RESEARCH ARTICLE

A two-year analysis of therapeutic apheresis practices in a tertiary center: are we chasing the new indications?

Ersan S[1], Ersan G[2]

[1]Department of Nephrology
[2]Department of Infectious Diseases and Clinical Microbiology, and Transfusion and Apheresis Center
Izmir Tepecik Research and Training Hospital, University of Health Sciences, Izmir, Turkey

Abstract

Background: Therapeutic apheresis (TA) as primary or adjunctive therapy proved itself in a broad spectrum of diseases. This study aims to present TA practices in a tertiary center with an emphasis on the rate of the utility of TA on the new American Society for Apheresis (ASFA) indications.

Methods: We conducted a retrospective analysis of data regarding TA applications through our electronic medical database from June 2016 to July 2018. The data included demographics, clinical indications, and procedural characteristics. We also searched for the rate of the utility of TA procedures on new ASFA indications by entering both the diagnostic and TA modality codes for these indications on the electronic database during the study interval.

Results: A total of 720 TA procedures were performed on 96 patients (54 males, 42 females, with a mean age of 48.15 ± 26.71 years). The procedures were 68.8 % therapeutic plasma exchange (TPE), 16.4 % leukocytapheresis, 11.5 % immunoadsorption (IA), 3.1 % double filtration plasmapheresis (DFPP), and 0.13 % erythrocyte exchange. The categorical indications included 60.41 % category I and category II, 28.12 % category III, and 1.04 % category IV. The most common indication was thrombotic thrombocytopenic purpura (TTP) (26.04 %). The procedure failure rate was 2.08 %. Patient-related adverse events were reported in 7.5 % of procedures. The case mortality rate was 16.66 %. TA utility rate was 0.98 % for the new indications in the ASFA 2016 guideline.

Conclusion: Therapeutic apheresis is a progressively developing, safe, and effective treatment modality with add-on indications. Physicians should keep track of new developments on this modality to implement the appropriate indications into clinical practice. HIPPOKRATIA 2018, 22(4): 167-172.

Keywords: therapeutic apheresis, indications, ASFA

Corresponding author: Ersan Sibel, MD, Department of Nephrology of Izmir Tepecik Research and Training Hospital, University of Health Sciences, 35170, Izmir, Turkey, tel: +902324696969, fax: +902324330756, e-mail: ersansibel1@gmail.com

Introduction

Therapeutic apheresis (TA) is a general term for all extracorporeal blood purification procedures in which components of blood are separated through an extracorporeal device to treat a disease[1]. Depletion of the offending pathogenic constituent from the blood is attained by discarding the collected constituents (antibodies, toxins, cellular elements, etc.) and replacing it with either patients' own plasma or donated human plasma, and albumin[2,3]. The scope of TA techniques is growing fast and includes therapeutic plasma exchange (TPE), cytoreduction modalities (erythrocytapheresis, leukapheresis, and plateletapheresis), immunoadsorption (IA), low-density lipoprotein (LDL) apheresis, and rheopheresis[1,4-6]. Application of TA does not entail a separate unit or hospitalization in the majority of cases.

TA proved itself as primary or secondary adjunctive therapy for a broad spectrum of diseases and syndromes from diverse fields such as neurology, hematology, nephrology, rheumatology, endocrinology, toxicology, and immunology[1,7-9]. In the last American Society for Apheresis (ASFA) 2016 guideline new indications for TA utility have been introduced. These include some relatively common disorders like recalcitrant atopic (neuro-) dermatitis (atopic eczema), pruritus due to hepatobiliary diseases, vasculitis, HELLP syndrome, hematopoietic stem cell transplantation-HLA desensitization, and RhD alloimmunization after red blood cell (RBC) exposure[1].

In this study, we retrospectively analyzed the distribution of TA procedures in various clinical conditions with respect to safety, efficacy, and outcomes. We also searched for the rate of the utility of TA on new ASFA 2016 indications for adults.

Materials and methods

This is a retrospective analysis of TA procedures performed between June 2016 and July 2018 at a tertiary care hospital. The study was approved by the local

ethical committee of the University of Health Sciences, Izmir Tepecik Training and Research Hospital (2018/14-9, 22/11/2018). TA indications based on the 2016 ASFA guideline[1]. As referred by ASFA[1]: Category I indications are first-line therapy, category II as adjuvant or secondary therapy, category III as the optimum role of TA unestablished, and category IV as either ineffective or harmful for the patients.

All procedures were carried out at bedside under the direct supervision of a trained apheresis technician and residents of the relevant clinical services. TPE and therapeutic cytapheresis procedures were offered with Haemonetics MCS+ system (Haemonetics Corp., MA, USA), DFPP with Asahi KASEI Plasauto∑ (Asahi Kasei Medical Europe GmbH, Frankfurt, Germany), and immunoadsorption with ADAsorb (Medicap GmbH, Ulrichstein, Germany). Vascular access was obtained through the insertion of central venous catheters to jugular or femoral veins. In some cases, it was readily available for other extracorporeal interventions (e.g., dialysis, chemotherapeutic infusions) as tunneled or not tunneled dual-lumen central venous catheters. Unless systemic heparin infusion was used for a specific indication, citrate dextrose (ACD-A) was used for circuit anticoagulation in all procedures, with concomitant oral calcium supplementation. The plasma volume was calculated using the formula described previously[10]. Treated amount comprised of one to one-and a half patient plasma volumes and was replaced by type specific fresh frozen plasma in all cases when needed.

Data regarding the demographic characteristics of the patients, clinical indications, outcomes, and procedural features were retrieved by entering the specific codes through the electronic patient data management system of the hospital. TA modality selected, the volume of the replacement fluid, anticoagulation, procedure-related complications/mortality, and procedure failures were recorded. The diagnostic codes for new indications and any practice of TA were searched through the system from September 2016 until August 2018. Any adverse event(s) occurred during the procedure were managed accordingly by the attending doctor and nurses. The procedure-related mortality rate was described as death due to TA procedure within 24 hour, and case mortality as the patient's death before discharge from the hospital admission for which TA was performed[11].

Statistical analysis was done using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). All results are presented as mean ± standard deviation. Data comparisons for continuous variables between disease categories were made using the one-way variance analysis (ANOVA). The significance was set at a p-value of <0.05. Wilcoxon signed-rank test was used to compare parameters before and after treatments. A p-value of less than 0.05 was considered statistically significant.

Results

During the study period, 720 TA procedures were performed on 96 patients (54 males, 42 females, with a mean age of 48.15 ± 6.71). Out of 96 patients, five with familial hyperlipidemias were consecutively treated by lipid apheresis during the two-year study period. The mean weight of the study group was 67.20 ± 10.88 kg, and the plasma volume exchanged was 2,558 ± 1,337 ml. Plasma volumes exchanged for TPE applied in hematological, nephrological, and sepsis with multiorgan failure patients were 2,882.59 ± 680.74 ml, 2,953.43 ± 846.44 ml, and 2,905 ± 50.08 ml, respectively. The difference was not significant between groups (p =0.936).

The most commonly performed modality was TPE (68.8 %). Category I and II indications comprised of 60.41 % of all patients, with hematological disorders as the leading causes (Table 1). The most common indications for TA were thrombotic thrombocytopenic purpura (TTP; n =25, 26.04 %), hyperleukocytosis due to acute/chronic leukemias (n =20, 20.83 %), familial hyperlipidemias (FH; n =11, 11.45 %), and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (n =10, 10.41 %), respectively. The majority of category III indications (n =28, 28.12 %) belonged to leukocytapheresis for acute leukemias (n =13). The only category IV indication was diarrhea-associated thrombotic microangiopathy (TMA) in a patient without severe neurological symptoms (1.04 %).

TTP patients received systemic steroids along with TPE. The increase of thrombocyte counts above 150 $x10^3/mm^3$ was encountered in 68 % of the patients (n =17). The cause of death in four patients was presumably due to thrombotic events, but the definite reason could not be inferred from medical records.

All ANCA-associated vasculitis patients received immunosuppressive therapy in adjunct with TPE. The creatinine levels on admission and discharge were 6.19 ± 3.63 mg/dl and 4.07 ± 2.68 mg/dl, respectively. The decrease was statistically significant (p =0.028). One patient died because of acute respiratory failure resulting from diffuse alveolar hemorrhage, and three patients remained hemodialysis dependent on discharge.

Lipid apheresis was done by either double filtration plasmapheresis (DFPP) or IA on 13 patients of whom 11 had heterozygote FH, and two had steroid-resistant focal segmental glomerulosclerosis (FSGS). LDL-cholesterol levels before and after procedures were 486.07 ± 134.70 mg/dl, and 178.92 ± 94.18 mg/dl, respectively, and the decrease was significant (p =0.001).

We applied IA on a patient with diarrhea-associated TMA with abducens palsy that developed during plasma exchange. The patient was successfully managed and discharged without sequela.

Leukocytapheresis was applied to 20 patients with leukocyte numbers exceeding 100,000 $/mm^3$ in acute myeloid leukemia (12 patients), acute lymphoblastic leukemia (1), chronic lymphocytic leukemia (4), and chronic myeloid leukemia (3). Leukocyte numbers ($x10^3/mm^3$), before and after procedures were 229.42 ± 112.18 and 99.75 ± 105.73, respectively, and the decrease was significant (p <0.001).

Table 1: The diseases, modalities, and indication categories for therapeutic apheresis procedures performed between June 2016 and July 2018 that were included in the study.

Diseases	Patient No	Modality Type	Sessions No	Indication category
Hematological diseases/disorders	57			
TTP	25	TPE	313	I
Hyperleukocytosis (acute/chronic leukemias)	13/7	Leukocytapheresis	118	III/ undefined
TMA (diarrhea +/complement mediated)	6 (4/2)	TPE	31	III(5)/IV(1)
Hyperviscosity (MM/WM)	4 (2/2)	TPE	33	I
Aplastic anemia	1	TPE	3	III
HELLP (postpartum)	1	TPE	3	III
Nephrological diseases	23			
ANCA-associated vasculitis	10	TPE	60	I
Antibody-mediated rejection	6	TPE	18	I
FSGS (post-transplantation/steroid resistant nephrotic syndrome with hyperlipidemia)	5 (3/2)	TPE/DFPP	21/4	I(3)/III(2)
Cast nephropathy (MM)	1	TPE	3	II
Scleroderma renal crise	1	TPE	5	III
Endocrinology and metabolism diseases	11			
FH	11	DFPP/IA	18/81	II
Neurological diseases	1			
Neuromyelitis optica	1	IA	2	II
Sepsis with multiorgan failure	3	TPE	6	III
Malaria	1	ErythrocyteExchange	1	III
Total	**96**		**720**	

No: number, TTP: thrombotic thrombocytopenic purpura, TMA: thrombotic microangiopathy, HELLP: hemolysis, elevated liver enzymes, and a low platelet count, ANCA: antinuclear cytoplasmic antibody, FSGS: focal segmental glomerulosclerosis, MM: multiple myeloma, WM: Waldenstrom macroglobulinemia, FH: Familial hyperlipidemias, TPE: therapeutic plasma exchange, DFPP: double filtration plasmapheresis, IA: immunadsorption.

Erythrocyte exchange was performed in a case with cerebral malaria admitted to the intensive care unit. The patient responded well with complete remission.

The search for the new TA indications reported in the 2016 ASFA guideline, excluding pediatric diseases, revealed that TA was performed only in one patient with postpartum HELLP syndrome. Although some other disease entities included in the new indications were diagnosed, no other case had any TA treatment (Table 2).

There were no deaths related to TA modality itself. Adverse events (related to procedures included nausea/vomiting (n =9, 9.37 %), hypotension (n =8, 8.33 %), muscle cramps due to hypocalcaemia (n =6, 6.25 %), allergic reactions (n =6, 6.25 %) with one patient requiring cardiopulmonary resuscitation with eventual recovery, thrombocytopenia (n =4, 4.16 %), and leukopenia (n =2, 2.08 %), respectively. Central venous catheter-related complications were hematoma at the catheter insertion site (n =3, 3.15 %), clotting in lines (n =2, 2.08 %) which resulted in procedure interruption, and reinsertion of the catheter at another site because of low flow (n =1, 1.04 %).

The case mortality rate was calculated as 16.66 % (n =16), and all mortalities were due to either primary disease or its complications (Table 3). The cause of death was sepsis with multiorgan failure in ten of the patients of whom seven had hematological diseases (leukemias). In the rest of the patients, a definite cause of death could not be inferred from medical records.

Discussion

TA modalities with developing more selective plasma separation and extracorporeal blood processing techniques have secured their place in clinical routine for many different disorders and with various techniques related to the diagnosis and equipment of the center[1,7,8]. The procedures available for clinical practice include TPE, DFPP, IA, cytapheresis (thrombocytapheresis, leukocytapheresis, erythrocytapheresis), erythrocyte exchange, high volume plasma exchange, filtration-based selective apheresis, extracorporeal photopheresis, and rheopheresis. As outlined by tandem ASFA guidelines, some of these modalities are the primary therapy for specific disorders (category I), and some are indicated to be secondary or adjunctive therapy (category II)[1,5].

The World Apheresis Registry reported web-based data of fifteen centers from seven countries between 2003 to 2007. According to this registry, plasma exchange was

Table 2: The data regarding the rate of diagnosed diseases included in the new ASFA guideline[1] and of the utility of therapeutic apheresis procedures in our center.

Diseases	Diagnosis No	TA (type/No)
Atopic (neuro-) dermatitis, recalcitrant	71	-
Complex regional pain syndrome	0	-
Erythropoietic porphyria, liver disease	0	-
Hashimoto's encephalopathy	1 (not definite, but as rule out)	-
HELLP syndrome	1	TPE/3
Hemophagocytic lymphohistiocytosis	9	-
N-methyl D-aspartate receptor antibody encephalitis	0	-
Prevention of RhD alloimmunization after RBC exposure	0	-
Progressive multifocal leukoencephalopathy associated with natalizumab	0	-
Pruritus due to hepatobiliary disease	6	-
Thrombotic microangiopathy-coagulation mediated	0	-
Vasculitis (Behçet's disease)	29	0
Total	**117**	**3**

No: number, TA: therapeutic apheresis, HELLP: hemolysis, elevated liver enzymes, and a low platelet count, RBC: red blood cell, TPE: therapeutic plasma exchange.

Table 3: Discharge and in-hospital death rates of patients for specific diseases with therapeutic apheresis indications.

Diseases	Patient No	Outcome rates (%) discharge/in-hospital death
TTP	25	84/16
Hyperleucocytosis (Leukemias)	20	65/35
TMA (diarrhea +/complement mediated)	6 (4/2)	83.4/16.66
Hyperviscosity	4 (2/2)	75/25
Aplastic anemia	1	0/100
HELLP (postpartum)	1	100/0
ANCA-associated vasculitis	10	90/10
Antibody-mediated rejection	6	100/0
FSGS	5 (3/2)	100/0
Cast nephropathy (MM)	1	100/0
Scleroderma renal crise	1	100/0
Neuromyelitis optica	1	100/0
FH	11	100/0
Sepsis with multiorgan failure	3	0/100
Malaria	1	100/0

No: number, TTP: thrombotic thrombocytopenic purpura, TMA: thrombotic microangiopathy, HELLP: hemolysis, elevated liver enzymes, and a low platelet count, ANCA: antinuclear cytoplasmic antibody, FSGS: focal segmental glomerulosclerosis, MM: multiple myeloma, FH: Familial hyperlipidemias.

the most commonly used modality, and neurological and hematological diseases dominated the activity followed by patients undergoing lipid apheresis[12]. Several national apheresis registries shared their experiences about usage, safety, and efficacy of TA modalities[13-17]. The trend regarding the use of plasma exchange as the most frequent procedure has prevailed; however, the scope of TPE indications may vary in different countries[6,8,9,16,18]. The World Apheresis Registry suggested that patients with malignancies in order to collect stem cells dominated the activity followed by neurological and hematological diseases[12]. The neurological diseases comprised the majority of indications in Italy and Peru[19,20]. Interestingly, dermatological disorders such as toxic epidermal necrolysis, and pemphigus vulgaris outnumbered nephrological diseases in Peru registry[20]. In our center, we used TPE mostly, with hematological and nephrological indications predominating and followed by lipid disorders. The rate of TPE use as category I indication was calculated as 50 % (48 patients) in this survey.

TTP was the most common indication in our survey compatible with the one reported from a center in

the same region[9]. TPE was found to be effective in 84 % of our patients, with an increase in thrombocyte counts above 150 x10^3/mm^3 in 68 %. The in-hospital death rate was found to be 16 % in our survey in TTP patients. The cause of death in four patients was presumably due to thrombotic events, but the definite cause could not be inferred from the medical records.

After TTP, more frequent indications were a number of nephrological diseases in which we used TPE as category I indication, namely ANCA-associated rapidly proggressive glomerulonephritis, and posttransplant antibody-mediated rejection, respectively (Table 1). Except for a case of ANCA-associated rapidly proggressive glomerulonephritis with diffuse alveolar hemorrhage, in-hospital death was not observed in the nephrological disorders.

Lipid apheresis is now accepted as an effective treatment modality in heterozygote FH patients. A single treatment reduces LDL-cholesterol levels by 65-70 %, and long-term outcome studies have demonstrated significant reductions in coronary events. The procedure has been applied indefinitely[1,21,22]. Lipid apheresis provided a significant reduction in LDL-cholesterol levels in our FH heterozygote patients without documented cardiac events so far.

Leukocytapheresis is not a definitive therapeutic modality in case of hyperleukocytosis. However, the rapid reduction of the cellular burden by this modality improves tissue perfusion and reverses pulmonary and central nervous system manifestations related to increased viscosity[1,5,23].

In the current study, although symptomatic relief was achieved with a significant reduction of the leukocyte numbers, the overall survival did not improve. This finding was compatible with other studies and could be partly due to the higher risk of the patients undergoing leukocytapheresis[8,23,24]. ASFA guidelines do not recommend leukocytapheresis in chronic leukemias[1,5]. In this study hyperleukocytosis due to chronic leukemias comprised seven patients (53.84 %) who underwent leukocytapheresis with uncategorized indication. The report from our National Survey disclosed that leukacytapheresis was performed to 81 patients with acute or chronic leukemia[13]. However, undetermined indications are not peculiar to our center. Tiwari et al[18] proved that the rate of undetermined indications significantly decreased from 20.5 % to 4.8 % by continuous medical education (CME) interventions.

Red cell exchange is preferentially preferred in malaria, sickle cell disease, babesiosis, and prevention of RhD alloimmunization after RBC exposure[1]. With the use of erythrocyte exchange, we successfully treated a case with severe cerebral malaria admitted to our intensive care unit[25]. Sharma et al[8] also reported two cases of malaria treated successfully using partial red cell exchange.

The modalities of apheresis can be used interchangeably in some cases[1]. This was encountered in our case with abducens nerve palsy that emerged during TPE sessions prescribed for diarrhea-associated TMA where we shifted to IA with complete remission[26]. IA as a primary modality, was utilized in one case of neuromyelitis optica in our study as compatible with other studies[27,28].

The rate of adverse events range between 3 to 20 % in TA procedures, and the overall mortality rate is estimated to be 1-3 per 10,000 procedures[8,9,11,18]. We observed patient-related adverse events in 54 sessions (7.5 %) with nausea/vomiting, hypotension, muscle cramps, and allergic reactions most frequently seen, as compatible with other studies[8,9,29]. Despite these minor side effects commonly encountered, the emergence of a serious event should not be overlooked. Severe anaphylaxis due to transfusion of fresh frozen plasma was observed in one patient in our study. The patient was managed by our institutional-based standard protocols, including bedside anaphylaxis kits. On the whole, we had no procedure-related mortalities.

A peculiar finding in this study was that the majority of the new indications put forward by ASFA did not have a place for TA interventions in our center (Table 2). This could be attributed to unawareness of the physicians of the appropriate indications based on scientific evidence. The role of CME on the change in TA practices was impressive, as shown by Tiwari et al[18]. We suggest that a remarkable improvement in physicians' TA practices would be ensured by multidisciplinary educational programs carried out in apheresis centers at specified intervals.

The current study has some limitations; first of all, it was a retrospective study. Secondly, as we had no chance to interview prescribers of TA modalities, we could not get a casual explanation of uncategorized indications. Further, causality may not be assigned between TA and mortalities as with any retrospective analysis.

In conclusion, TA is a growing field of applied therapeutics with developing techniques and add-on indications. Appropriate use of TA procedures based on a sophisticated understanding of molecular pathogenesis of diseases paves the way for effective primary treatment in many disorders. CME interventions would provide physicians to pursue evidence-based scientific developments in this field and have a positive impact on implementing TA in clinical practices.

Conflict of interest

Authors declare no conflict of interest.

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