Membrane-Based Therapeutic Plasma Exchange in Intensive Care

Sebastien Redant^a David De Bels^a Khalid Ismaili^b Patrick M. Honoré^a

^aDepartment of Intensive Care, Brugmann University Hospital, Université Libre de Bruxelles (ULB), Bruxelles, Belgium; ^bDivision of Nephrology, Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Université Libre de Bruxelles (ULB), Bruxelles, Belgium

Keywords

Therapeutic plasma exchange · Thrombotic thrombocytopenic purpura · Acute liver failure · Guillain-Barré syndrome · Antineutrophil cytoplasmic antibody-associated vasculitis

Abstract

The principles and use of plasmapheresis are often little understood by intensivists. We propose to review the principles, the main indications, and the methods of using this technique.

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Introduction

The evolution of the understanding of the molecular mechanisms of several pathologies has allowed the expansion of therapeutic plasma exchange (TPE) indications. The general principle is to remove a circulating molecule from the blood in the hope of improving the clinical condition of the patient [1]. In contrast to hemodialysis, TPE preferentially removes high-molecular-weight substances such as autoantibodies, antigen-anti-

body complexes, and paraprotein immunoglobulin [2]. Two different plasma separation techniques exist: centrifugal separation (cTPE) and membrane separation (mTPE). The 2 techniques use different physical principles, but both are capable of effectively separating plasma substances from whole blood and delivering replacement with plasma or albumin [2]. We reviewed the principles, modalities, and different indications of this technique (Fig. 1).

Principles of Centrifugal Separation

The first therapeutic application of this technique dates back to the 1960s [3]. Blood flows from the patient to a centrifuge, with citrate anticoagulation introduced before centrifugation, and the blood elements return to the patient with a replacement fluid such as albumin or plasma after the centrifugation [2]. In cTPE, the centripetal force from rotation of a blood chamber at a speed of 2,000–2,500 rpm is used to separate the blood components based on differences in density [2, 4, 5]. This ability to separate blood elements is useful as a treatment (via plasma exchange (PE) and/or blood component removal) for a range of pathologies and also as a means of collection (e.g., peripheral blood stem cells) or processing (e.g., bone marrow for transplant) [4].

Fig. 1. Representation of a plasmapheresis membrane with the cellular elements of the blood and plasma constituents.

Principles of Membrane Separation

The first difference when compared with cTPE is that mTPE cannot perform cytopheresis [2]. The plasma separator membranes resemble a continuous dialysis procedure operating in ultrafiltration mode only [2]. The plasma containing the pathological element is ultrafiltered and then replaced by plasma or albumin [2]. In order to avoid filter clogging, it is necessary to limit the filtration fraction to 30–35% of the plasma [2]. The pores of mTPE membranes are larger than those in conventional hemofiltration membranes, allowing for the removal of macromolecules (proteins and lipoproteins), while leaving behind cellular components [5]. The membrane used is nonselective and removes the beneficial as well as the pathological constituents of the plasma [2].

Compared to the membrane system, PE by centrifugation is often more cumbersome and complicated. Centrifugation has the disadvantage of contamination of the plasma by the elements of the blood. The membrane technique is similar to hemofiltration and allows plasma to pass through pores, leaving platelets and other cellular elements in the blood. In addition, this technique is simpler, less expensive, and more reliable [1].

Specificity of the Membranes

Currently, only 2 membranes are approved by the FDA for mTPE in the USA [1]. The first is the Plasmaflo

OP filter (Asahi Medical, Tokyo, Japan), which is compatible with continuous renal replacement therapy machines. The second is the Prismaflex TPE set (Gambro Renal Products, Lakewood, CO, USA) (Table 1). Continuous renal replacement therapy machines which contain 2 pumps to simultaneously hemofilter and reinject the replacement fluid are best suited for mTPE [1]. The main disadvantage of mTPE is the inability to perform cytopheresis, meaning that in order for an institution to provide a range of apheresis therapies and cell collection services, a cTPE system must also be available [1]. The typical mTPE filter has a structure like a sponge with openings of different sizes [1]. These pores vary in size from 0.2 to 0.5 μm with an average of 0.3 μm [1]. In comparison, the size of platelets and red blood cells is between 2 and 3 μm , which corresponds to 10 times the size of a pore. Albumin measures 0.01 μm , which is 30 times smaller than a pore and passes easily through the membrane, as do IgM (0.03 μm) and cryoglobulins (0.1 μm) [1].

Indications for TPE

The American Society for Apheresis (ASFA) publishes regularly updated guidelines regarding plasmapheresis indications, categorized according to their degree of evi-

Table 1. Different membranes approved in the USA

	Polymer	Effective surface area, m ²	Pore size, μ m	Maximum TMP	SC data
Plasmaflo ^{TM}	Polyethylene	0.5	0.3	100 mm Hg	Albumin 0.99 IgG 0.99 IgA 1.0 IgM 1.0 TotProtein 1.0 TotCholesterol 1.0
Prismaflex ®	Polypropylene	0.35	/	100 mm Hg (Qb = 50 mL/min) 140 mm Hg (Qb = 100 mL/min) 190 mm Hg (Qb = 180 mL/min)	Albumin 0.97 IgG 1.0 Apolipoprotein B 0.95 IgM 0.92

dence [1, 6]. Category I represents diseases for which TPE is a first-line treatment (e.g., Guillain-Barré syndrome [GBS]). Category II includes pathologies for which TPE is accepted as second-line (e.g., acute disseminated encephalomyelitis after steroid failure) therapy. Category III are indications that are not established and are considered on a case-by-case basis (e.g., IgA nephropathy), and category IV are the indications where the literature has proven no benefit or has shown deleterious effects [1, 6]. Four recommendations of TPE have a level of evidence I grade 1A and illustrate the principles of TPE: thrombotic thrombocytopenic purpura (TTP), acute liver failure, GBS, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (Table 2).

Thrombotic Thrombocytopenic Purpura

The acquired form of TTP is an entity caused by the presence of autoantibodies against a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS13). The low activity of this protease leads to the accumulation of von Willebrand factor multimers with platelet-rich clot formation and occlusion of arterioles, often with renal failure and/or neurological involvement [2, 7]. TPE is the cornerstone of treatment. Treatment failure is associated with a delay in the initiation of PE treatment, as well as the presence of coma or elevated Cr levels [7]. A randomized controlled study in 102 patients showed that PE was superior to plasma infusion alone in terms of platelet count increase, hospital mortality, and 6-month mortality [8]. This phenomenon is explained by an additive effect of both autoantibody removal and an increase in the amount of ADAMTS13 provided by the exchanged plasma [9].

TPE is started at a dose of 1.5 times the plasma volume (PV, 60 mL/kg), once daily. After confirmation of the diagnosis, the dose of $1.5 \times PV$ is continued for 3 days as per the Canadian Apheresis Study Group [8], followed by a maintenance dose of $1.0 \times PV$ [10]. This dose is maintained until signs of organ involvement – cerebral manifestations, renal failure, elevation of troponin, and abdominal pain – have resolved [10]. The addition of rituximab has shown a benefit in terms of platelet recovery rate and prevention of recurrence [11] and is commonly used to treat refractory or relapsing TTP, although it can also be used as an adjunct to TPE in newly diagnosed TTP [6]. An intensive schedule of rituximab dosing on days 1, 4, 8, and 15 following relapse diagnosis (to account for the removal of rituximab by TPE) has shown improved outcomes [11]. In refractory patients, twice-daily TPE in conjunction with rituximab has shown promise [12]. Various immunosuppressant agents and splenectomy can be considered in severe refractory cases [6]. TPE is discontinued when the platelet count exceeds $150 \times 10^9/L$ and the lactate dehydrogenase level is near normal for at least 2 days [6].

Regarding the type of plasma used, it has been reported that the plasma cryosupernatant, which is depleted of high-molecular-weight von Willebrand factor multimers, may be more effective than fresh frozen plasma (FFP) [13]. However, a more recent study did not show superiority of 1 type of plasma over another [14].

Acute Liver Failure

In acute liver failure, TPE can remove albumin-bound toxins as well as unbound toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phe-

Table 2. Category I recommendations for therapeutic apheresis

	Indication	Grade
Acute inflammatory demyelinating polyradiculoneuropathy/GBS	Primary	1A
Acute liver failure		1A
Goodpasture	Diffuse alveolar hemorrhage	1C
	Dialysis independence	1B
Chronic inflammatory demyelinating polyradiculoneuropathy		1B
Dilated cardiomyopathy idiopathic	NYHA II–IV	1B
Familial hypercholesterolemia	Homozygote	1B
Focal segmental glomerulosclerosis	Recurrent in transplanted kidney	1B
GVHD	Acute	1C
Hereditary hemochromatosis		1B
Hypertriglyceridemic pancreatitis	Severe	1C
Hyperviscosity in monoclonal gammopathies	Symptomatic	1B
	Prophylaxis for rituximab	1C
Liver transplantation	Desensitization, ABOi LD	1C
Myasthenia gravis	Acute	1B
N-methyl d-aspartate receptor antibody encephalitis		1C
Paraproteinemic demyelinating neuropathies	IgG, IgA	1B
	IgM	1C
Progressive multifocal leukoencephalopathy associated with natalizumab		1C
Renal transplantation ABO incompatible	Desensitization, LD	1B
Thrombotic microangiopathy complement mediated	Factor H autoantibodies	2C
Thrombotic microangiopathy drug associated	Ticlopidine	2B
TTP		1A
AAV	MPA/GPA/RLV:RPGN, Cr >5.7	1A
Wilson's disease fulminant	Fulminant	1C

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; GBS, Guillain-Barré syndrome; GVHD, graft-versus-host disease; TTP, thrombotic thrombocytopenic purpura; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; RLV, renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis; LD, living donor; NYHA, New York Heart Association.

nols, and other factors that may be responsible for hepatic coma, hyperkinetic syndrome, and decreased systemic vascular resistance and cerebral blood flow. The removal of inflammatory mediators seems to play a role in the treatment of acute liver failure. Several studies show improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure, cerebral metabolic rate, and increased hepatic blood flow and improvements in

other laboratory parameters such as cholinesterase activity or galactose elimination capacity [6]. Different purification systems exist, among them PE. PE is a simple technique but not devoid of side effects. It may be accompanied by hypernatremia, metabolic alkalosis, citrate intoxication, and abrupt changes in oncotic pressure. In Japan, where the Molecular Adsorbent Recirculating System (MARS) is not in use, Nakae et al. [15] developed a

combination of PE therapy and continuous diafiltration: plasma diafiltration (PDF). PDF is a blood purification therapy in which PE is performed using a plasma membrane separator, while the dialysate flows outside of the plasma separator and hemodiafiltration is performed simultaneously.

There are several case series of patients with acute hepatic insufficiency and fulminant hepatitis who underwent this technique using a membrane plasma separator (Evacure EC-2A plasma separator; Kuraray, Tokyo, Japan) [8, 16–19]. They observed a significant decrease in total bilirubin, interleukin-18 (IL-18), cystatin C, and citrate. IL-18 is a protein of molecular weight 18.5 kDa that is produced by activated macrophages, particularly in liver Kupffer cells [20], and leads to hyperproduction of TNF- α and other pro-inflammatory cytokines. Cystatin C is a marker of glomerular lesions unrelated to muscle mass, age, or sex [21].

The plasma separator used in their case series had a pore size of 0.01 μm , which is smaller than that of the conventional plasmapheresis membrane (0.2–0.4 μm). This membrane has a sieving coefficient of 0.3 for albumin and can extract small- to medium-molecular-weight molecules with preservation of coagulation factors [15]. One of the benefits of PDF is better control of citrate, first because the system uses less plasma and therefore less citrate and also because the citrate is eliminated by hemodiafiltration.

Given that conventional PDF is performed intermittently over a period of 8 h and can result in hemodynamic instability, continuous PDF has been proposed as an alternative [22]. Continuous PDF uses the same membrane EC-2A plasma separator with the following parameters: blood flow rate of 80 mL/min, dialysate flow rate of 400 mL/h, and replacement flow rate of 280 mL/h with FFP infused at 120 mL/h. This treatment regimen resulted in a significant fall in the Model for End-Stage Liver Disease (MELD) score from 34.5 to 28.0 ($p = 0.005$) and bilirubin from 10.9 to 7.25 ($p = 0.048$) and a tendency to decrease the INR of 1.89–1.31 ($p = 0.084$). The SOFA score went from 10.0 to 7.5 ($p < 0.039$). These techniques are especially useful in areas of the world where liver transplantation is less common [22].

High-volume plasmapheresis (HVP) is another technique for which improved outcomes have been reported in patients with acute liver failure [23]. In a prospective randomized multicenter study of 183 patients over a 13-year period, standard medical therapy (SMT) combined with HVP (15% ideal body weight [~ 8 –12 L FFP] over 9 h), as compared to SMT alone, resulted in a significant

increase in hospital survival, including in patients who refused liver transplantation due to contraindications (comorbidity and psychiatric pathologies) [23]. The main criticism addressed to this study was that SMT may have changed during the extended patient enrollment period (13 years), potentially influencing the results. However, the authors note that SMT was identical in both the treatment and control groups, and a midterm analysis demonstrated the same trend [24, 25]. While HVP is not an extracorporeal liver support therapy, it simulates some aspects of such support by removing toxic metabolites, replacing potentially beneficial factors, correcting coagulopathy and removing mediators of multiorgan failure (pro-inflammatory cytokines and damage-associated molecular patterns) [24, 26].

Another study by Yue-Meng et al. [27] showed survival benefit in chronic hepatitis B patients with hepatic decompensation and acute-on-chronic liver failure (ACLF) who were treated with PE in combination with entecavir. The cumulative survival rate at weeks 4 and 12 in the PE group and the control group was, respectively, 37 and 18%, and 29 and 14% ($p < 0.001$) [27].

A prospective observational study of 54 patients with ACLF secondary to hepatitis B examined the issue of potential citrate accumulation due to PE-centered therapy without concomitant filtration or dialysis [28]. The ratio of total to ionized calcium ($\text{Ca}_{\text{tot}}/\text{Ca}_{\text{ion}}$) was used as an indicator of citrate accumulation. The mean $\text{Ca}_{\text{tot}}/\text{Ca}_{\text{ion}}$ was 2.05 ± 0.14 prior to PE and was elevated in all patients immediately following PE (4.34 ± 1.52), but decreased within 1 h after PE (2.36 ± 0.32) and returned to baseline by the following morning (2.10 ± 0.14). The main metabolic abnormalities encountered were asymptomatic hypocalcemia and mild metabolic alkalosis. The authors concluded that citrate accumulation is well-tolerated by patients with ACLF in this setting [28].

Guillain-Barré Syndrome

The rationale for the use of TPE in GBS is the presence of an autoantibody directed against peripheral nerve myelin [6]. Several randomized controlled trials have shown a net benefit of using TPE versus supportive treatment alone in GBS management [29, 30]. TPE accelerates motor recovery and decreases mechanical ventilation time [30]. The Cochrane Neuromuscular Disease Group reviewed the use of TPE in GBS and recommended that TPE is an effective treatment in both mild and severe forms of GBS and should be initiated within 7 days of the onset of the disease [6, 31]. The sequential combination of intravenous immunoglobulin (IVIG) and TPE does not offer any benefit and is not

recommended. There are insufficient data to recommend TPE after IVIG treatment failure [6]. Caution should be exercised in these patients, as they may have autonomic dysfunction and therefore be sensitive to fluid shifts occurring during treatment. Up to 10% of patients may experience a relapse and require additional TPE [6].

ANCA-Associated Vasculitis

AAV is defined as necrotizing vasculitis predominantly in small vessels with little or no immune deposition [6]. ANCA can be specific for myeloperoxidase or proteinase 3 and is clinically divided into microscopic polyangiitis, granulomatosis with polyangiitis, and renal-limited vasculitis [6]. AAV can affect all organs but in particular the kidney (70% of the cases) in the form of rapidly progressive glomerulonephritis with a high risk of ESRD [6].

The presence of ANCAs is the rationale for the use of TPE in AAV. The characteristic lesion is vessel wall necrosis with release of plasma components and activation of coagulation [6]. Before the emergence of a precise classification of AAVs, various studies examined the utility of TPE in AAV via investigation of its use in the treatment of rapidly progressive glomerulonephritis, a clinical entity that is not exclusive to AAV [6]. A meta-analysis of those studies concluded that TPE can reduce the end-point of ESRD and death, and the use of TPE was recommended in patients with severely impaired renal function defined by a serum Cr level above 5.7 mg/dL or the requirement of dialysis [6, 32].

In patients with AAV presenting with diffuse alveolar hemorrhage, TPE has weaker evidence. A retrospective study reported a reduction in all-cause in-hospital mortality in patients who received TPE as compared to those who did not (35.6 vs. 54.2%, $p = 0.041$), but did not reach statistical significance in the multivariate logistic regression analysis of propensity-matched patients [33]. Furthermore, the median duration of hospitalization was longer (44 [27–84] vs. 30 [16–58] days, $p = 0.027$) for the PE group.

In the MEPEX study, 137 patients with a new diagnosis of AAV confirmed by renal biopsy and who had a Cr level $>500 \mu\text{mol/L}$ (5.8 mg/dL) were randomized to receive either 7 PEs ($n = 70$) or 3,000 mg intravenous methylprednisolone (1,000 mg/day $\times$ 3) [34]. A significant difference was reported in the number of patients independent from dialysis at 3 months (69% in the TPE group vs. 49% in the methylprednisolone group, $p = 0.02$), while the survival rate and severe adverse event rates were similar [34].

The PEXIVAS study was a randomized controlled trial that compared standard versus low-dose glucocorticoids, with or without TPE, in a cohort of 704 patients

recruited from 98 sites in 15 countries [32]. Patients were followed up for up to 7 years for the primary outcome of death of any cause or end-stage kidney disease. This study did not show a benefit of TPE in the first year. The use of TPE did not reduce the incidence of death or end-stage kidney disease in the overall analysis [32]. In the study, TPE consisted of 7 exchanges of 60 mL/kg over 14 days. Some patients require up to 12 PEs to achieve an improvement in renal function [35].

Plasmapheresis in COVID-19

Coronavirus disease 2019 (COVID-19) is a viral infectious disease caused by SARS-CoV-2 and is currently a World Health Organization (WHO)-declared pandemic. COVID-19 is increasingly well described and results from a complex interaction of cytokine storm, inflammation, endothelial dysfunction, and pathological coagulation [36]. A case report has been published of a 50-year-old patient with severe COVID-19 who was successfully treated with 4 sessions of plasmapheresis with 6,000 mL of plasma followed by 20 g of IVIG [37]. The use of TPE in severe COVID-19 patients has been associated with higher extubation rate and lower 14- and 28-day mortality [38]. PE may provide benefit by removing inflammatory cytokines, stabilizing endothelial membranes, resetting the hypercoagulable state, and decreasing viral load [36, 37]. SARS-CoV-2 has a diameter of 60–140 nm, also large enough to be eliminated with double filtration plasmapheresis [39].

Using Plasmapheresis

Dose

The usual dose of plasmapheresis is equivalent to 1.2 times the circulating PV (range 1.0–1.5). This range corresponds to the removal of 63–72% of the constituents of the plasma. The ratio between the extracted plasma constituents and the amount remaining in the plasma after TPE follows an exponential curve. Increasing the volume of plasma exchanged beyond 1.5 times the PV decreases very little the proportion of volume remaining. In addition, very often the pathogenic molecule extracted via TPE is also present in the interstitial fluid and slow transfer to the blood occurs after the end of the plasmapheresis session. This results in a late rebound effect, which explains the need for multiple sessions of TPE [40]. This is typical of diseases mediated by IgG antibodies (146 kDa), of which only 30% are present in the intravascular compartment, as compared to IgM (970 kDa), of which 90% is in the plasma. This explains why Waldenström's mac-

roglobulinemia disease can be successfully treated with only 1–2 sessions of TPE.

Anticoagulation

Citrate is the anticoagulant of choice for the preservation of blood derivatives and for low-flow extracorporeal circulation circuits (typically 30–70 mL/min) when citrate loading can be managed by clearance mechanisms (e.g., dialysate flow rate) [41]. Citrate anticoagulation can be used safely with less risk of bleeding than heparin [42]. On the one hand, when citrate is used in cTPE, it is separated and discarded with the rest of the components. On the other hand, in mTPE, it is possible that a large amount of citrate is delivered to the patient because of the small proportion extracted from the plasma [40].

Replacement Fluids and Supplements

When the replacement fluid is FFP, the citrate content of the FFP represents an additional load that the patient has to metabolize [40]. FFP replacement is universally used in TTP with the rationale of eliminating autoantibodies to ADAMTS13 and restoring ADAMTS13 protease activity [6].

TPE for indications other than TTP can be performed using 5% albumin, provided that the serum albumin does not exceed 5 g/dL. This avoids the possible complications of FFP transfusions. If the albumin level increases too much, a 0.9% NaCl infusion is used as a replacement fluid during the first quarter of the procedure at a rate 20% greater than the plasmapheresis withdrawal rate to compensate for the shift of saline serum to the interstitium [43, 44].

In repeated plasmapheresis with replacement with albumin and 0.9% NaCl, coagulation factors may fall. Fibrinogen levels taken at the beginning of the plasmapheresis procedure can be used to monitor this, and if the fibrinogen drops below 100 mg/dL, the use of FFP for the last 500 mL of the replacement solution may be indicated [44].

Safety and Efficacy

Serious complications are rare: anaphylactoid reactions 0.25%, cardiac 0.2%, respiratory 0.2%, and hemorrhage and infection 0.02%. Transfusion-related acute lung injury is possible [39]. Allergic reactions may be prevented by the administration of an antihistamine such as diphenhydramine and an antipyretic such as acetaminophen (paracetamol) [6].

During laboratory first evaluation of the membrane, a sieving coefficient of 1.0 was found for all plasma components [44]. A prospective, randomized, paired, cross-over study involving 21 patients showed that the membrane

technique took 10.5% more time than the centrifugation technique. However, the end result in terms of the decrease in markers (e.g., IgM and IgG) was equivalent [45]. The additional time could pose a problem in centers that frequently perform consecutive plasmapheresis but is not likely to be an issue in intensive care where staff are more accustomed to hemofiltration systems and the use of plasmapheresis is occasional.

Conclusion

Plasmapheresis is a life-saving technique in some conditions and should be a part of the armamentarium of every intensivist.

Acknowledgement

We would like to thank Dr. Melissa Jackson for reviewing our article.

Conflict of Interest Statement

The authors declare to have no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

S.R. and P.M.H. designed the study. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

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