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Retrospective evaluation of indications for therapeutic plasmapheresis procedures applied in our center

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ABSTRACT

Aims: Therapeutic plasma exchange (TPE) is a process in which pathological substances (autoantibodies, alloantibodies, immune complexes, lipoproteins, cryoglobulins, etc.) in the patient's plasma are removed from the body along with the patient's plasma and replaced with replacement fluid (allogeneic donor plasma, colloid, crystalloid). It is applied as a complementary treatment method in many diseases that can cause high morbidity and mortality, either in the primary treatment of the disease (main treatment) or as an adjunctive treatment in the main treatment of the disease. Today, TPE is increasingly used in various clinics (toxicology, endocrinology, etc.) for different diseases/causes, especially in hematological, neurological, and nephrological diseases.

Methods: Adult patients who underwent therapeutic plasma exchange in our therapeutic apheresis center between May 2017 and May 2019 were included in the study, and the data were obtained by retrospectively reviewing patient records in the therapeutic apheresis center and our hospital's automation system.

Results: In the two-year period, a total of 1957 TPE procedures were performed on 441 patients. It was determined that 255 of the patients undergoing TPE procedures (57.8%) had indications related to liver diseases (acute liver failure, acute exacerbation of chronic liver failure, and rejection after liver transplantation), while 186 (42.2%) had indications related to non-liver diseases. Among the 186 patients undergoing TPE for non-liver diseases, it was found that 69 (37.1%) were for hematological, 38 (20.4%) for neurological, 32 (17.2%) for renal, and 47 (25.3%) for other diseases.

Conclusion: Due to the large number of liver transplants performed in our Liver Transplant Institute, the majority of TPE indications at our hospital are related to liver diseases. However, the evaluation of TPE indications excluding liver diseases revealed that the indications and frequencies of patients undergoing TPE were consistent with the overall results reported in studies from both our country and abroad.

Keywords: Therapeutic plasma exchange, liver failure, plasmapheresis indications, apheresis types

INTRODUCTION

"Apheresis" is a term derived from Greek, originating from the word "aphairesis," meaning to separate or remove by force. The term was initially used by Rowntree, Turner, and Abel to describe the manual separation of plasma and cellular elements from whole blood using centrifugation methods with heparin.[1] Therapeutic plasma exchange (TPE) is a procedure involving the removal of pathological substances (autoantibodies, alloantibodies, immune complexes, lipoproteins, cryoglobulins, etc.) from the patient's plasma along with the replacement of the removed plasma with replacement fluid (allogeneic donor plasma, colloid, crystalloid).[2] When a substance needs to be removed from the body, and it is (I) too large to be adequately eliminated by treatment techniques such as hemofiltration/hemodialysis (with a molecular weight greater than 15.000 D), (II) has a prolonged half-life exceeding endogenous clearance, and (III) is acutely toxic and/or resistant to conventional treatments, TPE becomes a rational treatment option if at least one of these conditions is present. TPE is utilized in various diseases across different departments, including hematology, nephrology, neurology, rheumatology, and intensive care units, often proving to be life-saving.[3] Primary indications for TPE include diseases such as thrombotic thrombocytopenic purpura, ABO-incompatible kidney transplants, hyperviscosity syndromes, Guillain-Barre Syndrome, and Myasthenia Gravis.[4] The indications for TPE are increasing day by day, and the treatment method is continually evolving.[5] The exact frequency of Therapeutic Plasma Exchange (TPD) application worldwide is not fully known.[6]

In this study, TPE procedures conducted by the Therapeutic Apheresis Center affiliated with our Hematology Clinic were retrospectively examined, and the frequencies of indications for the performed procedures were investigated.

METHODS

The study was conducted at İnönü University, Turgut Özal Medical Center, Hematology Department's Therapeutic Apheresis Center. Patients who underwent therapeutic plasma exchange between May 2017 and May 2019 at our therapeutic apheresis center were included in the study. During this period, a total of 441 patients underwent therapeutic plasma exchange at our center. The therapeutic apheresis indications of the 441 patients who underwent a total of 1957 plasma exchange procedures were retrospectively examined in this study. Adult patients aged 18 and above who underwent plasma exchange at our therapeutic apheresis center were included in the study, while pediatric patients were excluded. Patient information included in the study was obtained by retrospectively reviewing patient records in the therapeutic apheresis center and our hospital's automation system.

For plasma exchange, central catheters were inserted in all patients. After the request for the procedure was made, plasma exchange was performed by calculating 1-1.5 times the plasma volume according to the patient's weight. Plasma exchange procedures were carried out using two different devices: Optia and Comtec, which operate with the centrifuge method.

The study received ethics committee approval from İnönü University Non-interventional Clinical Researches Ethics Committee (Date: 10.12.2019, Decision No: 2019/415). The analyses were conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis of the research data was performed using SPSS for Windows Version 22.0 software. Descriptive statistical criteria were used for qualitative and quantitative variables. Qualitative variable data were presented as number (n) and percentage (%), while quantitative variable data were presented as mean±standard deviation.

RESULTS

The plasma exchange procedures performed by our Therapeutic Apheresis Center over approximately a 2-year period were retrospectively evaluated. A total of 441 patients were included in the study, consisting of 232 (52.6%) male and 209 (47.4%) female patients. The average age of the patients was 46.6±16.3 years (range: 18-86 years). The average age of females was found to be 44.9±16.6, while males had an average age of 48.2±16.

The clinics/departments where therapeutic apheresis procedures were performed are shown in Figure, with a breakdown of 879 (45%) procedures in the Liver Transplant Institute, 444 (22.7%) procedures in the Nephrology Department, 153 (7.8%) procedures in the Gastroenterology Department, 134 (6.8%) procedures in the Internal Intensive Care Unit, 132 (6.7%) procedures in the Neurology Department, 87 (4.4%) procedures in Hematology, 52 (2.7%) procedures in the General Surgery Service and Intensive Care Unit, 43 (2.2%) procedures in the Reanimation Intensive Care Unit, 11 (0.6%) procedures in the Chest Diseases Department, 11 (0.6%) procedures in the Rheumatology Department, 5 (0.3%) procedures in the Infectious Diseases Department, 3 (0.2%) procedures in the Medical Oncology Service, 1 (0.1%) procedure in the General Internal Medicine Service, 1 (0.1%) procedure in the Orthopedics Service, and 1 (0.1%) procedure in the Brain Surgery Intensive Care Unit.

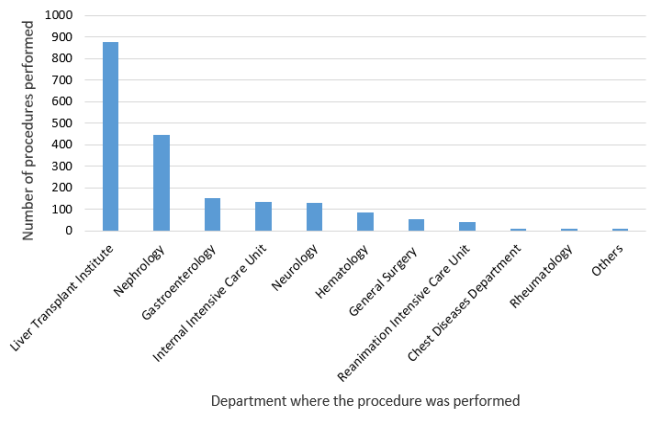

Figure. Departments/clinics where therapeutic apheresis procedures were performed and the number of procedures

Upon classification according to the diagnoses of the 441 patients included in the evaluation, the following results were obtained (Table). Plasma exchange procedures were performed on 228 patients (51.7%) due to conditions such as acute or chronic liver failure developed based on various etiologies such as viral hepatitis, toxic hepatitis. 29 patients (6.5%) underwent plasma exchange with a diagnosis of ANCA-positive vasculitis, including 9 cases of Wegener granulomatosis. Rejection after liver transplantation was observed in 27 patients (6.1%). 22 patients (5%) were diagnosed with rejection after renal transplantation. Plasma exchange procedures were conducted on 18 patients (4.1%) diagnosed with atypical HUS (atypical hemolytic uremic syndrome). HELLP syndrome (hemolysis, elevated liver enzymes, low platelet) led to plasma exchange in 16 patients (3.6%). Multiple sclerosis was diagnosed in 14 patients (3.2%). Thrombotic thrombocytopenic purpura (TTP) was identified in 10 patients (2.3%). Plasma exchange was performed on 10 patients (2.3%) diagnosed with multiple myeloma. Guillain-Barre Syndrome was diagnosed in 9 patients (2.1%). Plasma exchange was applied to 8 patients (1.8%) with a diagnosis of SLE (Systemic Lupus Erythematosus). GVHD (Graft versus Host Disease) was observed in 7 patients (1.6%). Myasthenia Gravis was diagnosed in 6 patients (1.4%). Plasma exchange was performed on 4 patients (0.9%) diagnosed with transverse myelitis. DIC (Disseminated Intravascular Coagulation) was identified in 4 patients (0.9%). Snake bites led to plasma exchange in 4 patients (0.9%). Desensitization before renal transplantation resulted in plasma exchange for 4 patients (0.9%). Good Pasture Syndrome was diagnosed in 3 patients (0.7%). Acute polyneuropathy was observed in 2 patients (0.5%). Plasma exchange was conducted for 2 patients (0.5%) diagnosed with RPGN (Rapidly Progressive Glomerulonephritis). ABY (Acute Kidney Injury) was identified in 2 patients (0.5%). Immune thrombocytopenia led to plasma exchange in 2 patients (0.5%). HSP (Henoch-Schönlein Purpura) was diagnosed in 1 patient (0.2%). Plasma exchange was applied for 1 patient (0.2%) diagnosed with

optic perineuritis. Autoimmune encephalitis was observed in 1 patient (0.2%).

Table 1. Distribution of diagnoses in patients undergoing plasma exchange

Diagnoses	Number of Patients (%)
Viral hepatitis, toxic hepatitis, liver failure	228 (51.7%)
ANCA-positive vasculitis	29 (6.5%)
Liver transplant rejection	27 (6.1%)
Renal transplant rejection	22 (5%)
Atypical HUS (hemolytic uremic syndrome)	18 (4.1%)
HELLP syndrome	16 (3.6%)
Multiple sclerosis	14 (3.2%)
Thrombotic thrombocytopenic purpura	10 (2.3%)
Multiple myeloma	10 (2.3%)
Guillain-Barre syndrome	9 (2.1%)
Systemic lupus erythematosus	8 (1.8%)
GVHD (Graft versus host disease)	7 (1.6%)
Myasthenia gravis	6 (1.4%)
Transverse myelitis	4 (0.9%)
Disseminated intravascular coagulation (DIC)	4 (0.9%)
Snake bites	4 (0.9%)
Renal transplant desensitization	4 (0.9%)
Good pasture syndrome	3 (0.7%)
Acute polyneuropathy	2 (0.5%)
RPGN (Rapidly progressive glomerulonephritis)	2 (0.5%)
Acute kidney injury (AKI)	2 (0.5%)
Thrombocytopenia	2 (0.5%)
Henoch-Schönlein purpura (HSP)	1 (0.2%)
Optic perineuritis	1 (0.2%)
Autoimmune encephalitis	1 (0.2%)
Inclusion body myositis	1 (0.2%)
Multiple organ failure	1 (0.2%)
MPGN (Membranoproliferative Glomerulonephritis)	1 (0.2%)
Intestinal transplantation	1 (0.2%)
Organophosphate poisoning	1 (0.2%)
Hemophagocytic syndrome	1 (0.2%)
Waldenström macroglobulinemia	1 (0.2%)
TOTAL	441 (100%)

Inclusion body myositis was diagnosed in 1 patient (0.2%). Multiple organ failure was observed in 1 patient (0.2%). MPGN (Membranoproliferative Glomerulonephritis) led to plasma exchange in 1 patient (0.2%). Plasma exchange was conducted for 1 patient (0.2%) after intestinal transplantation. Organophosphate poisoning resulted in plasma exchange for 1 patient (0.2%). Hemophagocytic syndrome was diagnosed in 1 patient (0.2%). Plasma exchange was performed on 1 patient (0.2%) diagnosed with Waldenström Macroglobulinemia.

Additionally, out of the 1957 plasma exchange procedures, fresh frozen plasma (FFP) was used as a replacement fluid in 1940 procedures (99.1%), while albumin was used in only 17 procedures (0.9%). Each patient included in the study underwent at least 1 session of plasma exchange, with a maximum of 109 sessions observed.

DISCUSSION

TPE is a treatment method employed for the removal of pathological substances from patients and their replacement with replacement fluid. The indications for TPE may vary from center to center and over time, depending on factors such as center capacity, the development of new treatments, and the intensity of specific patient groups. When considering Turkiye as an example, literature reviews indicate variability in TPE indications and patient diagnoses among different centers. This variability is attributed to factors such as center capacity, the evolution of new therapies, and the specific patient demographics. For instance, a study conducted in Turkiye reveals that TPE, performed on 96 patients, prominently serves as a treatment indication for hematological disorders, particularly conditions such as TTP.[7] In another study conducted at Ankara University, an examination of 658 TPE procedures reported a significant proportion attributed to diseases such as myasthenia gravis and TTP.[8] A broader study conducted across Turkiye, involving 5077 TPE procedures on 1160 adult patients, demonstrated that sepsis/adult respiratory distress syndrome and multiple organ dysfunction were the most common indications for TPE. Additionally, the study highlighted variations in TPE indications between geriatric and non-geriatric groups, with TTP being particularly prominent in the geriatric group.[9] The study titled "Turkiye Therapeutic Plasma Exchange Experience" encompasses 24,912 TPE procedures conducted by 28 therapeutic apheresis centers in Turkiye between 2007 and 2017. In this retrospective assessment, it was determined that the majority of patients fell into categories I and II according to the ASFA criteria. The top five TPE indications were identified as TTP, ABO-incompatible kidney transplantation, hyperviscosity in monoclonal gammopathies, myasthenia gravis and acute inflammatory demyelinating polyneuropathy/Guillain-Barre syndrome. Neurological diseases constituted 36.7%, hematological diseases 31.04%, renal diseases 25.8%, and rheumatological diseases 6.46% of the reported TPE indications.[10]

Excluding a study involving the geriatric patient population, it is generally observed in reported TPE indications from Turkiye that neurological or hematological diseases take precedence. However, this study highlights that liver diseases (such as liver failure and rejection after liver transplantation) constitute the most frequent TPE indication.

In the literature and the guidelines of the American Society for Apheresis (ASFA), the implementation of Therapeutic Plasma Exchange procedures is recommended for acute liver failures[11,12] Acute liver failure can occur due to viral or non-viral causes such as metabolic disorders and the intake of a hepatotoxic substance. As liver damage increases due to the continuous release of endogenous toxic substances and inflammation, on the other hand, the regeneration of the liver is inhibited. Despite various treatments being applied to protect the liver, mortality can exceed 70%. TPE is among these treatment modalities. It is effective in removing endogenous toxins such as endotoxins, bile

acids and bilirubin from the blood and partially replacing the deficiencies in coagulation factors associated with liver failure, thereby correcting coagulation disorders.[13] High-volume plasma exchange (HVP) is a life-saving therapy for acute liver failure (ALF) patients ineligible for liver transplantation (LT), recommended as a primary alternative treatment by the American Society for Apheresis (ASFA). HVP removes toxins, supplements physiological substances, modulates immune responses, promotes liver regeneration, and improves multiple organ dysfunction.[14] According to the results obtained from a study conducted with 31 patients followed up with a diagnosis of acute on chronic liver failure (ACLF); the potential efficacy of TPE in patients with ACLF, suggesting that while TPE may not be effective as a bridge to recovery, it could improve survival rates in selected patients when used as a bridge to transplantation. The retrospective data imply a potential role for TPE in ACLF treatment but underscore the need for cautious interpretation.[15] In another study evaluates the effect of plasma exchange in patients with ALF and ACLF. A literature review revealed that plasma exchange improves survival in ALF patients, particularly those who did not undergo liver transplantation. In ACLF patients, plasma exchange improved survival at 30 and 90 days in non-transplanted patients, indicating the need for further randomized controlled trials.[16]

The results of approximately a two-year period were examined in this study. It was determined that in 57.8% of the patients included in the study (255 out of 441 patients), TPE indications were attributed to liver diseases (such as liver failure and rejection after liver transplantation). This rate was found to be higher compared to those reported in both national and international studies. The primary reason for this is the significant number of liver transplantations conducted annually at the Liver Transplant Institute within the Turgut Özal Medical Center. In this context, the substantial influx of liver disease patients from various regions, particularly from Malatya and its surroundings, seeking treatment at our center, plays a crucial role.

As previously mentioned, our study identified liver diseases as the most common TPE indication. However, upon retrospective evaluation, we found that TPE procedures were performed in 42.2% of the 441 patients due to non-liver diseases. Among these 186 patients, TPE was conducted for hematological diseases in 37.1% (69 patients), neurological diseases in 20.4% (38 patients), renal diseases in 17.2% (32 patients), and other diseases 25.3% (47 patients). Excluding liver diseases and assessing the TPE indications of our center, we determined that our indications and their proportions within the patient population align with the majority of studies reported nationally and internationally.

CONCLUSION

In the retrospective evaluation of Therapeutic Plasma Exchange procedures conducted in our center over the past two years, we identified liver diseases as the most prevalent indication for TPE. The primary reason for this observation is the high number of liver transplantations performed annually within our Liver Transplant Institute. Moreover, when assessing TPE indications excluding liver diseases, we found that the indications and frequencies of patients undergoing TPE align closely with the results reported in studies conducted both nationally and internationally.

In summary, the indications and frequency of TPE may vary depending on the type of diseases, center capacity, and other factors. Studies indicate that TPE can serve as an effective treatment option across diverse clinical scenarios.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethics committee approval of the study was obtained from İnönü University Non-interventional Clinical Researches Ethics Committee (Date:10.12.2019, Decision No: 2019/415).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

There is no conflict of interest between the authors. The authors indicate no financial support or financial conflict of interest. The authors have indicated they have no financial relationships with any company and no external funding.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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