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Original article

Therapeutic plasma exchange in rheumatic diseases: a university hospital experience

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ABSTRACT

Introduction: Each day, evidence accumulates related to the use of therapeutic plasma exchange (TPE) in patients with rheumatic diseases. San Ignacio University Hospital has recorded all of the TPE sessions performed by the institution's apheresis group.
Objective: To describe the TPE experience of patients with rheumatologic diseases in a hospital setting.
Methods: Descriptive, observational, retrospective analysis. This study included analyses of the TPE sessions that were performed in patients with rheumatic diseases from November 2009 to November 2013.
Results: The apheresis group performed 136 sessions in 27 patients. The mean patient age was 43 years (SD 18.5), and 59.3% of the patients were female. Regarding the diagnosis, the most frequents ones where: ANCA-associated vasculitis followed by systemic lupus erythematosus and catastrophic antiphospholipid syndrome. The average number of sessions per patient was 5 (SD 1.8), and the average plasma exchange per patient was 1.3 plasma volume replacement units. The most used replacement solution was frozen fresh plasma (FFP; 63.2% of the sessions). Of all the sessions, 4.4% presented complications, and the majority of the complications were related to vascular access. Fifteen patients required renal replacement therapy (RRT) secondary to the same cause that created the need for TPE, 3 patients required RRT due to causes other than the TPE diagnostic intervention and 1 patient had undergone chronic dialysis.
Conclusions: TPE is a therapeutic alternative that is needed for the management of patients with rheumatic diseases with renal involvement and those who are refractory to conventional management. Our clinical results were in agreement with the global literature.

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Troca plasmática terapêutica em doenças reumáticas: a experiência de um hospital universitário

Palavras-chave:
Troca plasmática
Doenças reumáticas
Vasculite
Lúpus eritematoso sistêmico
Síndrome antifosfolipídica catastrófica

RESUMO

Introdução: Diariamente acumulam-se evidências relacionadas com a utilização da troca plasmática terapêutica (TPT) em pacientes com doenças reumáticas. O Hospital Universitário San Ignacio registrou todas as sessões de TPT realizadas pelo grupo de aférese desta instituição.

Objetivo: Descrever a experiência do Hospital Universitário San Ignacio na TPT em pacientes com doenças reumatológicas.

Métodos: Trata-se de uma análise observacional, retrospectiva, descritiva. Este estudo incluiu análises das sessões de TPT realizadas em pacientes com doenças reumáticas de novembro de 2009 a novembro de 2013.

Resultados: O grupo de aférese realizou 136 sessões em 27 pacientes. A idade média dos pacientes foi de 43 anos (DP 18,5) e 59,3% dos pacientes eram do sexo feminino. Quanto ao diagnóstico, os mais frequentes foram: vasculite associada ao ANCA seguida de lúpus eritematoso sistêmico e síndrome antifosfolipídica catastrófica. A quantidade média de sessões por paciente foi de 5 (DP 1,8) e a média de troca plasmática por paciente foi de 1,3 unidades de substituição do volume de plasma. A solução de substituição mais utilizada foi o plasma fresco congelado (PFC, 63,2% das sessões). De todas as sessões, 4,4% apresentaram complicações, a maioria delas relacionadas com o acesso vascular. Quinze pacientes necessitaram de terapia de substituição renal (TSR) secundária à mesma causa que levou à necessidade de TPT; três pacientes necessitaram de TSR em decorrência de outras causas além da intervenção diagnóstica de TPT e um paciente tinha sido submetido à diálise crônica.

Conclusões: A TPT é uma alternativa terapêutica que é necessária para o manejo de pacientes com doenças reumáticas com envolvimento renal e daqueles que são refratários ao tratamento convencional. Os resultados clínicos do presente estudo estão de acordo com o que é encontrado na literatura global.

Introduction

Therapeutic plasma exchange (TPE) is an extra-body therapy that involves the separation of the plasma from the blood-forming elements to eliminate circulating antibodies, immune complexes, cytokines and other inflammatory intermediaries.[1,2] The volume of plasma drawn is simultaneously replaced with another solution, such as albumin or fresh frozen plasma.[3,4]

TPE generates alterations in substances that may have roles in the pathophysiology of the disease. For example, TPE depletes plasma proteins, including antibodies, coagulating factors, complement components, vasoactive peptides, cytokines, hormones, minerals and other substances.[5,6]

In 1960, Schwab and Fahey performed the first TPE in a patient with macroglobulinemia.[1] The introduction of plasma exchange into clinical practice for patients with renal and immunologic disease was performed by Lockwood et al. in 1975 in a patient with Goodpasture's syndrome. TPE associated with immunosuppressant therapy resulted in an improvement in renal function and the resolution of the patient's alveolar hemorrhage.[7] Since then, the number of indications for this procedure has increased, with these indications initially based on anecdotal cases or non-controlled studies. The progression of medical knowledge and the understanding of the pathophysiology of several diseases support the role of TPE as a part of the treatment of several clinical entities. The current clinical evidence supports the use of this type of therapy in several diseases, including rheumatic diseases.

Apheresis is intended to physically remove immune complexes or humoral factors. Apheresis is considered to be a treatment alternative when medical therapy has been insufficient in controlling disease activity or in some cases as a supplement to conventional therapy intended to optimize the results. However, apheresis is a temporary measure and requires subsequent medical management or repeated apheresis sessions.[8]

The utility of apheresis has been repeatedly demonstrated in patients with essential mixed cryoglobulinemia, ANCA-associated vasculitis, Goodpasture's syndrome, catastrophic antiphospholipid syndrome and other conditions.[9]

In 1960, apheresis for rheumatoid arthritis was performed. Subsequently, several studies related to TPE and leukapheresis were published, and it was reported that TPE was not effective against this disease, whereas leukapheresis was associated with a temporary response. Since 1980, other blood purification techniques have been used, including protein A column immunoadsorption for *Staphylococcus aureus*. These columns have a high affinity for the Fc portion of immunoglobulin

and thus achieve the removal of the circulating immune complexes and antibodies involved in the pathophysiology of the disease. Following the use of apheresis in 91 patients with rheumatoid arthritis refractory to disease-modifying antirheumatic drugs, the Food and Drug Administration (FDA) approved apheresis as part of the treatment for this disease in 1999.[10]

Since 2008, San Ignacio University Hospital, which is an academic site located in Bogotá (Colombia), has employed a TPE system and transmembrane filtration using a technique that is controlled by volume and verified by the safety and precision of this therapy. The institution's apheresis group recorded all of the performed TPE sessions. In this study, we report our experience with TPE in the management of patients with rheumatologic diseases.

Objective: to describe the experience of our apheresis and nephrology group with TPE in patients with rheumatic diseases and to assess the clinical response to this therapy.

Materials and methods

Study population

We performed a descriptive analysis of the TPE sessions of patients with rheumatologic diseases that were performed over a period 4 years (from November 2009 to November 2013) at San Ignacio University Hospital. The protocol was accepted by the ethics committee of the institution and the Javeriana University. We recorded the patients' demographic characteristics, the techniques used, the indications for therapy, and the complications based on the information obtained from the clinical history of the institution and the database of our apheresis group. The population was classified by sex, age, race, site of hospital, number of TPE sessions per patient and therapy indication. A session was defined as a TPE therapy, and a procedure was defined as the group of TPE sessions that were performed in a patient with a specific diagnosis over a specified period of time.

Technique

In the development of the TPE technique, we used transmembrane filtration equipment systems and hemodialysis catheters for vascular access. The utilized replacement therapies involved frozen fresh plasma and 5% albumin. The selection of the solution was made according to the patient's disease, indication for therapy, clinical status and the likelihood of adverse events. The selected replacement solution has implications for the efficacy of the therapy, oncotic pressure, coagulating disorders and the occurrence of adverse events. The use of albumin is typically preferred over the use of FFP due to the reduced risks of hypersensitivity reactions and viral disease transmission associated with the use albumin.[10] However, in the treatment of some diseases, the solution of choice is FFP because it alleviates all plasma factor deficiencies. It is also preferable to use FFP when the patient is at risk for bleeding, exhibits hemostatic defects or low fibrinogen or exhibits active bleeding.[11–13]

Table 1 – Population characteristics.

Sex – N° (%)	
Male	11 (40.7%)
Female	16 (59.3%)
Age – years	
Mean	43 ± 17
Range	13–70
Race – N° (%)	
Black	0 (0%)
Mixed race	27 (100%)
Assignation – N° of sessions (%)	
Ambulatory	35 (25.7%)
General Room	0 (0%)
ICU	101 (74.3%)
Sessions per procedure – N°	
Mean	5 ± 2.2
Range	1–10

To perform the therapy, the patient's plasma volume is estimated using the Kaplan formula, and the patient is prescribed 1–1.5 plasma volume replacement units. The number of sessions prescribed depends on the underlying disease and the recommendations of the international apheresis guidelines. The therapies were monitored by nursing personnel with training in the responsible monitoring and recording of the therapy parameters, control of the patient's vital signs, and observation of symptoms that occur during the TPE session.

Statistical analysis

The categorical variables are described as frequencies (ratios and percentages), and the numeric variables are described as central trend measurements (means and medians) and the dispersion measurements (standard deviations and ranges). The abovementioned analyses were performed with STATA software, version 10.

Results

Demographic data

One hundred thirty-six sessions were performed in 27 patients. The average patient age was 43 years (SD 18.5). Three patients over the age of 65 and one patient under the age of 15 were treated. The population consisted of 59.3% females and 40.7% males. One hundred percent of the patients were of mixed race. Of all sessions, 74.3% were performed in intensive care units (ICUs), and 25.7% were performed on an ambulatory basis. The mean number of sessions per patient was 5 (SD 1.8). Forty-eight percent of the patients had new diagnoses, and 52% had known related autoimmune diseases; among the latter patients, 92% were receiving treatment, 78% were receiving corticoids, and 21% had received management with cytostatic agents. Twenty-six patients received treatments associated with TPE and treatments with corticoids (4 in pulses and 1 via the oral route), and 13 patients received cytostatic agents (Table 1).

Table 2 – Therapy indication.

Diagnostic	Number of patients	Number of sessions	Percentage of sessions	Sessions/patient	Number of procedures	Percentage of procedures
ANCA + RPGN + AH	8	46	33.8	5.8	8	29.6
SLE + refractory AH	7	27	19.8	3.9	7	25.9
ANCA + RPGN-AH	4	26	19.1	6.5	4	14.8
APS	3	14	10.2	4.7	3	11.1
Cryo + APS	1	7	5.1	7	1	3.7
SLE refractory	1	6	4.4	6	1	3.7
GS + AH	1	5	3.6	5	1	3.7
Cryo + AH	1	4	2.9	4	1	3.7
ANCA-RPGN + AH	1	1	0.7	1.0	1	3.7
Total	27	136	100		27	100

GS, Goodpasture's syndrome; APS, catastrophic antiphospholipid syndrome; SLE, systemic erythematosus lupus; AH, alveolar hemorrhage; Cryo, cryoglobulinemias; ANCA, ANCA-associated vasculitis; RPGN, rapidly progressing glomerulonephritis; session, a TPE therapy; procedure, group of sessions performed in patients with a particular diagnosis.

Therapy indication

The diagnoses in descending order of frequency were as follows: ANCA-associated vasculitis =with rapidly progressive glomerulonephritis (RPGN) and/or alveolar hemorrhage, systemic erythematosus lupus (SLE) with refractory alveolar hemorrhage, catastrophic antiphospholipid syndrome, cryoglobulinemias and Goodpasture's syndrome (Table 2). Most patients required TPE for concomitant renal and pulmonary disorders or solely pulmonary. Others required TPE for the proper disease as the ASFA guidelines recommended (Table 3).

Plasma exchange technique

All of the sessions were performed using the transmembrane filtration technique with an average plasma exchange of 1.3 volumes. Anticoagulation agents were not used in any of the sessions. Transient hemodialysis catheters were used in all of the sessions; 58.8% were located in jugular veins, and the other catheters were placed in femoral veins. The most frequently used replacement solution was FFP (63.2% of the sessions) followed by 5% albumin (31.6% of the sessions), a combination of plasma plus albumin (4.4% of the sessions) and 3.5% albumin (0.7% of the sessions).

Complications

Complications occurred in 4.4% of the TPE sessions and were mainly related to the vascular access. Vascular access complications were more common than those related to catheter dysfunction. Table 4 describes the complications observed during the TPE sessions (Table 4). Regarding electrolytic alterations that occurred during the procedures, the rates of hypocalcemia, hypokalemia and hypophosphatemia were 17%, 15% and 4%, respectively.

Outcomes

Fifteen patients required renal replacement therapy (RRT) secondary to the cause that necessitated TPE, 1 patient was on chronic dialysis, and 3 required RRT due causes other than those responsible for the indications for TPE. Among the 19 patients with RRT, 10 died, 5 recovered renal function, and 4 became dialysis-dependent by dismissal. Among the 27 patients, 13 died, and the majority of the deaths were due to septic shock. Table 5 describes patient outcomes after TPE.

Table 3 – Type of disorders in patients with TPE.

Type of disorder	Number of patients	Diagnosis
Renal	4	ANCA + RPGN-AH
Pulmonary	9	SLE + refractory AH
		Cryo + AH
		ANCA-RPGN + AH
Renal and pulmonary	9	ANCA + RPGN + AH
		GS + AH
Systemic	5	Catast APS
		Cryo + Catast APS
		SLE refractory

GS, Goodpasture's syndrome; APS, catastrophic antiphospholipid syndrome; SLE, systemic erythematosus lupus; AH, alveolar hemorrhage; Cryo, cryoglobulinemias; ANCA, ANCA-associated vasculitis; RPGN, rapidly progressing glomerulonephritis.

Table 4 – TPE-related complications.

Complications	Number
Vascular-access related	
Catheter dysfunction	5
Bleeding	1
Arterial puncture	0
Infection	1
Arterial hypotension	0
Systemic bleeding	1
Allergic reactions	0
Cardiac arrhythmias	0
Death	0

Table 5 – Outcomes.

	Death	Stable discharge	Discharge in hemodialysis
ANCA + RPGN + AH	2	2	4
SLE + refractory AH	3	2	2
ANCA + RPGN-AH	3	1	0
APS	2	1	0
Cryo + APS	0	1	0
SLE refractory	1	0	0
GS + AH	1	0	0
Cryo + AH	0	1	0
ANCA-RPGN + AH	1	0	0
Total	13	8	6

AH, alveolar hemorrhage; ANCA, ANCA-associated vasculitis; APS, catastrophic antiphospholipid syndrome; Cryo, cryoglobulinemias; GS, Goodpasture's syndrome; RPGN, rapidly progressing glomerulonephritis; SLE, systemic erythematosus lupus.

Discussion

TPE can remove immune complexes, auto-antibodies and other immune reactants that are involved in the pathophysiology of rheumatic diseases from the blood. Since the initial use of TPE, this technique has been examined in several rheumatologic studies; however, these studies have typically reported negative results or effects that were insufficient to warrant recommendations of the procedure (primarily in SLE), unless its use is associated with thrombotic microangiopathy or catastrophic antiphospholipid syndrome.[14,15]

The best evidence supporting the use of TPE is related to renal diseases, such as hemolytic uremic syndrome, vasculitis, glomerular basement membrane anti-bodies, in the context of renal transplantation for recurrent glomerulonephritis, and the management of transplant rejection.[15]

In studies of severe alveolar hemorrhage associated with Goodpasture's syndrome and other conditions that affect the pulmonary capillaries, TPE has been found to be a useful therapeutic alternative to the use of immunosuppressant agents[13] for renal diseases that result from glomerular basement membrane antibodies; however, the evidence regarding the application of TPE for ANCA-associated vasculitis is poor.[7,16]

Regarding renal involvement due to ANCA-associated vasculitis, the best available evidence is provided by the MEPEX study, which compared the use of methylprednisolone pulses to plasma exchange that was performed early and found the latter to be superior in terms of dialysis-free survival; however, no differences in mortality were detected.[17,18] Our cohort received both interventions consecutively; thus, it is not possible to make any comparisons with the MEPEX study in terms of the recovery of the renal function. Additionally, we do not have any follow-up data with which to assess the patient's long-term renal function recoveries.

A review of the available evidence about the TPE in ANCA-associated vasculitis[19] was recently published. This publication refers to eight randomized studies evaluating the role of TPE in pauci-immune vasculitis renal disease. The inclusion and exclusion criteria of studies were different, but the majority included patients with crescentic glomerulonephritis. Several studies have documented effect in favor of TPE in terms of recovery of renal function and renal survival. The results of these studies were analyzed in the Cochrane systematic review. This analysis supports the beneficial effect of TPE in the development of end-stage renal disease at 3 and 12 months of treatment. Patients included in these studies presented with severe kidney disease, so that the benefit of TPE cannot be extrapolated to people with less severe kidney dysfunction. The PEXIVAS study, which is ongoing, aims to resolve such questions.

There are no randomized studies evaluating the effect of TPE in patients with ANCA-associated vasculitis alveolar hemorrhage. Retrospective studies suggest that TPE can be useful based on rationale of removal of antibodies and the similarity of the pathophysiology between alveolar hemorrhage and rapidly progressive glomerulonephritis associated with vasculitis.[20]

Our study includes patients with ANCA-associated vasculitis with renal or pulmonary involvement. These patients were treated with immunosuppression and TPE. This type of study does not allow comparisons among the therapeutic modalities and does not allow long-term prognosis in patients treated with TPE. Mortality among these patients was high and so was the requirement of dialysis during hospitalization. Of the seven patients who survived, three continue with dialysis requirement to discharge (data not shown).

Plasma exchange has proved to be effective for essential mixed cryoglobulinemias; thus, plasma exchange has been proposed to be an effective treatment for patients with symptomatic cryoglobulinemias. A significant number of observations support the role of apheresis in improvements in acute renal disease, neuropathy and ulcerations due to treatments for essential mixed cryoglobulinemias. Furthermore, apheresis remains the first-line treatment for hyperviscosity syndrome due to cryoglobulinemia despite the limited number of available studies on the subject, which is primarily due to the low prevalence of this disease. The recommendations of the Italian group include the use of apheresis in cases of severe life-threatening manifestations secondary to cryoglobulinemia and when the other therapies have failed.[7,21,22] In our study, apheresis was administered in 2 patients with diagnoses of alveolar hemorrhage-associated cryoglobulinemia and catastrophic APS, as supported by the abovementioned recommendations.

According to the findings described above, the indications applied in our experience are similar to those recommended in the literature. It will also be useful to evaluate the responses and mortality of patients who undergo plasma exchange for ANCA-associated vasculitis in the presence of alveolar hemorrhage and RPGN.

In SLE patients treated with TPE, the evidence is less clear than in other diseases. Treatment with TPE is reserved for cases of first-line treatment refractory SLE. In this study, 8 patients with SLE were managed with TPE, of which 7 had alveolar hemorrhage and had received additional immunosuppressive therapy.[23]

Regarding the, The French Society of Hemapheresis has reported a 2.8% rate of complications and adverse events in 2003 and specifically documented hypocalcemia followed by allergic reactions. Bacterial or viral infections that are primarily due to herpes zoster or cytomegalovirus are common in

patients that have previously received glucocorticoids and/or cyclophosphamide and are also generally common in this type of patient.[24] In the present study, we observed a 4.4% rate of complications, and the complications were commonly associated with evidence of hypocalcemia, similarly to what was reported by the French Society of Hemapheresis.

The evidence is weak to generate recommendations on cost-effectiveness, however we believe that TPE will increasingly applications for these rheumatologic indications and requires further studies. Our study has weaknesses, as it is a descriptive and retrospective study with a small number of patients, which limits the statistical analysis; however we believe it is useful information for clinical practice.

Conclusion

This was an observational descriptive study of the experience of a University Hospital with TPE for rheumatic diseases in the period from November 2009 to December 2013. During this time, 136 sessions were performed in 27 patients. The primary indication for plasma exchange was ANCA-associated vasculitis with rapidly progressing glomerulonephritis and alveolar hemorrhage. The rate of complication was low and primarily driven by electrolyte alterations. Anticoagulation agents were not used in any of the plasma exchange sessions during these 8 years, and no secondary complications were observed. Further studies are required to assess the long-term responses and recurrence.

Conflicts of interest

The authors declare no conflicts of interest.

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