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Patient outcome in antibody-positive systemic vasculitis treated with therapeutic plasma exchange

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Abstract:

BACKGROUND: Therapeutic plasma exchange (TPE) has been advocated as an adjunct to steroids and cytotoxic drugs in treating patients suffering from vasculitis and presenting with active disease, but we still have insufficient evidence on its effectiveness in improving the clinical response, especially in India. This study was planned to study the clinical outcome in severe vasculitic presentations treated with TPE as an adjunctive therapy.

MATERIALS AND METHODS: A retrospective analysis of TPE procedures performed from July 2013 to July 2017 in the department of transfusion medicine at a large tertiary care hospital was done. All consecutive patients admitted with new diagnosis of systemic vasculitis presenting with active disease and severe presentations such as advanced renal failure or severe respiratory abnormalities or life-threatening vasculitis affecting the gastrointestinal tract, neurological and musculoskeletal system; who needed TPE for removal of preformed antibodies, were included in the study.

RESULTS: There were a total of 31 patients in whom TPE was performed for severe systemic vasculitis; 26 adults and five pediatric. Six patients tested positive for perinuclear fluorescence, 13 for cytoplasmic fluorescence (cANCA), two for atypical antineutrophil cytoplasmic autoantibody, seven for anti-glomerular basement membrane antibodies, two for antinuclear antibodies (ANA), and one patient tested positive for ANA as well as cANCA before the augmentation of TPE. Out of 31, seven patients showed no clinical improvement and succumbed to the disease. At the end of desired number of procedures, 19 tested negative and five tested weak positive for their respective antibodies.

CONCLUSION: Favorable clinical outcomes were observed with TPE in patients with antibody-positive systemic vasculitis.

Keywords:

Anti-glomerular basement membrane, antineutrophil cytoplasmic autoantibody, antinuclear antibodies, diffuse alveolar hemorrhage, glomerulonephritis, therapeutic plasma exchange, vasculitis

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Introduction

Vasculitis is defined by the presence of inflammatory leukocytes in vessel walls with reactive damage to mural structures leading to tissue ischemia. Therapeutic plasma exchange (TPE) has long been advocated as a potentially useful adjunct to combination therapy of steroids and immunosuppressants in treating patients suffering from primary as well as secondary vasculitis; especially those presenting with advanced disease, but we still have insufficient evidence on its effectiveness in improving the clinical response.

Plasma exchange was initially used for reducing anti-glomerular basement membrane (GBM) antibodies in patients with Goodpaster's disease but later

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its use was also advocated in vasculitis causing glomerulonephritis without anti-GBM antibodies. The knowledge of the presence of antineutrophil cytoplasmic autoantibody (ANCA) and its role in pathogenesis of severe vasculitis led to trials of plasma exchange for reducing the load of circulating ANCA in patients presenting with life-threatening complications. Untreated ANCA-associated vasculitis (AAV) carries a poor prognosis; almost 80% of the patients succumb to the disease within 2 years.[1] The most important factors which help in prediction of prognosis are the presence of pulmonary hemorrhage and the severity of renal failure at diagnosis.

Systemic lupus erythematosus (SLE)-induced vasculitis is an important cause of secondary vasculitis characterized by the presence of antinuclear antibodies. Around 20% of SLE patients have ANCA antibodies as well, usually described as SLE/ANCA AAV overlap syndrome.[2]

The role of TPE in ameliorating symptoms of such patients by removal of preformed antibodies needs more discussion. There is a paucity of data on the use, benefits, and adverse events of TPE in this patient category, especially in a country like India.[3-5] Therefore, we aimed at studying the clinical outcome in severe vasculitic presentations treated with TPE as an adjunctive therapy.

Materials and Methods

Settings and design

The present study is a retrospective analysis of TPE procedures performed from July 2013 to July 2018 in the department of transfusion medicine at a large tertiary care hospital. The study population included all consecutive patients admitted with new diagnosis of systemic vasculitis presenting with active disease. All patients with severe presentations such as advanced renal failure or severe respiratory abnormalities or life-threatening vasculitis affecting the gastrointestinal tract, neurological and musculoskeletal system; who needed TPE for removal of preformed antibodies till the adequate effect of immunosuppression was achieved, were included in the study. Patients < 18 years of age were included in the pediatric age group while patients equal to or more than 18 years were included in the adult age group. Patients who were not assessed for laboratory improvement along with clinical improvement, were excluded from the study. Patients who were lost to follow-up were also excluded from the study.

Therapeutic plasma exchange

All procedures were performed on a continuous flow cell separator, Com. Tec (Fresenius Kabi, Germany) with PL1 plasma exchange kit using central venous access with dialysis type double-lumen catheter. Informed consent was obtained before each procedure. Demographic details, provisional diagnosis, the American Society for Apheresis category, response, and complications were noted. Preprocedure and postprocedure laboratory investigations such as complete blood count, kidney function tests, coagulation profile, serum albumin, serum calcium, autoantibody profile, and chest radiography were also recorded. A careful note of procedure parameters such as blood and plasma volume processed, anticoagulant used, time taken, amount and type of replacement fluid administered, and patient vitals before, during, and after the procedure were noted. Albumin was the preferred replacement fluid. The only exceptions were patients with bleeding, especially diffuse alveolar hemorrhage (DAH) or deranged coagulation profile, where fresh frozen plasma (FFP) was used. All patients were given 10 ml (10%) calcium gluconate diluted in normal saline for every 1000 ml blood volume processed as per departmental standard operating procedure as prophylaxis to prevent citrate-related adverse reactions. Special care during catheter handling was taken to maintain strict asepsis and the lines were flushed with saline and heparin (10 IU/ml) to maintain patency.

Statistical analysis

Data were entered into an Excel sheet; numbers and percentages were calculated.

Ethics committee approval

Since anonymized retrospective patient data were analyzed without any active intervention, the ethical committee approval was not needed. However, informed consent for participation in the study was obtained from all 31 patients included in the study.

Results

There were a total of 31 patients from July 2013 to July 2018, presenting to the health-care center with various clinical manifestations of systemic vasculitis, who needed TPE.

Demographics

Out of these 31, 26 were adults and five belonged to the pediatric age group. The average age at presentation in the adult population was 47.15 ± 9.52 years and that in the pediatric age group was 11.60 ± 4.36 years. Five (16.13%) patients were admitted under pediatric nephrology, six (19.35%) under internal medicine, eight (25.8%) under nephrology, and 12 (38.71%) under rheumatology. Patient-wise details of all 31 patients are listed in Table 1.

Gender distribution among the two age groups and autoantibody profile of patients at presentation are listed in Table 1.

Table 1: Age group-wise, gender-wise, and antibody specificity wise distribution of included patients

Age group	Males affected	Females affected	Total	Autoantibody detected at presentation	Specificity	Number of patients
Adult (>18 years)	14	12	26	ANCA	PR-3 (cANCA)	10
					MPO (pANCA)	7
				Atypical ANCA	-	1
				Anti-GBM	-	6
				ANA	-	2
Pediatric (<18 years)	2	3	5	ANCA	PR-3 (cANCA)	3
					MPO (pANCA)	0
				Atypical ANCA	-	1
				ANA+cANCA	-	1
Total			31			31

GBM=Glomerular basement membrane, ANCA=Antineutrophil cytoplasmic autoantibody, ANA=Antinuclear antibodies, MPO=Myeloperoxidase, PR 3=Proteinase 3, pANCA=Perinuclear ANCA, cANCA=Cytoplasmic ANCA

A total of 188 TPE procedures were performed for these 31 patients. The mean number of procedures performed was 6 per patient. Ten patients had femoral venous access while 21 patients had jugular venous access for performing TPE. The mean blood volume and plasma volume processed per procedure were 5952 ± 50.08 ml and 3968 ± 43.46 ml, respectively. Acid Citrate Dextrose Formula A (ACD-A) was the preferred anticoagulant in all the procedures with an average amount of ACD infused per procedure being 307 ± 8.34 ml. The mean number of injectable calcium gluconate ampules (10 ml) used per procedure was five (5.3 ± 1.2). The replacement fluid administered during TPE consisted of 5% albumin in 74 procedures, FFP in another 80, and a combination of 5% albumin and FFP in the rest, i.e., 34. All 74 of the procedures with albumin as replacement fluid were performed for patients who did not have DAH. All the procedures were uneventful except six (3.3%) which included urticarial reaction in two and catheter-related complications (thrombosis, catheter-related infection, hematoma) in four.

All the patients were assessed for clinical as well as laboratory improvement (autoantibody strength profile) after completion of TPE procedures. Out of 31, seven patients who had signs of organ damage such as pancreatitis, hepatic failure, or comorbidities such as sepsis and anemia among others, before the initiation of TPE, showed none or minimal clinical improvement with augmentation of TPE as an adjunctive therapy and succumbed to the disease. Of the 24 patients who showed clinical improvement with the augmentation of TPE and started recovering, 19 tested negative for their respective antibodies while the rest of the five tested weak positive at the end of desired number of procedures. The survival rate in this patient category, during primary admission after initiation of TPE as an adjunct to steroids and immunomodulatory drugs, was thus 77.42%. Survival at 3 months from the date of discharge was 100%. Relapse with readmission was seen in 11 patients (45.83%).

In the present study, the most common organs affected were kidneys; 26 patients at presentation had renal impairment. Of the seven patients who succumbed to the disease, five had renal dysfunction. Twenty-one of the 24 patients who survived had renal dysfunction during their hospital stay, out of which, 17 required dialysis. Seven out of these 21 suffered from chronic kidney disease and four were dialysis-dependent at the time of writing this report. One of these four is planned for a renal transplant in the near future. Thus, two-thirds or 66.67% (14 out of 21) of the renal patients benefited from a combination therapy of drugs and TPE and 13 out of 17 (76.47%) patients became dialysis independent.

The second most common organ affected was the lungs. Eight patients presented with DAH during active disease. Two out of these seven succumbed, whereas five patients had radiological improvement along with clinical improvement during the course of treatment. None of these five patients had signs of significant residual fibrosis in 3-month follow-up period.

Discussion

According to Chapel Hill International Consensus definitions which are based on the vessel size, Wegener's granulomatosis, microscopic polyangiitis, and Churg–Strauss syndrome are known as small-vessel vasculitis which is commonly associated with the presence of ANCA in circulation.[6]

ANCA contributes by acting on cytokine-primed neutrophils and monocytes, which express ANCA antigens, proteinase 3 (PR3), and myeloperoxidase (MPO) on their surface. Wegener's granulomatosis is predominantly associated with PR3-ANCA/cytoplasmic, cytoplasmic fluorescence while microscopic polyangiitis is associated with ANCA which has specificity for MPO-ANCA/perinuclear and perinuclear fluorescence. Churg–Strauss syndrome is associated with MPO-ANCA in almost 50% of the cases.[7]

Vasculitis can affect any organ but the most frequently affected organs include kidneys (70% cases), lungs,

ear-nose-throat, joints, skin, and nerves.[8] In the kidneys, capillaritis leads to segmental glomerular necrosis, eventually ending up as necrotizing crescentic glomerulonephritis. These patients can present with hematuria, proteinuria, and red cell casts; which can be followed by a rapid deterioration in renal function. Most patients with histologic picture of an intense, neutrophil predominant inflammatory infiltrate lead to renal impairment with the presence of crescentic glomerulonephritis. ANCA AAV is the most frequent cause of rapidly progressive glomerulonephritis. Capillaritis in the lungs leads to alveolar hemorrhage, presenting as cough, hemoptysis, and dyspnea which can progress to life-threatening pulmonary hemorrhage. Ocular abnormalities such as episcleritis, uveitis, proptosis, and optic nerve ischemia can also occur. The disease can involve the gut, causing ischemia and hemorrhage. It may involve the peripheral nervous system leading to mononeuritis multiplex while the involvement of the heart may lead to life-threatening myocardial ischemia.

End-stage renal disease and mortality are familiar outcomes of vasculitis associated with the presence of antibodies; especially ANCA. The presence of circulating antibodies has provided physicians with a rationale for antibody and/or immune complex removal by TPE in such patients. Nineteen tested negative for their respective antibodies while the rest of the five tested weak positive at the end of desired number of procedures.

The conflict between the use of medical therapy alone in the form of steroids and immunomodulatory drugs and addition of an expensive intervention, i.e., TPE to the standard combination of steroids and cyclophosphamide is age-old. Published literature so far advocates two school of thoughts; those which prove TPE to be beneficial in the treatment of systemic vasculitis and other studies which remain unclear about its effect in such patients. Table 2 gives a brief comparison of a few studies which have assessed the role of TPE in treating systemic vasculitis.

Jayne *et al*. conducted a randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis.[9] They concluded that "plasma exchange increased the rate of renal recovery in ANCA AAV that presented with renal failure when compared with intravenous methylprednisolone. Patient survival and severe adverse event rates were similar in both the groups."

Nakamura *et al*. compared plasmapheresis with immunosuppressive therapy versus immunosuppressive therapy alone for rapidly progressive ANCA associated glomerulonephritis.[10] In their study, they also found that patient survival was 80% in the former and 100% in the latter after 6 months.

Pusey *et al*. performed a randomized controlled trial to determine whether plasma exchange was of additional benefit in patients treated with oral immunosuppressive drugs for focal necrotizing glomerulonephritis (without anti-GBM antibodies).[11] Forty-eight cases were analyzed. The study results gave evidence that patients who were initially dialysis-dependent were more likely to have recovered renal function if treated with plasma exchange as well as drugs rather than with drugs alone. Their long-term follow-up showed that improvement in renal function was generally maintained. The results of this trial confirmed that focal necrotizing glomerulonephritis related to systemic vasculitis responds well to immunosuppressive drugs when treatment is started early, and suggest that plasma exchange is of additional benefit in dialysis-dependent cases.

In the present study, two-thirds or 66.67% of the renal patients benefited from a combination of drugs and TPE while 23.53% of patients became dialysis independent. Furthermore, patient survival after recovery at 3 months from the date of discharge was 100%. The current data suggest that plasma exchange increases the rate of renal recovery in autoantibody-associated systemic vasculitis and that early treatment and TPE play an important role in the renal outcome of such patients.

Szpirt *et al*. performed a randomized controlled trial of plasma exchange for induction and Cyclosporine A for maintenance of remission in Wegener's Granulomatosis.[12] They included 32 patients with ANCA-positive Wegener's and treated them with standard immunosuppressive therapy, prednisolone and cyclophosphamide. They concluded that plasma exchange is recommended for induction therapy.

Clinical studies conducted to date have either recruited patients with one of the many causes of vasculitis (primary or secondary) or have addressed one of the many manifestations of systemic vasculitis, such as pulmonary or renal vasculitis, which form only a part of the vast spectrum of clinical presentations patients can present with. Treatment of ANCA AAV still remains a challenge. Trials have been limited by the rarity of this disease and affordability since TPE remains an expensive treatment, especially in developing countries like India. Therefore, it still remains unclear, that at what severity of disease TPE is beneficial and the optimal number of procedures that need to be performed for clinical improvement in such patients.

Table 2: Comparison of studies assessing the effect of plasma exchange in systemic vasculitis

	Jayne *et al*.[9] MEPEX trial	Nakamura *et al*.[10]	Pusey *et al*.[11]	Szpirt *et al*.[12]	Lewis *et al*.[13]	Present study
Sample size	137 67: No TPE 70: TPE	22	48 23: No TPE 25: TPE	32 16: No TPE 16: TPE	86 46: No TPE 40: TPE	31
Indication	New diagnosis of ANCA-associated systemic vasculitis confirmed by renal biopsy and serum creatinine >500 μmol/L	Biopsy proven RPGN	Focal crescentic necrotizing glomerulonephritis without anti - GBM antibodies	Wegener's granulomatosis	Severe lupus nephritis	Consecutive patients admitted with new diagnosis of systemic vasculitis presenting with active disease
Mean number of TPE procedures per patient	7	8	9	9	10	6
Survival advantage	73% at 1 year	100% at 6 months	52%	Relative risk of death: 0.50	80%	77.42%
Renal recovery and dialysis independence	At 3 months, 69% Reduction in risk for progression to ESRD of 24%	-	91% of patients had improved renal function at 12 months	5 years creatinine TPE: 200 μmol/l No TPE: 413 μmol/l	75% of patients showed renal recovery	66.67% of renal patients benefited from TPE and 76.47% became dialysis independent
Significant findings	Plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis with renal failure	Plasma exchange with immunosuppression is more effective in ameliorating podocyte injury than immunosuppression alone Early plasmapheresis prolongs renal survival	Plasma exchange reduces mortality in these patients	TPE showed improved renal survival in patients with Wegener's granulomatosis	Remission, death, and renal failure were similar in both groups	TPE improves patient survival and increases the rate of renal recovery

TPE=Therapeutic plasma exchange, ESRD=End-stage renal disease, ANCA=Antineutrophil cytoplasmic autoantibody, RPGN=Rapidly progressive glomerulonephritis, GBM=Glomerular basement membrane, MEPEX=Plasma exchange for renal vasculitis

Our study provides some guidance for use of plasma exchange in systemic vasculitis but additional data from controlled trials are needed for more accurate assessment of the indications, practical modalities, and benefits and shortcomings of this treatment approach. More studies are required to define the indications, frequency, and benefits of TPE in severe systemic vasculitis. Furthermore, integration of TPE with other therapies and assessment of selective methods such as immunoadsorption as an option to conventional nonselective TPE is much needed to avoid the adverse events related with conventional TPE.

Conclusion

Thus, we conclude that autoantibody-positive vasculitis that occurs with rapidly progressive glomerulonephritis or severe alveolar hemorrhage or other life-threatening systemic manifestations would benefit from TPE as an adjunctive therapy and improve patient survival, increase the rate of renal recovery and play an important role in predicting clinical outcome in this patient category.

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Conflicts of interest

There are no conflicts of interest.

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