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A 15-year report of indications, adverse events, and effectiveness of therapeutic plasma exchange in patients with rheumatic diseases

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Therapeutic plasma exchange (TPE) is a type of treatment, which eliminates harmful antibodies, immune complexes, cytokines, and inflammatory products. Due to the lack of sufficient data on indications, effectiveness, and side effects of TPE in patients with rheumatic disease, we evaluated TPE in our center. All consecutive patients registered in university hospitals with definite rheumatologic indications for TPE during 15 years were evaluated. 680 sessions of TPE were performed on 166 patients, aged between 19 and 83 years**.** The most common underlying causes were collagen vascular diseases (60%) including systemic lupus erythematosus (SLE) (98%), and antiphospholipid antibody syndrome (APS) (1%); and then, primary small vessel vasculitis (SVV) (39.8%). The main indications for TPE in all patients were rapidly progressive glomerulonephritis (RPGN) (69.8%) and pulmonary hemorrhage (39.1%). During 12 months follow-up, in SLE and SVV patients 17 (17.3%) and 20 (30.3%) entered complete remission; 37 (37.3%) and 12 (18.1%) entered partial remission; 44 (44.8%) and 34 (51.5%) had no recovery; and 37(37%) and 19 (28.7%) died, respectively. A total of 18 (10.8%) patients experienced TPE-related adverse events during TPE [hypotension 15 (9%), allergic reaction 1 (0.6%), fever 1 (0.6%), and hypocalcemia 1 (0.6%)]. The most common indication for TPE is SLE and primary vasculitis. The RPGN and pulmonary hemorrhage were the main indications. Although the rate of response to treatment was acceptable according to the fatal nature of these complications, further case-control studies are suggested to assess the effectiveness of TPE.

Keywords: *plasmapheresis; therapeutic plasma exchange; adverse event; vasculitis; systemic lupus erythematosus*

Introduction

Therapeutic plasma exchange (TPE), also known as plasmapheresis, is an extracorporeal treatment for separating the plasma from blood-forming components and eliminating large-molecular-weight substances such as harmful antibodies, immune complexes, cytokines, and pro-inflammatory and inflammatory products with replacement fluids such as plasma or albumin into the patients' blood [1, 2]. TPE was performed by Schwab and Fahey in 1960 for the first time in patients with macroglobulinemia [3]. Then in 1975, Lockwood et al. [4] introduced TPE as the treatment of choice in patients with immunologic, renal, and rheumatic diseases. Nowadays, TPE is commonly used in combination with other disease-modifying treatments, including immunosuppressive medications [2, 5]. Several studies confirmed the improvement of renal function and alveolar hemorrhage in patients who had undergone TPE in combination with other modifying treatments

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[6, 7]. Although there are recent controversies for this effectiveness [8] and early investigations have shown improvements in patients with rheumatic disease who have undergone TPE, the studies have no control groups and are not considered valid enough [9-11]

The potential indications for plasma exchange are categorized by the Apheresis Committee of the American Society for Apheresis (ASFA) from I to IV that are the gold standard treatment indications to effective recommendations [12]. The main TPE contra-indications are unavailability of central line access, hemodynamic instability, patients with known allergy to fresh frozen plasma (FFP) or albumin products and heparin, hypocalcemia, and consumption of angiotensin-converting (ACE) inhibitor 24 hours before TPE [1]. The major reported complications (ranging from 4.75-36%) are hypocalcemia or hypo-magnesemia due to the use of citrate anti-coagulation, hypotension, transfusion reactions, increased bleeding tendency due to hypo-fibrinogenemia or thrombocytopenia, fever and chills, fluid and electrolyte imbalance, and flushing and gastrointestinal symptoms, especially nausea and vomiting [1, 12, 13].

According to the lack of sufficient data on indications, effectiveness, and side effects of TPE in patients with rheumatic disease in our center, we decided to evaluate this issue. In this research, we evaluated the indications and role of TPE along with other immunosuppressive treatments in our patients with rheumatic disease admitted in rheumatology wards and Intensive care units (ICUs) and the outcome of their follow-up, if available, during 15 years retrospectively and found their basic poor prognostic factors as their presentation in hospital and organs that have been involved in their prognosis and also adverse events related to their disease or plasma exchanges.

Materials and Methods

This retrospective study was approved by ethics committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.480) and conducted from October 2004 to October 2019. All consecutive patients who were registered in Faghihi, Namazi, and Hafez hospitals affiliated to Shiraz University of Medical Sciences with definite rheumatologic and immunologic indications for TPE and admitted in rheumatology wards, internal medicine wards, or ICU were evaluated in this study. In case a subject had the inclusion criteria, the data were registered. Cases with any clinically significant infection and malignancy before TPE and those with incomplete records or missing data in their documents were excluded from our study. The name of the patients was found using their documents of registry in blood transfusion plasmapheresis center of Shiraz; then, their charts of admission and follow up were evaluated in Hafez, Namazi, and Faghihi Hospitals archives of patient charts. The data in the current retrospective cohort survey were extracted from Shiraz University of Medical Sciences (SUMS) Specific Diseases Affairs electronic database. The subjects were divided into patients with any connective tissue diseases including systemic lupus erythematosus (SLE) that fulfilled the American College of Rheumatology Revised Classification Criteria for SLE [14] with severe manifestations; patients with catastrophic antiphospholipid antibody syndrome (CAPS) [15]; those with primary small-vessel vasculitis (SVV) including anti-neutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV), [granulomatosis with polyangiitis (GPA) or eosinophilic granulomatosis with polyangiitis (EGPA)], renal limited vasculitis and unclassified SVV by nephrologists or rheumatologists [16] who had undergone sessions of TPE for their first episode because of any major organ involvement including diffuse alveolar hemorrhage (DAH), renal insufficiency, or other manifestations with severe organ involvement; and other indications of plasma exchange which had been scheduled. Other patients with diagnosis of primary SVV in the biopsy of any organs without exclusion criteria, like leukocytoclastic vasculitis or necrotizing/crescentic glomerulonephritis, were included as unclassified SVV. Then, they were followed by finding their documents and follow-up charts in Hafez, Namazi, and Faghihi Hospitals or calling the phone numbers available in their charts, and finding their prognosis and response after 2 months and 1 year of TPE, if

available.

The disappearance of primary manifestations was followed after 2 months using the terms of complete recovery, partial recovery, or no recovery. The time interval from the start (2 months after the TPE) to the end of the study was considered as censored time if the event of interest, i.e. death, did not occur in that interval. We divided the response of patients to the TPE and medications into four categories: complete recovery, partial recovery, no recovery, and death. The complete recovery of a disease was defined as complete response of lung, skin or renal manifestations, and the partial response of a disease were defined as no complete response of any of primary organ involvement of lung, skin or kidney.

Patients' survival and renal survival were also evaluated with the following variables for nephritis remission [17]: 1) complete remission (serum creatinine of ≤ 1.4 mg/dl and proteinuria ≤ 0.33 g/d); 2) partial remission: a ≤ 25% increase in baseline creatinine; and ≥ 50% reduction in baseline proteinuria to ≤ 1.5 g/d (but ≥ 0.33 g/d); 3) end stage renal disease which was defined by a serum creatinine of ≥ 6 mg/dl or the initiation of renal replacement therapy; and 4) death. Pulmonary involvement was defined as hemoptysis and diffuse alveolar hemorrhage in first High-resolution computed tomography (HRCT). The recovery was evaluated by follow up chest X-ray or HRCT. The response was defined as: complete response when dyspnea resolved, partial response when no need for mechanical ventilation (MV) but needs O2 treatment, and treatment failure when needs persistent MV.

According to the protocol for all TPEs, the cell separator was primed with red blood cell if the patient weighed less than 20 kg and/or if his/ her hemoglobin level was less than 10 g/dL. The plasma volume removed per exchange was about 121 ± 47 mL/kg (2.2 ± 0.6 plasma volume) and replacement solution consisted of 74 ± 11% fresh-frozen plasma or albumin combined with saline. The sessions were done at least 5 times every other day or daily based on disease.

The obtained data were evaluated using SPSS version 22.0 software. Numerical variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Qualitative variables were compared using Chi-square tests or Mann-Whitney test. Correlations were assessed using Pearson's coefficient correlation, and P-value < 0.05 was considered as statistical significance.

Results

A total of 187 patients underwent TPE in our study duration. Of them, 21 patients were excluded due to the incomplete information and missing data. About 5-7 sessions for each patient were held with a total average of 680 sessions of TPE. Finally, a total of 166 patients aged 19- 83 (mean: 38.50 ± 11.54) years were enrolled in this study. Out of 166 patients, 42 (25.3%) were male and 124 (74.7%) were female. The frequency of underlying diseases and indications for undergoing TPE were evaluated; they are reported in Table 1. The most common underling cause for TPE was collagen vascular disease which accounted for more than half (60%) of all causes including SLE (98%), antiphospholipid syndrome (APS) (1%), and systemic sclerosis (SSc) (1%). The next category was primary small vessel diseases (40%) including AAV (93.9%) [granulomatosis with polyangiitis (GPA) (83%), renal-limited vasculitis (11%)]; and unclassified vasculitis (6%). The most common indication for TPE in all patients was rapidly progressive glomerulonephritis (RPGN) (69.8%). The next common indications for TPE in patients with SLE were thrombotic thrombo-cytopenic purpura (TTP) (40.8%), pulmonary hemorrhage (34.6%), and cerebritis (22.4%), but the second common indication in primary SVV was pulmonary hemorrhage (46.9%). As to the duration of the disease, out of 166 patients, 73 (44%) were new cases that needed TPE. Indications for TPE in our population regarding the type of disease and the clinical response to TPE after 2 and 12 months of follow-up are summarized in Table 1.

We evaluated the difference of complete recovery in 2 months and 12 months of follow-up. Statistical analysis showed no significant difference in complete recovery of patients with SLE, primary vasculitis, and its subgroups in 2 months and 12 months of follow-up (P-value >

Table 1. The comparison of TPE indications and outcomes after 2 and 12 months of follow-up

Diagnosis		Number (%)	Sex (male/ female)	Age, (Mean ±SD)	Complete recovery			Partial recovery		No recovery	
					2 months	12 months	P-value	2 months	12 months	2 months	12 months
SLE	**Total**	98 (100)	8/90	35.97 (9.43)	24 (24.4)	17 (17.3)	0.68	36 (36.7)	37 (37.7)	38 (38.7)	44 (44.8)
	RPGN	62 (63.2)	6/56	36.29 (9.83)	15 (24.1)	9 (14.5)		4 (6.40)	5 (8.06)	43 (69.3)	48 (77.4)
	DAH	34 (34.6)	1/33	33.11 (8.28)	1 (2.90)	2 (5.80)		12 (35.2)	11 (32.3)	21 (61.7)	21 (61.7)
	TTP	40 (40.8)	4/36	36.29 (9.23)	3 (7.50)	2 (5.00)		19 (47.5)	19 (47.5)	18 (45.0)	19 (47.5)
	Cerebritis	22 (22.4)	2/20	38.18 (9.73)	6 (27.2)	6 (27.2)		2 (9.09)	2 (9.09)	14 (63.6)	14 (63.6)
Primary vasculitis	**Total**	66 (100)	33/33	48.17 (8.67)	24(36.3)	20 (30.3)	0.31	20 (30.3)	12 (18.1)	22 (33.3)	34 (51.5)
	RPGN	54 (81.8)	30/23	49.1 (7.94)	23(42.5)	19 (35.1)		13 (24.0)	3 (5.50)	18 (33.3)	32 (59.2)
	DAH	31 (46.9)	17/14	35.3 (9.01)	1(3.20)	1 (3.20)		15 (48.3)	9 (29.0)	15 (48.3)	21 (67.7)
GPA	**Total**	55 (100)	25/30	38.27 (8.71)	18(32.7)	12 (21.8)	0.49	18 (32.7)	12 (21.8)	19 (34.5)	31 (56.3)
	RPGN	43 (78.1)	22/21	41.21 (7.50)	18(41.8)	12 (27.9)		10 (23.2)	3 (6.9)	15 (34.8)	28 (65.1)
	DAH	30 (54.5)	16/14	38.60 (8.79)	0	0		15 (50.0)	9 (30.0)	15 (50.0)	21 (70.0)
Renal limited vasculitis	**Total**	7 (100)	6/1	64 (4.31)	4 (57.1)	4 (57.1)	0.84	0	0	3 (42.8)	3 (42.8)
	RPGN	7 (100)	6/1	64 (4.31)	4 (57.1)	3 (42.8)		0	0	3 (42.8)	4 (57.1)
Unclassified vasculitis	**Total**	4(100)	2/2	42.25 (9.31)	2 (50.0)	4 (100)	0.29	2 (50.0)	0	0	0
	RPGN	4 (75)	2/1	57.31 (5.28)	1 (25.0)	4 (100)		3 (75.0)	0	0	0
	DAH	1 (25)	0/1	32 (0)	1 (100)	1 (100)		0	0	0	0

TPE, therapeutic plasma exchange; SLE, systemic lupus erythematosus; RPGN, rapidly progressive glomerulonephritis; DAH, diffuse alveolar hemorrhage; TTP, thrombotic thrombocytopenic purpura; GPA, granulomatosis with polyangiitis

0.05). The rate of complete recovery in 2 and 12 months of follow-up of patients with SLE was 24.4% and 17.3% , respectively. In this group, the rate of complete recovery after 12 months of follow- up in patients with RPGN, TTP, pulmonary hemorrhage, and cerebritis was 14.5%, 5%, 5.8%, and 27.2%, respectively. The rate of complete recovery in 2 months of follow up of patients with primary vasculitis, GPA, renal limited vasculitis, and unclassified group was 36.3%. 32.7%, 57.1%, and 50%, respectively. Also, that of 12 months of follow up was 30.3%, 21.8%, 57.1%, and 100%, respectively. In primary vasculitis, the rate of complete recovery after 12 months of follow-up in patients with RPGN, pulmonary hemorrhage was 35.1% and 3.2%, respectively. The rate of complete recovery, partial recovery, and death after 12 months of follow-up in SLE patients who referred with pulmonary hemorrhage was 5.80%, 32.3%, and 61.7%, respectively; however, in patients with primary vasculitis who referred with pulmonary hemorrhage, it was 3.2%, 29%, and 67.7%, respactively. In 12 months of follow-up, RPGN in patients with primary vasculitis better responded to TPE (35.1%) compared with patients with SLE (14.5%), but pulmonary hemorrhage in SLE patients showed a better response (5.8%) compared with primary vasculitis (3.2%).

The rate of treatment failure in 2 months and 12 months of follow-up of patients with SLE was 38.7% and 44.8%, respectively. The total rate of treatment failure among patients with primary vasculitis in 2 months and 12 months of follow up was 33.3% and 51.5%, respectively. In patients with GPA, the rate of treatment failure was 34.5% and 56.3% in 2 months and 12 months of follow-up. Also, that of patients with renal limited vasculitis in 2 months and 12 months of follow-up was 42.8%. No one (0%) in the unclassified group had failure in treatment. In SLE after 12 months of follow-up, 77.4% and 59.2% of the patients with RPGN and primary vasculitis needed hemodialysis, respectively.

A total of 56 patients (33.7%) who underwent TPE died in 12 months of follow-up. The mean time of death in was 267.72 ± 155.3 days, with a range of 10-365 days. The indications for TPE in SLE patients who died were RPGN + pulmonary hemorrhage + TTP in 5 (5%), RPGN + cerebritis + TTP in 4 (4%), RPGN + TTP in 4 (4%), cerebritis + TTP in 3 (3%), pulmonary hemorrhage in 3 (3%), RPGN + pulmonary hemorrhage in 2 (2%), cerebritis in 2 (2%), pulmonary hemorrhage + TTP in 1 (1%), RPGN

in 1 (1%) and TTP in 1 (1%) case. The indications for TPE in patients with primary vasculitis were RPGN + pulmonary hemorrhage in 13 (19.6%), RPGN in 13 (19.6%), pulmonary hemorrhage in 6 (9%) case. In patients with GPA, RPGN + pulmonary hemorrhage in 12 (21.8%), pulmonary hemorrhage in 5 (9%) and RPGN in 2 (3.6%) case were indications of TPE. In patients with renal limited vasculitis, RPGN in 7 (12.7%) case was reason of TPE. In patients with unclassified SVV, RPGN in 4 (7.2%), RPGN + pulmonary hemorrhage in 1 (1.8%) and pulmonary hemorrhage in 1 (1.8%) case were an indication for TPE.

Out of 99 patients with SLE, 59 had available kidney biopsy, out of which 4 demonstrated vasculitis, 3 granulomatosis, 14 had crescent formation, and 36 and 2 had class IV and V nephropathies, respectively. From 55 patients with GPA, 38 kidney biopsies, 3 sinus biopsies, and 3 skin biopsies were available. All of these samples had vasculitides in histopathologic evaluation.

A total of 18 (10.8%) patients developed adverse events during TPE. Fifteen (9%) patients developed hypotension, 1 (0.6%) developed allergic reaction, 1 (0.6%) had fever, and 1 (0.6%) developed hypocalcemia. No one developed dyspnea, angina, abdominal pain, or convulsion.

We also recorded all medications used in combination with the TPE in our patients. A total of 52 (31.5%) patients received only glucocorticoid (GC) medications. Ninety-six patients (58.1%) received GC plus cyclophosphamide (CYC). Eleven (6.6%) and 6 (3.6%) patients received GC plus rituximab (RTX) and GC plus RTX plus CYC, respectively.

Regarding the mean death time in each group, there was no significant association in survival of patients in each treatment group (P-value 0.752). The mean death time in those treated with GC in combination with TPE was 234.654 (22.87) days. Also, that of patients treated with GC plus CYC and GC plus RTX was 248.063 (16.32) days and 271.727(45.92) days, respectively. The mean death time in patients treated with GC, RTX, and CYC was 308.167 (51.88) days. As to the mean death time in each group, there was no significant association in the survival of patients in each treatment group (P value 0.752) (Figure1).

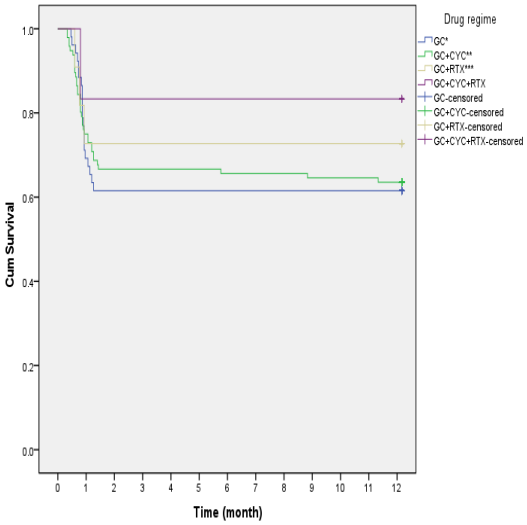

Figure 1. Time of death in patients treated with different medications in combination with TPE
GU, glucocorticoid; CYC, cyclophosphamide; RTX, rituximab, TPE, therapeutic plasma exchange

The mean (SD) level of BUN at baseline was 55.45 (22.65) (mg/dL). In two and twelve months of follow-up, the BUN level decreased to 39.54 (23.73) and 38.86 (12.62), respectively. The alteration in the BUN level was statistically significant (P-value = 0.037). The mean (SD) level of creatinine (Cr) at baseline was 5.25 (2.23) mg/dL. In two months of follow-up, the Cr level decreased to 3.60 (1.87) and increased again to 4.31 (2.23) in 12 months of follow-up. The alteration in BUN level in two months of follow-up was statistically significant. The mean (SD) of glomerular filtration rate (GFR) at baseline was 19.40 (12.45). In two months of follow-up, it increased to 30.05 (20.39) and again decreased to 27.11 (23.61) in 12 months of follow-up. The change in GFR in 2 months of follow-up was statistically significant (p value 0.028). The mean (SD) level of hemoglobin (Hb) at baseline was 8.93 (4.15). In 2 and 12 months of follow-up, the Hb level improved to 9.18 (5.01) and 9.26 (4.93), respectively. The change in the hemoglobin level was statistically significant (P-value 0.048).

Discussion

In this study, we aimed to evaluate the TPE indications, side effects, and effectiveness in patients with rheumatic diseases and the main causes of death and survival, and we followed them for their response in a cohort study during 15 years in university centers. Of note, SLE was the most common underlying disease in, representing 59.6% of all the cases. The next common disease was primary vasculitis. A recent cohort study by Bai et al. also showed that SLE accounted for about 50% of all cases who had undergone TPE [18].

Among patients with SLE, the most common indications for TPE were RPGN and then TTP, pulmonary hemorrhage and cerebritis, respectively. In addition, common indications among patients with primary vasculitis were RPGN and then pulmonary hemorrhage. In a previous study by Aguirre-Valencia et al., the main indication for TPE among 66 patients with SLE was diffuse alveolar hemorrhage (n = 11, 27.5%) [19]. The next common indications for TPE among such patients were neuropsychiatric involvement (n = 9, 22.5%), TTP (n = 5, 12.5%), catastrophic APS (n = 4, 10%), lupus nephritis (n = 4, 10%), severe cutaneous involvement (n = 2, 5%), gastrointestinal involvement (lupus pseudo-obstruction; n = 1, 2.5%), severe SLE (n = 1, 2.5%), severe resistance to type B insulin (n = 1, 2.5%), Evans syndrome (n = 1, 2.5%), and kidney allograft rejection (n = 1, 2.5%) [19]. In another study by Al Hamzi et al. on 68 patients with SLE and AAV (58 patients with SLE and 10 with AAV), the main indication for TPE was renal involvement that was seen in all the patients [17]. The next indications for TPE among patients with SLE were pulmonary hemorrhage (n = 28, 48%), cerebritis (n = 24, 41%), TTP (n = 10, 58%), and crescent formation (n = 5, 9%). The indications among patients with AAV were pulmonary hemorrhage (n = 5, 50%) and crescent formation (n = 5, 50%) [17]. Moreover, the findings of another study by Soyuöz et al. on 24 patients with SLE and primary antiphospholipid syndrome (APS) showed that the main indications for TPE were hematologic, neurologic, pulmonary involvement, and APS-related symptoms [20]. Another single-center study by Samanci et al. showed that the indications for TPE were renal transplantation (23.6%), AAV (16.4%), RPGN (15.5%), hemolytic uremic syndrome (HUS) (10%), TTP (8.2%), autoimmune hemolytic anemia (5.5%), FSGS (5.5%), multiple myeloma (3.6%), and chronic inflammatory demyelinating polyradiculoneuropathy (2.7%) [21].

In our study, females were more susceptible to performing TPE. Although in patients with SLE who underwent TPE the number of females was higher than males, in patients with primary vasculitis the number of females and males was equal.

In our study, the highest rate of complete recovery in two months after TPE was seen in patients with renal limited vasculitis; in 12 months of follow-up, it was seen in those with unclassified primary vasculitis. The lowest rate of complete recovery in 2 and 12 months of follow-up was among patients with SLE. The highest rate of treatment failure after 12 months of follow-up was seen in patients with renal limited vasculitis and then GPA. However, the lowest treatment failure rate was observed among patients with unclassified primary vasculitis. In a study by Al Hamzi et al. on 58 patients with SLE who underwent TPE, the rate of complete response, partial response, and treatment failure was 22%, 17%, and 33%, respectively [17]. Moreover, the rate of death among these patients was 16% (n = 9). Also, among patients with AAV, the rate of complete response to TPE, partial response, treatment failure, and death was 25%, 12.5%, 50%, and 12.5 %, respectively [17]. In a study by Samanci et al. on 110 patients with renal transplantation (26 cases), AAV (18 cases), RPGN (17 cases), hemolytic uremic syndrome (11 cases), TTP (9 cases), autoimmune hemolytic anemia (6 cases), FSGS (6 cases), and other diseases who underwent TPE, partial response was seen in 59.1%, and 21.8% of patients had complete response to treatment. Failure to treatment occurred in 12.7% of patients [21]. Vellinga et al. evaluated the patients who underwent TPE in a 7-year retrospective study. In this study, complete response to TPE was observed in 24.6% of patients [22]. Partial response and treatment failure rate in these patients were 60.9% and 14.5%, respectively [22].

In our study, RPGN in patients with primary vasculitis showed a better response to TPE compared with those with SLE, but pulmonary hemorrhage in SLE patients had a better response. In patients with unclassified primary SVV, RPGN had a better response to TPE compared with GPA and renal limited vasculitis. Also, pulmonary hemorrhage showed a better response to TPE in patients with unclassified primary SVV compared with AAV.

There were few adverse effects during TPE in our study. In a study by Sutton et al., the incidence of side effects due to the TPE among a total of 5235 procedures was 12% (612 procedures) [23]. In another study by Maxted et al., side effects were seen in only 13 sessions, accounting for 8.4% of all sessions. [24]. In our study, in all the patients, the most common adverse effect was hypotension that occurred in only 15 cases. Other complications were allergic reactions, fever, and hypocalcemia that developed in our population. The rate and kind of adverse events in our center were different from previous investigations in which allergic reaction was the most common complication during TPE. A similar retrospective cohort study showed that the rate of allergic reaction was 9.6% followed by dizziness (6.8%), palpitation (4.1%), and nausea (1.4%)[18]; also, in another study by Sutton et al., the most common reactions in this study were fever, chills, urticaria, muscle cramps, and paresthesia [23]. The common complications in another prospective cohort study conducted by Jagdish et al. on patients who had undergone double filtration plasmapheresis (DFPP) for renal indications were hypotension (33%), bleeding (20%), and access failure (6.6%) [12]. These complications were rare in our study. The difference between complications may be due to the type of exchanged solutions used in different centers. It seems that solutions with higher amounts of plasma and albumin pose higher complications and adverse effects. Therefore, further studies are recommended to be conducted by paying more attention to the device, techniques, and materials to determine the exact cause of this variation in adverse effect in different centers.

Our results were in the same line with those of a study by Vucic et al. on patients with neurological disorders who underwent TPE, showing that among 1283 plasmapheresis procedures (on 73 patients) no fatalities, no cases of Hepatitis B or C or HIV transmission, no allergic or febrile reactions, thrombosis, bleeding diathesis, or severe citrate toxicity were seen [25]. However, infections of venous access occurred in 0.5% of the procedures and septicemia seen in 0.2% of procedures. Similar to our study, hypotension occurred in 1.2% of procedures [25]. The citrate toxicity developed as nausea, vomiting, cramping, or paresthesia in 1.2% of procedures [25].

Our studies showed the BUN and Cr level decreased significantly during the 2 months of follow-up of patients although after 12 months the Cr level increased again. GFR level in our study improved significantly, but it slightly decreased after twelve months. This finding is consistent with that of a previous study by de Joode et al. on 26 patients with AAV which showed a significant improvement in renal function; however, during the long-term follow-up, there was no difference in renal function [26].

After dividing our patients regarding the other medicines prescribed, we observed no difference in the survival rate of patients in different groups. However, more prospective studies with more population and long follow-up are required to assess the efficacy of different combination treatments in the improvement of patients.

The highest rate of death in our population was seen among patients with GPA who presented with RPGN and pulmonary hemorrhage simultaneously. Among those with SLE, the highest rate of death was seen in patients who presented with TTP and RPGN and pulmonary hemorrhage simultaneously; also, the lowest rate was seen in patients with TTP or RPGN separately or TTP and pulmonary hemorrhage simultaneously. The rate of death among patients with primary vasculitis who presented with RPGN or RPGN with pulmonary hemorrhage was equal. No death was seen in patients with other indications for TPE. One of the novelties of our study is the evaluation of death rate among patients with each indication for TPE.

There were several limitations to our study. As to the retrospective method of this study, selection and information bias were inevitable. Moreover, we excluded several patients who had undergone TPE in our center due to the missing information. The sample size of several diseases in our study was small, which is another limitation to our study. Therefore, further evaluations with a larger sample size and longer duration of follow-up with frequent short intervals compared to the control group will be the best way to evaluate the efficacy of TPE in patients.

Conclusion

The current study showed that the most common indication for TPE in patients with rheumatic diseases in the south of Iran was SLE and primary vasculitis which presented with RPGN, TTP, and pulmonary hemorrhage, respectively . The most common causes of mortality in patients who underwent TPE in patients with SLE was the simultaneous occurrence of RPGN with pulmonary hemorrhage and TTP; also, in patients with primary vasculitis, RPGN with pulmonary hemorrhage was the cause of death. The side effects of plasmapheresis were rare, being mostly hypotension, allergic reaction, fever, and hypocalcemia. Although the rate of response to treatment is acceptable according to the fatal nature of these diseases in their exacerbations, further controlled studies are recommended to be performed to assess the effectiveness of applying other medications on the improvement of response to treatment and complete recovery.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this study.

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