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Original Article

Therapeutic plasma exchange for refractory SLE: A comparison of outcomes between different sub-phenotypes

Aynur Soyuöz[1], Ömer Karadağ[2], Tülay Karaağaç[3], Levent Kılıç[2], Şule Apraş Bilgen[2], Osman İlhami Özcebe[2,3]

Abstract

Objective: Therapeutic plasma exchange (TPE) offers an alternative therapeutic modality for patients with systemic lupus erythematosus (SLE) and primary antiphospholipid syndrome (APS). However, there is conflicting evidence regarding its efficacy in different sub-phenotypes. This study aimed to investigate the main clinical characteristics and outcomes of patients with different phenotypes of SLE and APS treated with TPE at a tertiary care center.

Methods: The database of the Blood and Apheresis Unit between 2001 and 2013 was screened for patients with SLE and primary APS. SLE disease activity index (SELENA-SLEDAI), the indications for treatment, complications, and outcomes were obtained from a review of medical records and phone calls. A total of 24 patients (SLE: 20, APS: 4) were recruited for the study.

Results: Mean ages of SLE (M/F: 1/19) and primary APS (PAPS) patients (M/F: 2/2) were 32.4±12.89 and 52.0±10.7 years, respectively. The main indications for TPE were hematologic, neurologic, and pulmonary involvement and APS-related symptoms. TPE was preferred in eight patients because of leucopenia and co-infection. SLEDAI was significantly decreased after TPE (16.7±8.3 before vs. 8.8±3.1 after, p=0.001). Both primary APS and SLE-related catastrophic APS (CAPS) patients had completely responded to TPE. The success rate of TPE in patients with thrombocytopenia was lower than patients with hemolytic anemia. The median (IQR 25%-75%) number of TPE sessions was 6.5 (5-10.5). In total, five patients experienced TPE-related major adverse events (catheter infections in three patients, bleeding in one patient, and hypotension in one patient). The median (IQR 25%-75%) follow-up time was 33.5 (6.75-81.25) months. In total, four patients died during follow up, of which three died during the period of TPE administration.

Conclusion: Our data suggest that CAPS and other APS-related problems respond well to the TPE treatment. TPE should be kept in mind for the treatment of patients with other features of SLE, especially those resistant to other agents and in the presence of leucopenia.

Keywords: Therapeutic plasma exchange, Systemic lupus erythematosus, Primary antiphospholipid syndrome

ORCID IDs of the authors:
Ö.K. 0000-0002-3443-3117;
L.K.0000-0003-1064-9690;
Ş.A.B. 0000-0001-8208-1585.

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[1] Division of Haemotology, Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey
[2] Division of Haemotology, Department of Internal Medicine, Hacettepe University School of Medicine, Ankara, Turkey
[3] Blood and Apheresis Unit of Hacettepe University School of Medicine Hospital, Ankara, Turkey

Address for Correspondence:
Levent Kılıç, Department of Internal Medicine, Division of Rheumatology, Hacettepe University School of Medicine, Ankara, Turkey

E-mail: drleventkilic@yahoo.com

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Introduction

Systemic lupus erythematosus (SLE) is a remarkably complex autoimmune disease with considerable heterogeneity in clinical manifestations and disease course (1). While the clearest guidelines for the treatment of SLE exist in the context of lupus nephritis, patients with other lupus manifestations such as neuropsychiatric, hematologic, musculoskeletal, and severe cutaneous lupus frequently require immunosuppressant and/or biologic therapy (2). In a subgroup of patients, SLE can be severe and potentially life threatening requiring prompt management strategies. Therapeutic plasma exchange (TPE) removes pathological substances from the blood, such as monoclonal paraproteins and autoantibodies, as well as replaces the deficient plasma components when plasma is used as the replacement fluid (3). These extracorporeal treatments have been used for more than 40 years in diseases such as SLE and antiphospholipid syndrome (APS) (4). The first randomized controlled trial comparing the efficacy of standard of care combined with plasma exchange alone in lupus patients revealed no difference in terms of renal outcome (5). Apart from this study, the literature of TPE in SLE and APS is mainly based on observational studies and case reports (6). Beneficial effects have been reported in patients with

refractory disease and APS. Heterogeneity of patients' findings and concomitant use of immunosuppressive medications might partially explain this discordance. Additional studies comparing the different sub-phenotypes of SLE patients would further clarify the role of TPE in clinical practice. This study aimed to present our tertiary center's experience of using TPE for patients with SLE and APS and to compare the different indications for its use.

Methods

Patient selection

The local ethics committee approved this study. The database of the Blood and Apheresis Unit of our University Hospital between October 2001 and May 2013 was retrospectively reviewed for patients with SLE and primary APS. TPE had been administered to 69 patients with autoimmune diseases. In total, 23 SLE and 4 primary APS patients were identified. Three SLE patients were excluded due to missing data. Informed consent was obtained from available (alive) patients.

Clinical evaluation

The demographic and clinical characteristics of the patients were obtained from hospital records. The following clinical features were collected and analyzed: sex, fever, malar rash, photosensitivity, oral ulcer, alopecia, arthritis, serositis, neurologic disorder, anemia, leucopenia, thrombocytopenia, hematuria, proteinuria, and leucocyturia. Disease activity at the time of TPE and following TPE sessions was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (7). The main indication for TPE was determined according to hospital records.

Laboratory assessment

Laboratory data were collected before and after treatment for further analysis, and these included complete blood count, plasma lactate dehydrogenase, urine analysis, serum creatinine, and titers of serum antinuclear antibodies (ANA), anti-double-stranded DNA (ds-DNA) antibodies, anti-extractable nuclear antigen (ENA) antibodies, anti-cardiolipin antibodies (ACA), lupus anticoagulant, and C3.

Pre and peri-procedural immunosuppressive therapy of patients

The pre-TPE therapy history, including concomitant immunosuppressive medications, was recorded. All of the SLE and APS patients were on daily doses of prednisolone between 15-60 mg.

Therapeutic plasma exchange procedures

Each patient's TPE procedure, total number of sessions, complications, and follow up were recorded. Nine patients had plasma exchange using fresh frozen plasma (FFP), 11 patients used albumin, and two patients used both FFP and albumin. TPE sessions were stopped in one patient because of serious catheter problems.

Outcome and follow up of patients

Outcomes of interest included complete response, partial response, treatment failure, and death. Treatment response to TPE was defined according to Table 1. The post-TPE SLEDAI score was also calculated. Follow up of the peri- and post-TPE period was performed, which included phone calls for those patients who did not have regular follow-up visits.

Statistical analysis

The data were analyzed using Statistical Package for Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Values are presented as the mean±standard deviation or as the median (inter quartile range 25-75% [IQR]). Changes in pre- and post-TPE parameters were assessed with non-parametric related samples test.

Results

The mean ages of SLE and primary APS (PAPS) patients were 32.4±12.89 and 52.0±10.7 years, respectively. Except for one male patient, all SLE patients were female, whereas two of four PAPS patients were female. Three (75%) of the PAPS patients and five (25%) of the SLE patients were newly diagnosed. The median (IQR 25-75) disease duration was two (0-6) years. Demographic and clinical characteristics, disease activity parameters, and pre- and peri-TPE treatment are shown in Table 2. Eight of the SLE patients had nephritis. The mean pre-TPE SLEDAI score was 16.7±8.3. The main indications for TPE were hematologic, neurologic, pulmonary involvement, and APS-related symptoms as shown in Table 2. TPE was preferred in eight patients due to additional problems (leucopenia in five patients and co-infection in three patients). One patient had pulmonary fibrosis resulting in pulmonary failure and skin ulcers requiring TPE treatment. One patient with primary APS had catastrophic APS (CAPS), and one had hemolytic anemia and concomitant infective endocarditis. The APS patient with hemolytic anemia was resistant to IVIG. Two of the other patients with primary APS had venous and arterial thrombosis in addition to

Table 1. Outcome definitions of patients with different main indications for TPE

	Complete response	Partial response	Treatment Failure
Renal failure	Normal serum creatinine levels	Serum creatinine > upper normal limits, but no need for HD	HD, death
Pulmonary fibrosis, skin	Dyspnea resolved	No need for MV	Persistent MV
Alveolar hemorrhage	Dyspnea resolved	No need for MV	Persistent MV
Neuromyelitis optica	>50% improvement in motor functions and findings of myelitis in MRI	Less than 50% improvement in clinical and laboratory findings	No improvement in motor functions and/or findings of myelitis in MRI
Myasthenia gravis	>50% improvement in clinical examination	Less than 50% improvement in clinical examination	No improvement in weakness or sensorial examination
Longitudinal myelitis	Full recovery, No tetraparesis/ paraparesis	Paraparesis/ paraplegia	No improvement
CAPS[8]	Clinical improvement	Partial improvement	No improvement
Hemolytic anemia	Coombs tests (-), LDH Normal	Only minor findings in blood smear	No improvement
Thrombocytopenia	Thrombocyte >100.000/μL	<100.000/μL, more than baseline	No improvement
TTP	Increase in thrombocytes, LDH Normal blood smear	Minor findings in blood smear	No improvement

HD: hemodialysis, MV: mechanical ventilation, MRI: magnetic resonance imaging, CAPS: catastrophic antiphospholipid syndrome, LDH: lactate dehydrogenase, TTP: thrombotic thrombocytopenic purpura

Table 2. Clinical, disease activity, and treatment findings and TPE outcomes of SLE patients

Patient number	Major TPE Indication	Age/ Sex	H/o Nephritis	Pre-TPE Drugs	Pre-TPE SLEDAI	Concomitant problem/ treatment procedures	Post-TPE SLEDAI	Outcome	Follow-up (months)
1	TTP	29	no	MP, CYC	13		13	CR	144
2	Thrombocytopenia, bleeding	59	no	MP	5		4	PR	5
3	Thrombocytopenia, cerebral hematoma	24	yes	MP, CYC, IVIG	37	L / MP, HD	NA	Death	
4	Thrombocytopenia, bleeding	22	yes	MP, CYC	31	MP, RTX, HD	14	PR, HD	58
5	Thrombocytopenia, bleeding	15	no	IVIG	9	L	9	TF	12
6	Renal Failure, Cytopenia	54	yes	MP, CYC, MMF	27	L / MP, CYC, HD	5	CR	31
7	Renal Failure	22	yes	MP, CYC, MMF, RTX, IVIG	16	Pn / HD	8	CR	3
8	Alveolar hemorrhage	30	yes	MP, CYC, IVIG	16	MP, CYC, HD, MV	NA	Death	
9	Alveolar hemorrhage	18	yes	MP, CYC	38	MP, CYC, RTX, HD, MV	NA	Death	
10	Pulmonary fibrosis, Dyspnea, Skin	33	no	MP, CYC, IVIG	13	MP, CYC	7	PR, PHT	21
11	Psychosis, Active disease	26	no	MP, CYC	23	L / MP, CYC	11	CR	48
12	Neuromyelitis optica, vision loss, paraplegia	32	no	MP, CYC, IVIG	20	MP, CYC	10	CR	96
13	Myasthenia gravis, generalized weakness	32	no	AZA	12	L	12	CR	132
14	Myasthenia gravis, generalized weakness	30	no	IVIG	11		NA	Death	
15	Longitudinal myelitis, quadriplegia	23	yes		29	Pn / MP, CYC, RTX	10	PR, paraplegia	16
16	CAPS	25	no		24	MP, CYC	10	CR	84
17	APS-widespread thrombosis	60	no	MP, CYC, IVIG	11		8	CR	4
18	Evans syndrome	33	no		9		8	CR	36
19	Hemolytic anemia	47-M	yes	MP, CYC, IVIG	28	MP, CYC	NA	Give up TPE	12
20	Hemolytic anemia	34	no	MP, CYC	8		3	CR	73

TPE: therapeutic plasma exchange; TTP: thrombotic thrombocytopenic purpura; CAPS: catastrophic antiphospholipid syndrome; APS: antiphospholipid syndrome; PHT: pulmonary hypertension; IVIG: intravenous immunoglobulin; L: leukopenia; Pn: pneumonia; MP: pulse methyl prednisolone; CYC: cyclophosphamide; AZA: azathioprine; RTX: rituximab; HD: hemodialysis; MV: mechanical ventilation; CR: complete response; PR: partial response; TF: treatment failure; NA: not available

acute cerebral infarct. Widespread skin necrosis, intestinal infarct, and pulmonary and cranial involvements were the main findings of CAPS in our patients. Most of the patients had been previously treated with various conventional immunosuppressive treatments such as cyclophosphamide, which was used in 65% of the patients. During TPE sessions, concomitant treatments and procedures were used and are shown in Table 2. Hemodialysis was required in 30% of patients, and mechanical ventilation was needed in 10%. Both primary APS and SLE-related CAPS patients had completely responded to TPE. The success rate of TPE in patients with thrombocytopenia was lower than patients with hemolytic anemia. The worst outcomes were observed in patients with alveolar hemorrhage. Patients with neurologic involvement had partially responded to treatment (Table 2). The SLEDAI score was significantly decreased after the TPE procedures (16.7±8.3 before vs. 8.8±3.1 after, p=0.001). Autoantibodies became negative or decreased in titer in most patients (Table 3). The median (IQR 25%-75%) number of TPE sessions was 6.5 (5-10.5). In total, five patients had TPE-related adverse events (catheter infections in three patients, bleeding in one patient, and hypotension in one patient). In one patient, TPE could not be continued due to catheter-related problems. The median (IQR 25%-75%) follow up was 33.5 (6.75-81.25) months. During follow up, TPE was repeated in the 1st, 15th, and 16th patients (5 sessions at the 60th month, two more courses of sessions each with 5 sessions at the 28th and 35th month and 5 sessions at the 77th month, respectively). Follow up of APS patients was 62, 84, 3, and 3 months, respectively. TPE was administered once during the follow up period in each of the APS patients. In total, four patients died during the follow-up period, of which three died during the peri-TPE period. The 2nd patient died due to intracranial hematoma. The 8th and 9th patients died due to pulmonary problems. The 19th patient died due to vertebral fracture and post-fracture infectious complications not related to the main TPE indication.

Discussion

This study suggests that CAPS and other APS-related problems respond well to the TPE treatment. Despite the small patient numbers, patients with pulmonary hemorrhage had the worst outcome. Because immunosuppressive drugs can markedly suppress the immune system and blood counts, TPE might be considered as an alternative treatment modality where conventional immunosuppressive therapy is contraindicated due to concomitant infection and leucopenia (as in eight of our patients). CAPS is a rare life-threatening autoimmune disease characterized by disseminated intravascular thrombosis resulting in multiple organ failure. CAPS can manifest in both the absence and presence of SLE (8-10).

Table 3. Laboratory findings and TPE sessions of SLE and primary APS patients

Patient number	Pre-TPE positive autoantibodies& decrease in C3 level	Post-TPE positive autoantibodies& decrease in C3 level	Pre-TPE results of ACA, LA	Post-TPE results of ACA, LA	Number/extent of TPE sessions	Outcome
1	NA	NA			10/20 days	CR
2	NA	Negative			7/days	PR
3	1/320	1/100	ACA (+)	ACA (-)	8/16 days	Death
4	1/320, dsDNA, C3	1/320, dsDNA, C3			25/35 days	PR, HD
5	1/320, dsDNA, C3	1/100			5/10days	TF
6	1/100, C3	Negative, C3			10/20days	CR
7	NA	NA			5/10days	CR
8	1/80, C3	Negative	ACA (+), LA (+)	ACA (-)	29/44 days	Death
9	1/640, dsDNA, C3	1/80			5/12 days	Death
10	1/320	1/100			9/19 days	PR, PHT
11	1/160, Sm, SSA, dsDNA, C3	Negative			4/11 days	CR
12	SSA	Negative	ACA (+)	ACA (-)	5/14 days	CR
13	1/160, SSA, SSB, C3	SSA, SSB, C3			5/8 days	CR
14	1/160	Negative			NA	Death
15	1/320, Sm, RNP, dsDNA, C3	1/100, dsDNA	ACA (+)	ACA (-)	4/8 days	PR, paraplegia
16	1/320, Sm, RNP, dsDNA, C3	1/100, dsDNA	ACA (+), LA (+)	NA	3/5 days	CR
17	1/320	1/100			12/12 days	CR
18	1/100, SSA, SSB	Negative, C3			NA	CR
19	1/100, SSA	Negative	ACA (+)	NA	3/3 days	Give up
20	1/160, dsDNA, C3	1/80			6/12 days	CR
21	NA	NA	ACA (+), LA (+)	Negative	17/44 days	CR
22	NA	NA	ACA (+), LA (+)	LA (+)	33/39 days	CR
23	NA	NA	ACA (+), LA (+)	LA (+)	27/ 65 days	CR
24	NA	NA	ACA (+), LA (+)	LA (+)	2/ 2 days	CR

Patients 21 to 24 were primary APS patients.

ACA: anticardiolipin antibodies; LA: lupus anticoagulant; NA: not available; CR: complete response; PR: partial response; TF: treatment failure; HD: hemodialysis; PHT: pulmonary hypertension

We have two CAPS patients in our cohort, one for each group. The diagnosis of CAPS requires the finding of typical biopsy features and the involvement of at least three organ systems (8). Even though our 17th patient did not fulfill the diagnostic criteria for CAPS (due to lack of biopsy), she was resistant to previous methyl-prednisolone, cyclophosphamide, and IVIG. Both patients with CAPS and the 17th patient responded very well to TPE. Bayraktar et al. (9) mentioned that SLE is a poor prognostic factor in patients with CAPS and that cyclophosphamide might be beneficial in those with SLE-CAPS. We use intravenous methyl-prednisolone and cyclophosphamide in combination with TPE for both of these SLE patients. There were four primary APS patients in our cohort. One had CAPS and one had co-infection and hemolytic anemia resistant to IVIG and thus received TPE. The two other primary APS patients had venous and arterial involvement, including a cerebral infarct and an intestinal infarct. Therapeutic apheresis can be considered life saving in patients with severe APS (11). All of our APS patients completely responded to TPE. Even though APS patients do not fulfill the CAPS criteria, if they have life-threatening problems we feel that TPE might be an important life-saving alternative. Neurological diseases are the most common indication for TPE (12). Some of those SLE patients with severe central nervous system manifestations, neuropsychiatric symptoms such as psychosis or catatonia, acute myelopathy, or neuromyelitis optica have been successfully treated with adjunctive TPE (13). One patient with myasthenia gravis (MG) died during disease flare and another responded well. One longitudinal myelitis patient partially responded, and their quadriplegia decreased into paraplegia. Our SLE-neuromyelitis optica patient had completely responded to TPE, but during follow up two further courses were needed. For the patient with psychosis, TPE was preferred as a main treatment option because of disease flare and contraindication of corticosteroids, and the patient responded well. For patients with myasthenic crisis and selected patients with neurologic involvements, TPE might be an effective modality in disease management (14).

Thrombotic thrombocytopenic purpura (TTP) is characterized by thrombocytopenia, microangiopathic hemolytic anemia with negative Coombs' test, variable fever, neurological signs, and/or glomerulonephritis. The American Society for Apheresis recommends TPE as the

first-line therapy in TTP patients (14). Our TTP patient responded very well, and TPE was repeated after 5 years. TPE could be an alternative in SLE patients with hematologic problems, especially those resistant to other treatments. In three of our SLE patients with thrombocytopenia, TPE was used because of life-threatening bleeding and resistance to other agents. Two patients also had leucopenia. We used TPE in two patients with hemolytic anemia and in one patient with Evans syndrome due to drug resistance. We observed good responses in hemolytic conditions but less impressive responses in thrombocytopenic patients. As mentioned in the guideline of American Society for Apheresis, TPE treatment might temper the disease course until immunosuppressive therapy takes effect or if other treatments have failed (14). The role of TPE in lupus nephritis is controversial (6). It has been argued that TPE could serve as an adjunct treatment in patients with severe lupus nephritis who do not respond to conventional therapy or those who demonstrate a rapidly progressive decline in renal function. The 6th and 7th patients in our cohort were resistant to multiple cytotoxic agents. Furthermore, the 6th patient also had leucopenia. Both patients responded to TPE and remained dialysis-independent. A recently published paper examining patients in whom TPE was added to conventional therapy for lupus nephritis showed favorable outcomes for the TPE-treated patients (15). TPE could be a successful treatment for patients with resistant multisystem disease. We had three patients with pulmonary problems. Two of them had diffuse alveolar hemorrhage (DAH). Alveolar hemorrhage is uncommon in SLE, although TPE is effective in alveolar hemorrhage in similar conditions such as anti-GBM disease and in ANCA-associated vasculitis. In a previous study, TPE in patients with DAH did not improve survival as it did in our patients (13). Our patient with pulmonary fibrosis and skin ulcers partially responded with regard to pulmonary functions. Concurrent skin ulcers were another indication for TPE in this patient. The median number of TPE sessions patients was 6.5 (5-10.5). This number is concordant with the PEXIVAS study in vasculitis and in other SLE studies (6, 16). More sessions might be necessary in cases of CAPS. We observed an acceptable number of adverse events. An organized team approach is required for optimal effectiveness and to minimize the number of adverse events.

This study has some limitations, including the retrospective design and the definitions of composite outcome measure for TPE. However, the clinical and laboratory findings in addition to SLEDAI scores and treatments were given with all details. Readers might thus evaluate the effectiveness case by case by reviewing the tables.

In conclusion, our data suggest that TPE might be a good option for SLE patients with TTP, MG, and CAPS. TPE should be kept in mind for patients with other features of SLE, especially those patients who are resistant to other agents or in the presence of leucopenia and psychosis. Furthermore, concurrent TPE treatment in life-threatening conditions might temper the disease course until immunosuppressive therapy takes effect.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of Hacettepe University (GO 13/143-27).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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