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Plasmapheresis Experience in Patients with Acute Kidney Injury

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ABSTRACT:

Plasmapheresis experience in patients with acute kidney injury

Objective: Plasmapheresis has been used in the management of immune-mediated renal diseases for the last 40 years. The rationale behind this approach is to remove pathogenic immune mediators, such as autoantibodies and immune complexes, from the circulation. In this study, we aimed to evaluate retrospectively the patients treated with plasmapheresis in our clinic.

Material and Method: A total of 27 patients who had been hospitalized and treated in our clinic in the last 10 years were evaluated. Demographic characteristics, biochemical parameters, biopsy results, plasmapheresis complications and survival analyses following treatments were recorded.

Results: The mean age of the patients was 39±18 (17-71) years and the mean number of plasmapheresis sessions was 13.9±8.8 (2-41). Six patients had Goodpasture Syndrome, 5 patients had ANCA (+) small vessel vasculitis, 5 patients had thrombotic microangiopathy, 4 patients had Systemic Lupus Erythematosus, 3 patients had Acute Humoral Rejection, 3 patients had primary crescentic glomerulonephritis and 1 patient had multiple myeloma. One patient died, 9 patients had renal improvement and 12 patients underwent dialysis due to end stage renal disease during the treatment. One patient with renal improvement experienced recurrence, and including this patient, Grade 2-3 renal failure continued in a total of 6 patients.

Conclusion: In conclusion, plasmapheresis should be considered as an adjuvant treatment in some specific groups in Nephrology Clinics. It can prevent progression to end stage renal failure and accelerate renal improvement.

Keywords: Acute kidney injury, plasmapheresis, vasculitis

ÖZET:

Akut böbrek hasarlı hastalarda plazmaferez tecrübesi

Amaç: Plazmaferez, immunolojik renal hastalıkların tedavisinde son 40 yıldır kullanılmaktadır. Bu yaklaşımın altında yatan mekanizma antikorlar ve immun kompleksler gibi patojenik immun mediatörlerin dolaşımdan temizlenmesidir. Bu çalışmada kliniğimizde plazmaferez tedavisi gören hastaların retrospektif olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Son 10 yılda kliniğimizde yatan ve terapötik plazmaferez tedavisi alan toplam 27 hastanın kayıtları değerlendirildi. Demografik özellikleri, biyokimyasal parametreleri, biyopsi sonuçları, plazmaferez komplikasyonları ve tedavisi sonrası sağkalımları kayıt edildi.

Bulgular: Hastalarda ortalama yaş 39±18 (17-71) yıl, ortalama plazmaferez seans sayısı 13.9±8.8 (2-41) olarak saptandı. Altı hastada Goodpasture hastalığı, 5 hastada ANCA (+) küçük damar vasküliti, 5 hastada trombotik mikroanjiyopati, 4 hastada sistemik lupus eritematozus, 3 hastada akut humoral rejeksiyon, 3 hastada primer kresentik glomerulonefrit ve 1 hastada ise multipl myelom saptandı. Tedavi esnasında bir hasta exitus oldu, 9 hastada renal iyileşme görüldü, 12 hastada son dönem böbrek yetmezliği nedeniyle diyaliz tedavisine başlandı. Renal düzelme saptanan hastalardan birinde nüks saptandı ve bu hasta ile birlikte toplam 6 hastada da Evre 2-3 böbrek yetmezliği devam etti.

Sonuç: Plazmaferez nefroloji kliniklerinde bazı özel grup hastalarda adjuvan tedavi olarak düşünülmelidir. Son dönem böbrek yetmezliğine ilerlemeyi önleyebilir ve renal iyileşmede hızlanmaya neden olabilir.

Anahtar kelimeler: Akut böbrek hasarı, plazmaferez, vaskülit

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INTRODUCTION

Plasma exchange (plasmapheresis) is a treatment method based on the principle that the blood is taken out of the body, followed by seperation of plasma, which is one of the 4 components of the blood, and the remainder is returned to circulation with the replacement fluid (1). Plasmapheresis has been used for the last 40 years in the treatment of immunologic renal diseases. The underlying mechanism of this approach is the clearance of pathogenic immunomodulators, such as antibodies and immunocomplexes, from circulation. It may also be useful for the reduction of proinflammatory molecules, such as complement components and coagulation factors (2).

This study describes the role of plasmapheresis in the 6 most frequent renal diseases mentioned in the records of the Canadian Apheresis Group in 2013 and the evidence underlying current practice and guidelines. These kidney indications include thrombotic microangiopathy, anti-glomerular basal membrane disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, cryoglobulinemia, focal segmental glomerulosclerosis recurrence in allograft and renal transplantation (3,4). In this study, it was aimed to retrospectively evaluate the patients who were treated with therapeutic plasmapheresis in our Nephrology Clinic, our plasmapheresis indications and to have information about their results.

MATERIAL AND METHOD

The records of 27 patients who were treated with therapeutic plasmapheresis in the last 10 years in Şişli Etfal Training and Research Hospital, Nephrology Clinic were evaluated retrospectively.

Demographic characteristics such as age, gender, reasons for receiving plasmapheresis treatment, frequency of plasmapheresis treatment and total number of sessions, total fresh frozen plasma (TDP) amount used for plasma exchange and complications during plasmapheresis were recorded from the files. Plasma volume (L) was calculated using the formula: 0.07xWeight (kg)x(1-hematocrit). In each procedure, 1-1.5 plasma volume change was used (5). The regimen of plasmapheresis applied was as follows: Daily or every other day and for 2-3 weeks with TDP as replacement fluid. Transeint femoral or when needed, jugular venous catheter was used as a vascular access during plasmapheresis.

Biochemical parameters (serum urea, creatinine, sodium, potassium, calcium, phosphorus, albumin, alanine and aspartate transaminases, lactate dehydrogenase, total and direct bilirubin levels) of the patients before and after plasmapheresis treatment, complete urine analysis, complete proteinuria amounts in 24-hour urine, blood count, coagulation tests (INR), complement C3 according to the indication, antinuclear antibody, ANCA and anti-glomerular basement membrane antibody (anti-GBM) levels were recorded. The biopsy results of the patients, steroid and immunosuppressive treatments outside plasmapheresis, and the number of sessions when hemodialysis was performed were determined from the patient records. All patients' data about their renal and clinical course after the treatment were obtained and recorded.

The data were loaded into the SPSS 11.0 statistical program and analyzed. Chi-square test was performed in the analysis of non-parametric data. Parametric data were given as mean±standard deviation (minimum-maximum).

RESULTS

The data of twenty-seven patients were reviewed retrospectively. Fifteen of the patients were female,

Table-1: Biochemical and blood count parameters of patients before and after treatment

	Before tretment	After treatment
Urea (mg/dl)	169±75	127±99
Creatinine (mg/dl)	7.4±3.9	3.7±2.6
Uric acid (mg/dl)	7.9±2.4	6.8±1.2
Albumin (mg/dl)	3.1±0.7	3.6±0.6
Calcium (mg/dl)	8.3±0.9	8.7±0.8
Phosphorus (mg/dl)	6.5±2.4	5.0±1.5
ALT (U/L)	17±10	12±5
AST (U/L)	26±18	11±3
LDH (U/L)	847±992	381±248
T.bilirubin (mg/dl)	1.2±1.4	0.5±0.3
Hemoglobin (g/dl)	8.1±1.9	9.4±2.7
Platelet (10^3/mcgL)	222±146	169±66

and the mean age was 39±18 years. Hematuria and proteinuria were detected in all patients at first admission during renal failure and urine examinations, and biochemical and hematological parameters before and after treatment were shown in Table-1.

The mean number of sessions of plasmapheresis was 13.9±8.8 (2-41). When the renal-immunological diseases in which plasmapheresis has been performed is considered; 6 patients had Goodpasture syndrome, 5 patients had ANCA-associated rapidly progressive glomerulonephritis (4 patients with Granulomatosis polyangiitis, 1 patient with microscopic polyangiitis), 5 patients had thrombotic microangiopathy (TMA), 4 patients had systemic lupus erythematosus (2 patients with antiphospholipid antibody syndrome), 3 patients had primary crescentic glomerulonephritis, 3 patients had acute humoral rejection and 1 patient had multiple myeloma (Table-2).

When the renal survival of 27 patients were investigated; renal failure healed in 9 patients (3 patients with acute humoral rejection, 3 SLE, 2 TMA, and 1 with Goodpasture syndrome) (creatinine levels returned to normal limits) and renal replacement therapy was initiated in 12 patients due to end-stage renal disease. One patient with TMA diagnosis who recovered renal failure had recurrence after 18 months and plasmapheresis therapy was repeated 7 times. A total of 6 patients including this patient were diagnosed and followed-up with Stage 2-3 chronic renal disease. During plasmapheresis treatment, 3 patients developed allergic reaction, 2 developed catheter infection and one developed symptomatic hypocalcemia due to citrate use that responded to medical treatment. One patient diagnosed with TMA was intubated due to neurological complications and died. Methylprednisolone (iv) 1 gr/day for 3 consecutive days, followed by 0.5 mg/kg/day prednisolone (oral) treatment was initiated for all patients, beside plasmapheresis treatment. In addition, 17 patients were treated with 1 g/month cyclophosphamide (IV), and 1 patient receieved 100 mg/day Azothiopurine treatment.

Table-2: Plasmapheresis session distribution according to etiologic distribution of patients

	Number of Sessions (minimum-maximum)
Goodpasture syndrome (n:6)	7 - 22
ANCA (+) Vasculitis (n:5)	12 - 29
Thrombotic microangiopathy (n:5)	7 - 41
Systemic lupus erythematosus (n:4)	2 - 18
Acute humoral rejection (n:3)	7-14
Primary crescentic glomerulonephritis (n:3)	6 - 15
Multiple myeloma (n:1)	4

DISCUSSION

Plasmapheresis came up in the mid-1970s for use in the treatment of immunological renal diseases, when it was found to be useful when added to immunosuppressive drugs in the Goodpasture syndrome (6). Following this period, plasmapheresis or therapeutic plasma exchange (TPE) has bee used in various renal diseases with a pathogenesis including immunocomplexes or various autoantibodies. While most of the previous literature consists of case reports or uncontrolled series, controlled trials comparing TPE with standard treatment have been published in increasing numbers in recent years (7).

In Goodpasture syndrome, plasmapheresis

Table-3: Recent status of patients according to renal function

	Normal renal function	CRF*	ESRF**	Exitus
Goodpasture syndrome (n:6)	1	2	3	
ANCA (+) Vasculitis (n:5)		2	3	
Thrombotic microangiopathy (n:5)	2		2	1
Systemic lupus erythematosus (n:4)	3		1	
Acute humoral rejection (n:3)	3			
Primary crescentic glomerulonephritis (n:3)	-	1	2	
Multiple myeloma (n:1)			1	

*CRF: Chronic renal failure, **ESRF: End-stage renal failure

therapy has been shown to rapidly clear anti-GBM antibodies and to improve renal function and reduce the progression to end-stage renal failure (8). However, in large published series, it was reported that renal functions returned to normal in 44% of patients and in 41%, there was need for one of the replacement therapies (9,10). It has been reported that patients who are oliguric in the acute phase, have a serum creatinine level above 6.8 mg/dl, or are in need of dialysis when diagnosed, the improvement is inadequate (10). Serum creatinine level was above 6.8 mg/dL in 3 of 6 patients with Goodpasture syndrome and renal function was not improved in these patients. Of the remaining 3 patients, complete recovery of renal function was detected in 1 patient, while 2 patients were followed with Stage 2-3 CRF.

Approximately 40% of patients with rapidly-progressive glomerulonephritis (RPGN) constitute pauci-immune RPGNs due to granulomatosis with polyangiitis, microscopic polyangiitis, and polyarteritis nodosa and generally have poor prognosis (11). There is controversial results regarding plasmapheresis treatment in addition to immunosuppressive treatment in these patients. Two randomized controlled clinical trials reported that plasmapheresis has no beneficial effect (12,13), while in three trials, evidences has been reported that it is beneficial in subgroups with severe disease (14-16). In a prospective, randomized controlled trial by Janne et al. (17), plasmapheresis was reported to be indicated in patients with severe renal insufficiency (serum creatinine level <5.8 mg/dL) or with ANCA (+) crescentic glomerulonephritis with alveolar hemorrhage. In our study, we found serum creatinine levels below 5.8 md/dl in only two of our patients with ANCA (+) vasculitis who were treated with plasmapheresis and these patients were followed up as stage 2-3 CRF.

Clinical or pathological evidence of a specific class of primary glomerulonephritis or systemic immune complex disease, such as systemic lupus erythematosus, is present in the majority of rapidly-progressive immunocomplex glomerulonephritic patients. Plasmapheresis is reported that it may be used in the crescentic course of lupus, cryoglobulin, and IgA nephritis/Henoch-Schönlein purpura (18). In a randomized trial, it was reported that plasmapheresis treatment in proliferative lupus nephritis was not beneficial but could be useful in over-aggressive, catastrophic patients and in patients with antiphospholipid syndrome (19-21). Half of the patients treated with plasmapheresis had antiphospholipid syndrome and we detected a response to treatment in these patients.

There is significant evidence that plasmapheresis improves renal healing and mortality in adult patients with TMA. It has been proposed as a primary indication for TMA by the study conducted by the Canadian Apheresis Group and also in the US guidelines (22,23). In our patients with TMA, plasmapheresis treatment resulted in renal improvement in nearly the half, but a patient in this group was also lost due to neurological complications.

Three types of plasma replacement fluid; human albumin, human albumin-saline, and fresh frozen plasma (TDP), are used (5). Human albumin is the basic replacement fluid. The major disadvantages are that it does not contain coagulation factors and is expensive. Hypotension, anaphylaxis, citrate-related paresthesia, and urticaria can occur as a complication when TDP is used as replacement fluid. Infection (viral infection) risk is minimal in both products. In our study, TDP was used in all cases since it is cheaper and easily available.

Antibody-mediated rejection is one of the important causes of acute and chronic allograft dysfunction and graft loss. Plasmapheresis has begun to be used in antibody-mediated rejection therapy since the 1980s and has recently begun to be applied as part of desensitization protocols in patients with positive anti-HLA antibodies prior to renal transplantation or prior to ABO-incompatible renal transplantation (24,25). In many studies, it was often useful when administered with intravenous immunoglobulin in acute antibody-mediated rejection therapy (26). In our study, 3 patients who were diagnosed as humoral rejection as a result of kidney biopsy were treated with intravenous immunoglobulin therapy and plasmapheresis together, and all of them showed an improvement in renal functions to basal levels.

Complications of TPE are not common. These

usually occur due to complications of vascular access pathways, allergic reactions due to TDP, increased risk of bleeding, and hypocalcemia.

In a study reporting complications of over 15,000 plasmapheresis treatments, complications were more frequent (1.4% vs. 20%) in plasmapheresis treatments with TDP compared to albumin replacement (27). In a Swedish group report, over 20,000 procedures were performed with no mortality, with a side effect rate of 4.3% and a severe side effect rate of only 0.9% (28).

In the Canadian Apheresis Group report, there were side effects (mostly minor) in 12% of the procedures and severe side effects were seen in only 0.4% of procedures in over 144000 procedures (29). World Apheresis Association reported a 5.7% adverse event rate in over 12,000 treatments, a severe side effect rate of only 0.5%, and no procedural mortality (30).

In our study, only 1 case of citrate-related paraesthesia, hypocalcemia was detected and it responded to medical treatment; and 2 patients had catheter infection. Patient loss due to plasmapheresis has been observed with a rate of 0.03-0.05% in studies, whereas in our study, there was no mortality due to treatment, and the loss of single patient was observed to be due to neurological involvement in TMA.

As a result; plasmapheresis therapy has a place in the practice of Nephrology and when properly administered within indications, it is seen to increase the survival effectively in severe renal diseases. Larger well-designed studies are required to explain the role of plasma exchange in renal diseases.

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