The European Research Journal 2018;4(4):343-348 ORIGINAL ARTICLE

Therapeutic plasmapheresis: an eleven-year clinical experience

Yasemin Tekdöş Şeker, Gülsüm Oya Hergünsel, Deniz Özel Bilgi

Department of Anesthesia and Reanimation, University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital, İstanbul, Turkey

DOI: 10.18621/eurj.356552

ABSTRACT

Objective: Therapeutic plasma exchange (TPE) is currently indicated as an alternative treatment regimen in a number of guidelines for various medical conditions. In this article we retrospectively reviewed cases who underwent TPE in Bakırköy Dr. Sadi Konuk Training and Research Hospital intensive care unit between 2007 and 2016 and compared the findings to the current reports in the literature.

Methods: A total of 80 cases were treated with TPE between 2007 and 2016 in our intensive care unit. Information on demographic variables, therapeutic indications, catheterized veins, complications during the procedure, number of sessions, replacement products used and survival data was collected. In addition, pre- and post-procedure serum triglyceride, cholesterol and amylase levels were also collected in acute pancreatitis cases associated with hypertriglyceridemia.

Results: A total of 501 TPE sessions were performed on 80 cases comprising 35 neurology, 18 hematology, 12 hypertriglycemic acute pancreatitis and 7 acute hepatic insufficiency patients, along with 8 cases with less common indications including sepsis, hyperthyroidism resistant to medical therapy and toxic epidermal necrolysis. The age of the subjects ranged between 12 and 82 years (mean; 45.08 ± 14.67 years). Sixteen (23.19%) cases died before the completion of the planned sessions. Pre- and post-procedure serum triglyceride, cholesterol and amylase levels were significantly different in acute pancreatitis cases ($p < 0.05$).

Conclusion: Timely implementation of TPE in applicable indications may be helpful in preventing morbidity and mortality in a wide spectrum of disorders.

Keywords: plasmapheresis, plasma exchange, pancreatitis, Guillain barre syndrome, intensive care unit

Received: November 20, 2017; Accepted: January 29, 2018; Published Online: March 30, 2018

In therapeutic plasma exchange (TPE), blood is separated into components outside the body and cellular elements are reinfused into the body. TPE and double filtration plasmapheresis is a technique in which blood is removed extracorporeally by a method in which the plasma is separated from the rest of the blood. This process is usually performed to remove increased toxins or autoantibodies in the plasma [1]. Blood is broken down into components with the help of a filter or pump and the separated plasma is cleansed by absorbent surfaces. The depleted volume is corrected with replacement fluids composition of which is akin to plasma. A main goal in the broad clinical spectrum is to remove large molecular weight substances from the plasma, including lipoproteins containing pathological autoantibodies, immunocomplexes, cryoglobulins, endotoxin or cholesterol. TPE indications were identified and revised by the American Apheresis Community in 2010 and are divided into four categories, from 1 to 4, based on available literature [2]. Diseases in Category 1 are diseases that are considered as primary treatment

Address for correspondence: *Yasemin Tekdöş Şeker, MD., University of Health Sciences, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Anesthesia and Reanimation, İstanbul, Turkey*
E-mail: yasemintekdos@gmail.com

e-ISSN: 2149-3189

for plasma exchange or in combination with other treatment modalities. The main ones of these diseases are; Guillain-Barre syndrome (GBS), myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, thrombotic diseases thrombocytopenic purpura, Goodpasture syndrome and atypical hemolytic uremic syndrome (aHUS) [3-5].

Removal of proinflammatory and inflammatory mediators enhances the reticuloendothelial functions as well as immune regulation. Rapid reduction of specific autoantibodies on the surface can sometimes cause excessive production of similar antibodies. It is thought that rebound production of antibodies in this way leaves the multiplied pathogenic cells more vulnerable to cytotoxic drugs. For this reason, it can usually be applied to increase the efficacy of cytotoxic drugs (eg, cyclophosphamide). The number of treatments varies greatly depending on the severity of the disease and the general condition of the patient [4, 6, 7].

Plasmapheresis is an extracorporeal procedure requiring special filters and equipment. A central venous line through jugular, subclavian or femoral vein is necessary to achieve the required blood flow rate but hemodynamic balance should not be disturbed during the removal of the blood out of the body. Hemodynamic instability or hypersensitivity reactions may develop during the procedure. Acute pulmonary edema, thromboembolism, anaphylaxis, bleeding diathesis and mechanical complications of the venous catheter may be associated with mortality [8, 9]. Therapeutic plasmapheresis, generally used in the treatment of autoimmune disorders and those affecting neurologic, hematologic or immunologic systems with or without known etiologies, has recently been utilized in the treatment of sepsis cases to reduce mortality and morbidity [1, 4, 10, 11]. TPE is performed at our intensive unit since 2007 for a wide spectrum of disorders. In this article we aim to review our plasmapheresis experience in the light of the current articles in the literature.

METHODS

Records of the cases who underwent TPE in Bakırköy Dr. Sadi Konuk Training and Research Hospital Training and Research Hospital intensive care unit between 2007 and 2016 have been reviewed retrospectively. Data on demographic variables including age and sex, indication for plasmapheresis, method and site of venous access, complications developed during or following the procedure, total number of sessions, replacement fluids used (albumin, fresh frozen plasma, etc.), survival and the serum triglyceride, cholesterol and amylase levels of the acute pancreatitis cases before and after the procedure were collected. The hospital Institutional Ethics Committee approved the study.

Complete blood count, coagulation panel and serum electrolyte levels were run for all cases transferred from their primary clinics with different etiologies. Hemodynamic and pulmonary status were monitored with Nihon-Kohden BSM 4113 K® bedside monitor (Nihon-Kohden Corporation, Tokyo, Japan). The most convenient central vein was accessed using a double lumen 12F dialysis catheter under sterile conditions. Following the catheterization plasmapheresis was initiated with Prismaflex® (Gambro Lundia AB, Branding & Market Com, Sweden) system using Prismaflex TPE 2000® filters (Gambro Lundia AB, Branding & Market Com, Sweden). There were 2 or 3 day intervals between the sessions. Total plasma volume to be processed was calculated with the formula (1-hematocrit %) × total blood volume (weight in kg × coefficient). Minimum and maximum blood flow rates, 100 and 400 ml/hr, respectively, were determined regarding the hemodynamic parameters of the subject and the technical specifications of the filter. Total plasma volume was processed 1 to 1.5 times in each session. Fresh frozen plasma was used as the preferred replacement fluid. Heparine sodium was infused at 10 U/kg/hr through the plasmapheresis system in order to prevent the activation of the coagulation cascade in the extracorporeal circuit and anticoagulation activity was monitored with activated partial thromboplastin time (aPTT). Number of plasmapheresis sessions was determined by the progress of the subject in light of the reported similar cases in the literature.

Statistical Analysis

SPSS® version 13.0 was used for the statistical analysis of the data. Data on demographics, indications for plasmapheresis and survival were

analyzed using descriptive statistics. Pre- and post-procedure serum triglyceride, cholesterol and amylase levels in acute pancreatitis subjects were evaluated with paired t-test. A p value of < 0.05 was considered significant.

RESULTS

A total of 80 patients, 38 (47.5%) female and 42 (52.5%) male, aged between 12 and 82 years (mean: 45.08 ± 14.68 years) received 501 TPE sessions between 2007 and 2016. Most common site for catheterization was internal jugular vein (n = 44, 55%), followed by femoral vein (n = 33, 41.25%) and subclavian vein (n = 2, 2.5%). A pre-existing brachial arteriovenous fistula was used in one (1.25%) subject for plasmapheresis. Total number of plasmapheresis sessions varied between 4 and 14 (median: 6). Demographic variables and technical information the plasmapheresis procedure are summarized in Table1. Underlying etiologies necessitating plasmapheresis constitute five major groups which are neurologic, hematologic, pancreatic, hepatic and other disorders. Neurologic disorders are the most common pathologies requiring TPE in the study group with 35 subjects (43.75% of all subjects) which include Guillain-Barre syndrome (n = 13, 16.25 %), myasthenia gravis (n = 6, 7.5%), neuromyelitis optica (n = 4, 5%), transverse myelitis (n = 3, 3.75%), multiple sclerosis (n = 2, 2.5%), acute disseminated encephalomyelitis (ADEM) syndrome (n = 1, 1.25%), stiff person syndrome (n = 1, 1.25%), resistant epilepsy (n = 3, 3.75%), Isaac syndrome (n = 1, 1.25%) and Eaton-Lambert syndrome (n = 1, 1.25%). Hematologic disorders are the second most common group with 18 subjects (22.5% of all subjects) including the diagnoses of hyperviscosity syndrome (n = 10, 12.5 %), disseminated intravascular coagulopathy (DIC) (n = 3, 3.75%), microscopic polyarteritis nodosa (PAN) (n = 1, 1.25%) and thrombotic thrombocytopenic purpura (TTP) (n = 4, 5 %). Acute pancreatitis associated with hypertriglyceridemia constituted the third group with 12 (15%) subjects. Fourth most common disorder was hepatic insufficiency with 7 subjects (8.75% of all subjects) consisting of Wilson's disease (n = 1, 1.25%), autoimmune hepatitis (n = 2, 2.5%) and toxic hepatitis due to mushroom (n = 3, 3.75 %) and drug (n = 1, 1.25%) intoxication. There were seven complications that occurred during or following the total 501 TPE sessions. Three cases complained of dyspnea following plasmapheresis and displayed infiltrations on chest X-rays. All three cases responded

Table 1. Demographics, technichal properties of plasma exchange, complications (n = 80)

Characteristics	Data
Sex (female/male) (n)	38/42
Age (year)	45.08 ± 14.67
Localisation of catheterisation (n)	
Vena Jugularis Interna	44
Vena Femoralis	33
Vena Subclavia	2
Fistula	1
Complications (n)	
Dispnea	3
Rush	2
Pulmoner emboli	1
Labile hemodynamics	1

Table 2. Therapeutic plasma exchange indications

Indications	Data (n = 80)
Neurologic, n(%)	**35 (43.75%)**
Guillain-Barre syndrome	13 (16.25%)
Myasthenia gravis	6 (7.5%)
Neuromyelitis optica	4 (5%)
Transverse myelitis	3 (3.75%)
Multiple sclerosis	2 (2.5%)
Syndromes[+]	7 (8.75%)
Haematologic	**18 (22.5%)**
Hyperviscosity	10 (12.5%)
TTP	4 (5%)
DIC	3 (3.75%)
Microscopic PAN	1 (1.25%)
Pancreatitis	**12 (15%)**
Liver	**7 (8.75%)**
Toxic hepatitis	4 (5%)
Wilson	1 (1.25%)
Autoimmune hepatitis	2 (2.5%)
Others	**8 (10%)**
Sepsis	4 (5%)
Goodpasture syndrome	2 (2.5%)
Toxic epidermal necrolysis	1 (1.25%)
Resistant hyperthyroidism	1 (1.25%)

DIC = disseminated intravascular coagulopathy, PAN = polyarteritis nodosa, TTP = thrombotic thrombocytopenic purpura, Syndromes[+] = Adem's syndrome, Stiff-Person's syndrome, resistant epilepsy, Isaac's syndrome, Eaton-Lambert's syndrome

Table 3. Survival data (n = 80)

	Healed n = 40 (50%)	No benefit n= 16 (20%)	Exitus n = 24 (30%)
Neurologic	14	16	5
Haematologic	8	-	10
Liver	4	-	3
Pancreatitis	12	-	-
Others	2	-	6

Others = Toxic epidermal necrolysis, Goodpasture syndrome, hyperthyroidism resistant to medical treatment, sepsis

Table 4. Evaluation of pancreatitis cases due to hypertriglisemia

	Before PE	After PE	*p* value
Triglyceride (mg/dl)	3223 ± 1974.094	612 ± 239.513	**< 0.001**
Cholestrol (mg/dl)	365.83 ± 114.638	182.2 ± 52.174	**< 0.001**
Amylase (U/L)	203.42 ± 82.656	70.33 ± 50.68	**0.001**

PE = Plasma exchange

to noninvasive mechanical ventilations. One subject who developed dyspnea and hypotension during the third plasmapheresis session and required orotracheal intubation for mechanical ventilation was diagnosed with pulmonary embolism. This patient was discharged with full recovery after seven plasmapheresis sessions. In two patients, plasmapheresis was stopped due to widespread rash developing on the subjects. The lesions resolved with antihistaminic agents and plasmapheresis therapy was continued with the addition of antihistaminics to the treatment regimen. Fourty (50%) of the cases were discharged with full recovery after plasmapheresis. Sixteen (20%) cases were transferred back to their primary clinics after the acute exacerbation requiring plasmapheresis was resolved. Remaining 24 (30%) cases died due to complications related to the primary disorder. Medical indications for TPE and survival data are summarized in Tables 2 and 3. Twelve subjects with acute pancreatitis due to hypertriglyceridemia had TPE in order to normalize the serum lipid levels. Baseline mean serum triglyceride level of 3223 mg/dl was reduced to 612 mg/dl and mean serum cholesterol was reduced from the baseline level of 286.7 mg/dl to 135.4 mg/dl after TPE ($p < 0.05$ for both parameters). Baseline mean serum amylase level was reduced from 203.42 U/l to 70.33 U/L after the procedure ($p < 0.001$). Changes in serum lipid and amylase levels are summarized in

DISCUSSION

TPE is currently accepted as a treatment option for a wide variety of medical disorders [3, 4, 12]. Still, there are no clear cut guidelines for the number and frequency of TPE sessions recommended for given disorders and the treatment is planned according to the medical progress of the subject. The ASFA guideline recommends that neurological diseases can be performed daily for 5 days, daily for 3 days, non-neurological disease for 3 days, or longer and more frequent than the clinical severity of the disease [2]. Plasma exchange is considered to be a symptomatic treatment. Because it does not remove the basic source of pathogenic factors. For this reason, the success of TPE is dependent on whether the pathogens can be accessed by circulation and whether the transfer rate of production and transfer to the plasma component can be adequately addressed by the TPE.

McLeod 2012 compared the alternative replacement solutions for TPE and reported albumin as the replacement product of choice [1]. Among these two solutions, both recommended in the previous reports [1, 4, 13], we preferred fresh frozen plasma due to excessive financial burden associated with albumin.

Central veins or arteriovenous fistulas may be used for catheterization in plasmapheresis. Subclavian veins were used for vascular access in only two subjects and the last one was performed in 2009, as it is not a preferred site for catheterization due to higher risk of thrombosis [9]. No mechanical complications or infections related to catheterization were reported in our case series. For the 501 plasmapheresis sessions over 9 years, the complication rate in our clinic was 8.75% (mostly minor). Most common reason for mortality during plasmapheresis is cardiac arrhythmias and none of the cases in our series had arrhythmias during the sessions [12, 14]. Neutrophils located at the pulmonary endothelium play a major role in transfusion related acute lung injury (TRALI). When used as a replacement fluid, fresh frozen plasma may trigger neutrophil activation in pulmonary endothelium and lead to TRALI [11, 12]. Noninvasive mechanical ventilator support was necessary because of the development of respiratory distress only in three of our cases. Following the resolution of respiratory distress, TPE was completed without any other

problems.

Following the 2012 review of Cortese and Cornblath [15] covering 2263 reports, neurology guidelines began including plasmapheresis as a therapeutic alternative for various disorders. The most common neurologic disorder requiring TPE is Guillain-Barre syndrome (GBS). GBS is an autoimmune subacute polyneuropathic demyelinating disorder with unknown etiology that is associated with acute inflammation. Recent studies support the use of plasmapheresis for the recovery of muscle strength in GBS [4, 16, 17]. Of the 13 GBS subjects in our study group, 11 had full recovery of the muscle strength after plasmapheresis and only one subject did not benefit from this procedure. Our study results are similar to the study of 63 patients with neurological disease by Tombak *et al*. [18]. Myasthenia gravis is another common neurologic disorder requiring plasmapheresis. It presents with a neuromuscular transmission defect due to autoantibody mediated damage to the acetylcholine receptors. TPE is thought to be beneficial by reducing circulating humoral factors (i.e., anti-ACHR antibodies and immunocomplexes) in the circulation. It can be used as part of other immuno-regulatory treatments or in crisis management [19, 20]. Similar to intravenous immunoglobulin treatment, plasmapheresis is often reserved for myasthenic crises and refractory cases. Recovery is usually expected within a few days, but not more than 2 months [21]. Of the 6 myasthenic crises cases in our study group, four responded very well to treatment and were mostly relieved of their symptoms during the crisis. Our success rate in myasthenic crises is similar to another case series. In the acute attacks of the demyelinating disorders of the central nervous system, high dose corticosteroid therapy is indicated. For patients who do not respond to corticosteroid therapy, suggested next step is plasmapheresis. Hematologic disorders formed another major group in our study group. Removal of autoantibodies may improve survival in autoimmune based hematologic disorders [3, 22, 23]. TPE administration has been observed to reduce serum triglyceride levels rapidly and in retrospective studies, hypertriglyceridemia-induced pancreatitis (HIP) has been considered as a potential therapeutic treatment [24]. The potential role of TPE in HIP has not been adequately confirmed by large prospective studies. The 2013 Guidelines for the Use of Therapeutic Apheresis discussed the potential role of plasma exchange for HIP and found 2C (poor evidence). However, there are many cases of hepatitis infusion in HIP with severe pancreatitis, which is the clinical benefit of TPE as well as heparin infusion [25]. There were 12 cases, including 2 pregnant women, with acute pancreatitis due to hypertriglyceridemia undergoing plasmapheresis in order to normalize the high lipid levels. We were able to decrease the mean triglyceride levels by 80%, cholesterol levels by 50% and amylase levels by 65% and discharged all pancreatitis cases with full recovery. Our pancreatitis results are comparable to previous reports. There were 6 cases, including one with drug intoxication and 3 others with mushroom poisoning, undergoing plasmapheresis for acute hepatitis. It has been reported that initiating plasmapheresis within 36-48 hours from the onset of intoxication symptoms is associated with higher survival rates. All four intoxication cases in our study had plasmapheresis within 48 hours of admission and all had achieved full recovery. In toxic hepatitis, plasmapheresis is as effective as hemoperfusion, another extracorporeal treatment method [26]. Unfortunately, the remaining 3 hepatitis cases who had Wilson's disease and acute hepatic insufficiency on an autoimmune basis did not improve after plasmapheresis and both cases died shortly thereafter.

CONCLUSION

Between 2007 and 2016, 80 subjects in our clinic received a total of 501 plasmapheresis sessions. Our results suggest that timely initiation of plasmapheresis for the proper indications may reduce the morbidity and mortality rates in various disorders associated with unfavorable prognosis.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

REFERENCES

[1] McLeod BC. Plasma and plasma derivatives in therapeutic plasmapheresis. Transfusion 2012;52(Suppl 1):38S-44S.
[2] Schwartz J, Padmanabhan A, Aqui N, Balogun RA, Connelly-Smith L, Delaney M, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher 2016;31:149-62.
[3] Wozniak K, Urbanowska E, Snarski E. [Plasmapheresis in haematology]. Wiad Lek 2015;68:173-8. [Article in Polish]
[4] Lainez-Andres JM, Gascon-Gimenez F, Coret-Ferrer F, Casanova-Estruch B, Santonja JM. [Therapeutic plasma exchange: applications in neurology]. Rev Neurol 2015;60:120-31. [Article in Spanish]
[5] Matsumoto M. New developments in treatment modalities of thrombotic thrombocytopenic purpura. Rinsho Ketsueki 2017;58:2081-6.
[6] Stefanutti C, Morozzi C, Petta A. Lipid and low-density-lipoprotein apheresis. Effects on plasma inflammatory profile and on cytokine pattern in patients with severe dyslipidemia. Cytokine 2011;56:842-9.
[7] Saito A. Current progress in blood purification methods used in critical care medicine. Contrib Nephrol 2010;166:100-11.
[8] Golestaneh L, Mokrzycki MH. Vascular access in therapeutic apheresis: update 2013. J Clin Apher 2013;28:64-72.
[9] Stegmayr B, Wikdahl AM. Access in therapeutic apheresis. Ther Apher Dial 2003;7:209-14.
[10] Nguyen TC, Han YY. Plasma exchange therapy for thrombotic microangiopathies. Organogenesis 2011;7:28-31.
[11] Rimmer E, Houston BL, Kumar A, Abou-Setta AM, Friesen C, Marshall JC, et al. The efficacy and safety of plasma exchange in patients with sepsis and septic shock: a systematic review and meta-analysis. Crit Care 2014;18:699.
[12] Pruijm MT, Cherpillod A, Vogt B, Burnier M. [Plasmapheresis: technique, complications and indications]. Rev Med Suisse 2008;4:581-2, 584-6, 588. [Article in French]
[13] Stevenson ME, Leung N, Winters JL. What are the newer applications for therapeutic apheresis in Nephrology?: Current Indications for Therapeutic Plasma Exchange in Nephrology. Semin Dial 2016;29:350-3.
[14] Sutton DM, Nair RC, Rock G. Complications of plasma exchange. Transfusion 1989;29:124-7.
[15] Cortese I, Cornblath DR. Therapeutic plasma exchange in neurology: 2012. J Clin Apher 2013;28:16-9.
[16] Nomura K. [Treatment of Guillain-Barre Syndrome]. Brain Nerve 2015;67:1397-410. [Article in Japanese]
[17] Kulkantrakorn K, Sukphulloprat P. Outcome of Guillain-Barre Syndrome in tertiary care centers in Thailand. J Clin Neuromuscul Dis 2017;19:51-6.
[18] Tombak A, Ucar MA, Akdeniz A, Yilmaz A, Kaleagasi H, Sungur MA, et al. Therapeutic plasma exchange in patients with neurologic disorders: review of 63 cases. Indian J Hematol Blood Transfus 2017;3397-105.
[19] Hassan A, Yasawy ZM. Myasthaenia Gravis: clinical management issues before, during and after pregnancy. Sultan Qaboos Univ Med J 2017;17:e259-67.
[20] Deguchi K, Matsuzono K, Nakano Y, Kono S, Sato K, Deguchi S, et al. A case of anti-MuSK antibody-positive myasthenia gravis successfully treated with outpatient periodic weekly blood purification therapy. Intern Med. 2018. doi: 10.2169/internalmedicine.9466-17.
[21] Prakash S, Hans R, Sharma RR, Lal V, Marwaha N. Therapeutic plasma exchange in a patient of myasthenic crisis, refractory to intravenous immunoglobulin and immunosuppressive therapy. Neurol India 2017;65:1409-12.
[22] Niewold TB, Bundrick JB. Disseminated intravascular coagulation due to cytomegalovirus infection in an immunocompetent adult treated with plasma exchange. Am J Hematol 2016;81:454-7.
[23] Winters JL. Plasma exchange in thrombotic microangiopathies (TMAs) other than thrombotic thrombocytopenic purpura (TTP). Hematology Am Soc Hematol Educ Program 2017;2017:632-8.
[24] Click B, Ketchum AM, Turner R, Whitcomb DC, Papachristou GI, Yadav D. The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: a systematic review. Pancreatology 2015;15:313-20.
[25] Uyar S, Harmandar F, Kok M, Tas Z, Dolu S, Tokuc A, et al. Management of hypertriglyceridemia induced acute pancreatitis and therapeutic plasmapheresis : report of nine cases and review of literature. Acta Gastroenterol Belg 2017;80:71-4.
[26] Disel NR, Akpinar AA, Sebe A, Karakoc E, Surer S, Turhan FT, et al. Therapeutic plasma exchange in poisoning: 8 years' experience of a university hospital. Am J Emerg Med 2015;33:1391-5.