, and the mean session number was 7.42±3.77.

To decide the duration, there are specific markers for monitoring the results. For thrombotic microangiopathy syndromes, platelet count, LDH levels, and evaluation, consecutive blood smears are recommended. In the anti-GBM disease, TPE has to be continued until the serum anti-GBM antibody gets negative.

Clinical guidelines update the indications, procedures, and details about TPE therapy. TPE is recommended for various diseases of different systems. In nephrology practice, out of the transplantation population, TPE is frequently used for IC-associated diseases. The main indications are TMA syndromes, anti-GBM disease, ANCA-associated vasculitis especially accompanied by alveolar hemorrhage, and active glomerular involvement, treatment unresponsive particular glomerular diseases. Furthermore, additional and consecutive immunosuppressive treatment is usually administered[3-6]. Consistent with guidelines and recommendations we performed TPE for indicated patients.

Additionally, the patients in whom a TPE was performed had challenging diseases with accompanying renal failure, alveolar haemorrhage, multisystemic involvement, and poor treatment responses[7]. In these critical patients, TPE has favourable renal and patient outcomes with TMA syndromes and vasculitis. However, mortality rates were considerably high.

In conclusion, TPE is still an important component of our practice. Although the indicated population is hard to manage, TPE has to be considered and added to the treatment in time to get beneficial results.

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