Review Article

Plasma Filtration

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Abstract

Therapeutic plasma exchange (TPE) or plasmapheresis involves the separation of plasma from whole blood. In so doing, plasma-borne humoral disease mediators are removed from the body. This can attenuate the course and severity of the underlying disease. Diseases that can be treated with TPE are classified into the following categories: (1) endocrinological, (2) neurological, (3) renal/rheumatological, and (4) haematological. TPE is adjuvant in most of these settings. Disease-specific pharmacological treatment remains the cornerstone of treatment in many of these conditions. Plasma separation can be achieved with either (1) centrifugation (CF) or (2) membrane plasma filtration (PF). The latter is the focus of this review. It can be performed using either a continuous renal replacement therapy (CRRT) or haemodialysis (HD) machine. Standard plasma filtration has also been modified to incorporate sorbent technology which obviates the need for plasma volume replacement fluids. Larger clinical issues such as timing of initiation and intensity of therapy are examined.

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Introduction

Many immune-mediated and autoimmune diseases are caused by dysregulation of the cell-mediated and/or humoral-mediated arms of the immune system.[1-3] Some conditions are caused mainly by cellular immune mechanisms involving the macrophage/lymphocyte system.[4,5] The immunopathogenesis of other diseases involve both the cellular and humoral pathways.[6,7] Humoral disease mediators consist of a diverse range of substances of varying molecular weights (MW). These could be pathogenic antibodies, antibody complexes, immune complexes, autoantibodies and antigen appearing de novo during acute disease. Cytokines are one such group of mediators, consisting of many distinct subtypes such as interleukin-4 (IL-4), interleukin-6 (IL-6) and interleukin-10 (IL-10).[8] A study by Reeves et al[9] comparing continuous plasma filtration with protocol-driven, standard critical care without plasma filtration in patients with severe sepsis showed that both groups of patients at baseline had comparably elevated cytokines such as interleukin-6 (IL-6) and granulocyte colony-stimulating factor. Evidence supporting the role of plasma-borne humoral disease mediators is found in other studies. Sera from patients with Guillain-Barré syndrome (GBS) was shown to disrupt the function of the blood-nerve barrier (BNB). A factor identified as anti-GM1 antibody was implicated since incubation with pure GM1 antigen appeared to attenuate the BNB damage induced by this pathogenic antibody.[10] Besides causing disease, certain humoral mediators also have diagnostic value in clinical management. It is well established that the anti-dsDNA antibody is diagnostic of systemic lupus erythematosus (SLE). A recent study by Villalta et al[11] demonstrated the importance of differentiating high-avidity anti-dsDNA autoantibodies, which is more specific for SLE, from the low-avidity forms, since the latter can also be found in other inflammatory diseases. Another aspect of SLE relates to the increased apoptosis of peripheral T-lymphocytes in active disease. Moreover, this is associated with increased expression of both membrane-bound and soluble (s) Fas. It was found that sFas had a pro-apoptotic effect, which partly explains the increased apoptosis seen in active lupus.[12] Further evidence of the

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importance of humoral and cellular immune mechanism interactions was found in a study of patients with thrombotic thrombocytopaenic purpura (TTP).[13] TTP is a clinical syndrome consisting of microangiopathic haemolytic anaemia, consumptive thrombocytopaenia, predilection for neurological involvement and formation of platelet thrombi in small vessels. Plasma from 4 such TTP patients was studied for their effects on human blood phagocyte activation as measured by reactive oxygen species production and CD11b expression. Plasma from these patients with active TTP contained activated phagocytes. Cryoglobulins are another group of blood-borne humoral disease mediators. These are circulating immunoglobulin (Ig) complexes that can deposit on small vessel walls and elicit inflammatory tissue injury. They are currently classified into 3 types: Type I cryoglobulins are monoclonal and found in association with lymphoproliferative diseases, type II cryoglobulins are mixed monoclonal and polyclonal IgG or IgM antibodies and type III are mixed polyclonal IgG antibodies. Of these, type II cryoglobulins are the most common and are usually found in association with viral hepatitis C infection. These mediators can be cleared from the blood compartment with therapeutic plasma exchange (TPE).[14] Specific humoral-cellular immune system interaction causing disease can also be seen, albeit indirectly, in a case report of 2 SLE patients who responded to long-term rituximab (anti-CD20 monoclonal antibody) therapy.[15] Accelerated acute humoral rejection (AHR) can occur in renal transplant recipients and is diagnosed by the twin findings of characteristic histopathological changes on renal biopsy and detection of anti-HLA antibodies in the serum. In one series, these patients were treated with TPE and intensification of their immunosuppressive regimen. Such an approach appeared to reverse AHR in their renal allografts and maintain graft function.[16]

It is beyond the scope of this review to discuss all the known humoral immunopathogenic factors and their interactions with individual cellular components of the immune system in every immune-mediated condition reported to be responsive to TPE. Nevertheless, a few key points should be observed when reviewing TPE data. Many immune-mediated conditions are caused by both humoral as well as cellular mechanisms. It is important to recognise the main immunogenic factor(s) in each disease and understand how these act either by themselves and/or through interaction with inflammatory cells to cause clinical disease. The second step is to determine if the main pathogenic factor(s), especially if blood-borne, can be eliminated using TPE. Most can be removed from the blood compartment unless they are extensively bound to cells and organs in the extravascular compartment or unless the mediator MW exceeds the plasma filter membrane pore size cut-off limit. The last but most important question is whether the elimination of such mediators attenuates specific inflammatory pathways and the overall inflammatory cascade. Clinical disease remission is, however, the ultimate aim of TPE. However, the quality and durability of such remission needs to be considered. This may be very difficult to do since many conditions treated with TPE also require concomitant intensive pharmacological immunosuppressive therapy such as corticosteroids, cyclophosphamide and intravenous immunoglobulin.[17,18] The net immunomodulatory effect of TPE per se is thus difficult to discern and quantitate. This situation is exacerbated by the lack of specific and sensitive biomarkers of inflammatory disease course and severity, except in a few conditions. The assessment of disease remission and relapse of most immune-mediated diseases is thus based on a combination of clinical and laboratory data. Many of these commonly used clinical indices are, however, insensitive and nonspecific. Therefore, the clinical use of TPE cannot be precisely titrated against disease treatment response.

Clinical Indications

Many diseases have been reported to benefit from TPE. The majority of these have been uncontrolled case series and anecdotal accounts. In some cases, TPE is used as the treatment of last resort, when the underlying disease is already very advanced and intractable to standard medical therapy. Moreover, in those which have been reported as being unresponsive to TPE, one has to determine if plasma exchange is truly of no use or whether it is a question of late initiation and/or inadequate immunomodulatory intensity (for example, alternate day instead of daily exchange therapy). Thus, timing of initiation and intensity of immunomodulation [intermittent (alternate day versus daily) versus continuous mode and the total plasma volume exchanged] are crucial considerations when evaluating data on the clinical efficacy of TPE. However, such data are lacking in the literature. There are, however, already analogous answers in the realm of acute renal failure (ARF) in critically ill patients. A retrospective study by Gettings et al[19] showed that earlier initiation of acute renal replacement therapy (aRRT) is associated with a more favourable outcome in a series of polytrauma patients with ARF. A higher ultrafiltration volume/dose used in continuous venovenous haemofiltration (CVVH) was found to be associated with improved patient survival in a separate prospective, randomised study by Ronco et al.[20] Both studies support the view in ARF management that earlier initiation and a higher intensity approach to acute RRT are important in achieving optimal clinical outcomes. In the field of apheresis/TPE, similar analogous data are presently lacking.

Two large national Apheresis Registry data are worth

examining at this stage. The Swedish Apheresis Group examined data from >20,000 plasma exchange procedures and found that adverse events requiring either medication(s) or disruption of exchange therapy developed in about 1% of all procedures. These were either hypotension or arrhythmia developing during exchange treatment and were more likely to occur in those with TTP/haemolytic-uraemic syndrome (HUS) and GBS than in those with hyperviscosity syndrome, hypercholesterolaemia and septic shock/multiple organ dysfunction syndrome. The Swedish experience also showed that the overall incidence of adverse events during plasma exchange was 4.3% and technical problems were more frequently experienced when performing LDL apheresis and immunoadsorption.[21] The French Apheresis Registry is even larger and contains data from about 80 centres since 1985 of 16,700 patients who underwent a total of 153,641 apheresis sessions over the period of time. There were a total of 5 broad indications for plasma exchange treatment: neurological, haematological, nephrological, rheumatological and endocrinological. Until 2000, neurological indications for exchange treatment of GBS and MG represented the most important group receiving TPE. However, since then, with the greater use of intravenous immunoglobulin (IVIg), patients with these 2 neurological diseases have had proportionately fewer apheresis sessions. In contrast, the haematology group became more highly represented with increased numbers of TTP/HUS cases being treated with plasma exchange. This accounted for increased sessions in the haematological group. The endocrinological group consisted mainly of patients with severe familial hypercholesterolaemia and accounted for only 10% of all sessions. The standard angioaccess since 1985 had been the peripheral vein and in the early days of the French Apheresis Registry, albumin was the only plasma substitution fluid used. After 1990, albumin was mixed with hydroxyethylstarch (HES) solution. However, the use of HES was associated with increased complications. This prompted the use of albumin again as the preferred plasma replacement fluid in the later years of the French Apheresis Registry.[22]

Besides knowing that it is generally safe, the central question remains: is TPE clinically effective in treating the clinical conditions alluded to earlier? Ideally, prospective, randomised, multi-centre clinical trials are needed to answer this question. Otherwise, any clinical improvements that result from TPE may be attributed to confounding factors and not to TPE per se. Of these, patient selection is the most likely cause of confounding. Patients with mild, early disease may be more likely to respond to TPE. At the other end of the spectrum, those who are starting to recover may continue to do so with pharmacological therapy alone, regardless of whether TPE is used. Different plasma exchange initiation criteria and dose intensities adopted to treat the same condition in different studies render data comparisons meaningless. Ultimately, in the absence of proper randomised, controlled trials and a lack of standardisation of plasma exchange treatment protocols for different diseases, doubts about the therapeutic efficacy of TPE will always persist.

Neurological conditions that have been treated with TPE are myasthenia gravis (MG), GBS, acute and chronic inflammatory demyelinating polyneuropathy (CIDP) and acute demyelinating encephalomyelitis (ADM). GBS has been shown to benefit from TPE.[23,24] Pharmacological treatment with corticosteroids and IVIg is still the cornerstone of treatment for long-term disease control in CIDP.[25] MG associated with the presence of thymoma should be treated with TPE before elective thymectomy and during myasthenic crises. However, what is less clear is the role of plasma exchange in the chronic management of thymomatous MG in association with conventional immunosuppression and anticholinesterase therapy. A single case report from Macedonia[26] documented a positive role for TPE as an adjunct to standard MG maintenance pharmacotherapy in sustaining disease remission. TPE has also been reported to be useful in the treatment of acute disseminated encephalomyelitis (ADM), which is often difficult to differentiate from a first attack of multiple sclerosis (MS). A differentiating point is a positive therapeutic response to intravenous methylprednisolone in ADM compared to MS but this is not definitive. The definitive role of TPE in both ADM and MS remains to be further elucidated.[27]

Haematological indications for TPE are mainly TTP and HUS. Given that TPE may be logistically difficult to organise in an acute situation, a retrospective study was conducted comparing the use of intravenous infusions of fresh frozen plasma (FFP) with standard TPE. Coppo et al[28] compared the infusion of high-dose plasma (25 to 30 mL/kg/day) (n = 19) versus plasma exchange (n = 18) as first-line treatment at a single centre. Both groups of patients were comparable at baseline in terms of clinical and laboratory indices. Eight patients from the high-dose plasma infusion group had to be crossed over to the plasma exchange group because of clinically significant fluid overload and another 2 patients were also switched to TPE because of disease resistance to plasma infusion. Thus, high-dose plasma infusion may be a useful first-line early treatment if TPE cannot be instituted at initial presentation. However, fluid overload is the main adverse event with this approach.[28] Nevertheless, the treatment of choice for acute TTP-HUS is still plasma exchange with an exchange volume of $\geq$40 mL plasma/kg body weight (BW).[29] Besides the use of TPE in non-renal transplant TTP patients, its use has also been documented in renal transplant (RTx) patients

with acquired thrombotic microangiopathy. This is usually secondary to calcineurin inhibitors such as cyclosporin A, although other factors such as acute vascular rejection and concomitant viral infections can also precipitate this complication. In an uncontrolled series of 29 post-RTx patients with thrombotic microangiopathy (TMA), all of them had cessation of calcineurin-inhibitors and also underwent plasma exchange treatment.[30] During active TMA, haemoglobin and platelet counts dropped 66% and 64% respectively and peak serum creatinine was 7.4 ± 2 mg/dL. The mean duration of TPE was 8.5 (range, 5 to 23) days. Recovery of platelet count to 150,000/mm^3 and haemoglobin to 8 to10 g/dL were taken as end-points for TPE cessation. Graft function was salvaged in 80% of the study population and calcineurin-inhibitor treatment reinstituted without any relapse of TMA in the majority of patients.[30] Current thinking on the pathogenesis of acquired TTP suggests that the main problem lies in a deficiency of a specific plasma metalloprotease, which is responsible for the physiological processing of von Willebrand factor multimers. This von Willebrand factor-cleaving protease has been identified as belonging to the ADAMTS family of metalloproteases, designated ADAMTS13. The acquired form of TTP is believed to be due to the presence of inhibitory autoantibodies to ADAMTS13.[31] TPE works in TTP possibly through the clearance of this pathogenic autoantibody. Pharmacological management of TTP has also been advocated. The addition of IVIg was found, however, to be no better than a standard regime of corticosteroids, anti-platelet agents and TPE without IVIg.[32] A retrospective Taiwanese study[33] showed that for resistant cases of TTP, the use of cytotoxic agents such as cyclophosphamide and vincristine may even be needed.

Another haematological indication for TPE is hyperviscosity syndrome. This can be due to an excess of abnormal plasma components such as pathogenic antibodies, immune complexes, paraproteins and cryoglobulins. Common causes of paraproteinaemias are Waldenström's macroglobulinaemia and Ig A and Ig G (3) multiple myeloma. Hyperviscosity syndrome can also be due to an excess of cellular components as in polycythaemia, leukaemias and other myeloproliferative diseases. Technically, a single plasma exchange of 3 L is sufficient to improve the condition of patients with macroglobulinaemia as most of these paraproteins are in the intravascular compartment due to their large MW. For those paraproteins with lower MW ranges, repeated plasma exchanges may be needed due to re-equilibration between the intra- and extra-vascular compartments. Cryofiltration apheresis is a modified apheresis technique involving the use of a large-capacity cryofilter and is used specifically for cryoglobulinaemia treatment.[34]

The treatment of severe familial hyperlipidaemia with lipopheresis constitutes the main endocrinological indication. A study by Yeh et al[35] compared the use of standard plasma exchange with double-filtration plasma exchange for the treatment of hypertriglyceridaemia, a known precipitating factor of acute pancreatitis. A total of 18 patients were studied. Triglyceride and cholesterol concentrations decreased from 1977 to 693 mg/dL and 437 to 222 mg/dL, respectively. The experience from other centres also corroborate the role of plasma exchange as an adjuvant blood-lipid lowering technique.[36,37] The role of plasma exchange for the chronic management of less severe forms of hyperlipidaemia, however, remains uncertain.

Nephrological and rheumatological indications for plasma exchange are closely interlinked. Rheumatological diseases are generally systemic in nature but with predilection for certain organs such as the kidneys. An example is lupus nephritis in SLE. More aggressive histological forms of lupus nephritis were found in untreated overt nephritis compared to asymptomatic forms of the disease, as data from Zabaleta-Lanz et al[38] show. Immune-mediated renal disorders span a continuum in clinical presentation and disease severity. The most severe form is rapidly progressive glomerulonephritis (RPGN), which may be primary idiopathic or secondary to systemic disease. A subset of RPGN patients may have autoantibodies and/or other forms of blood-borne humoral disease mediators. These include Goodpasture's syndrome with anti-glomerular basement membrane (GBM) antibody, Ig A glomerular mesangial deposition as part of the renal component of Henoch-Schonlein purpura, SLE, cryoglobulinaemia and the anti-neutrophil cytoplasmic antibody (ANCA)-positive pauci-immune group. Plasma exchange has been shown to be of use in each of these groups of immunological renal disease.[39] Apheresis has also been shown to be useful in renal transplantation in salvaging renal allograft function in certain humoral-mediated renal graft rejections and in pre-renal transplant immune optimisation through the elimination of preformed cytotoxic antibodies. Finally, there is a small group of renal conditions in which the immunopathogenetic mechanisms are not so well-defined, yet these diseases have been noted to respond to plasma exchange therapy. These are cast nephropathy in multiple myeloma with meylomatous kidney involvement and in recurrent renal allograft focal segmental glomerulosclerosis.[39,40] Other reviews have alluded to the role of plasma exchange in treating polyarteritis nodosa and Churg-Strauss syndrome, although more definitive data are needed.[41] A retrospective uncontrolled study by Klemmer et al[42] examined therapy of patients with small-vessel vasculitis with positive ANCA. All patients in this

series were treated with a standard protocol of intravenous methylprednisolone, cyclophosphamide and plasma exchange. Diffuse alveolar haemorrhage arising from pulmonary small-vessel vasculitis, resolved in 100% of cases after a mean of 6.4 plasma exchange sessions. No apheresis complications were noted. Renal function improved with this protocol in those who presented with azotaemia. In a separate review comparing standard plasmapheresis with immunoadsorption,[43] patients with advanced lupus nephritis (serum creatinine >600 umol/L) on dialysis generally failed to benefit from TPE. However, TTP in SLE is a strong indication for plasma exchange. Pharmacological treatment with corticosteroids and cyclophosphamide remain the cornerstone in the management of chronic SLE with lupus nephritis. The role of plasma exchange in primary vasculitides such as Wegener's granulomatosis and microscopic polyarteritis, however, remains controversial. Plasma exchange is useful in Wegener's granulomatosis if there is concomitant anti-GBM antibody with pulmonary haemorrhage.

Severe sepsis with septic shock is another condition that has been treated with plasma exchange. Cytokines play an important part in the pathogenesis of this condition and eliminating these cytokines from the circulation attenuates the inflammatory septic process, thereby preventing the development of frank multi-organ failure (MOF). TPE can be used to control hypercytokinaemia in severe sepsis. Stegmayr et al[44] studied the effect of CF-TPE in progressive disseminated intravascular coagulation, MOF and ARF. As a salvage treatment in these critically ill septic patients, TPE was associated with a survival of 82% compared to non–TPE-treated historical controls, whose survival was <20%. An earlier uncontrolled study reported a survival of 81% in a similar population of ARF/MOF patients.[45] A meta-analysis of the role of plasma exchange in sepsis by Reeves[46] showed that case reports of more than 40 patients treated with TPE for severe sepsis had an average survival rate of more than 70%. A prospective, randomised, controlled trial by Busund et al[47] of TPE in severe sepsis and septic shock involved 106 consecutive patients. They were randomised to either standard intensive care unit (ICU) therapy alone or ICU care with add-on TPE. The primary end-point was the 28-day survival. Septic shock was diagnosed in 57% of TPE-treated cases and 54% of the control group. Mean APACHE III scores at entry were 56.4 (TPE group) versus 53.5 (control group). The 28-day all cause mortality rate was 33.3% (TPE) and 53.8% (control). The absolute reduction in the risk of death in the TPE group was 20.5%. Complications noted in this trial were 6 transient episodes of hypotension and 1 allergic reaction to FFP. TPE may have an adjuvant therapeutic role in severe sepsis in critically ill patients.

Technique

Blood from the patient is pumped through an extracorporeal blood circuit during PF-TPE via a standard double-lumen, venovenous dialysis catheter. Various plasma-borne humoral disease mediators have been described. To remove them from the intravascular blood compartment, the first step is to separate plasma from whole blood. There are 2 physical methods of doing this: centrifugation (CF) and membrane plasma filtration (PF). Centrifugation (CF) TPE involves the use of an apheresis machine such as PCS[2] (Haemonetics, Minnesota, Minneapolis, USA) (Fig. 1). It separates out different cellular and non-cellular components of whole blood depending on the centrifugation speed and the time interval used. Thus, leukocytes, platelets, stem cells and plasma can be fractionated from peripheral blood. These machines are usually used in the haematology/blood banking and blood transfusion services. With the development of haemodialysis and continuous renal replacement therapy (CRRT) machines, nephrologists and intensivists have been able to use membrane plasma filtration as an alternative TPE technique. Examples of RRT machines that can perform membrane plasma filtration using hollow-fibre, capillary plasma filters, include the Prisma (Hospal, Lyon, France) (Fig. 2) fluid bag-based CRRT system and the ARrT plus (Fresenius Medical Care AG, Bad Homburg v.d.H., Germany) on-line CRRT platform. The operating principle is similar to CVVH in that blood is pumped across the plasma filter, which is part of an extracorporeal blood circuit. Plasma is extruded from the intraluminal blood compartment of the plasma filter into the plasma effluent pathway and drained into a collection bag. Membrane plasma filters typically have pore size cut-offs that exceed those of haemofilters. The polypropylene plasma filter used with the Prisma system has a pore size cut-off $\geq$60,000 Da. Large molecules such as albumin (MW 68,000 Da), immunoglobulin G (MW 160,000 Da), apolipoprotein B (apo B) (MW 512,000 Da) and immunoglobulin M (Ig M) (MW 950,000 Da) can be removed from the blood compartment during TPE with this membrane. The sieving coefficients of all these proteins have been reported to be $\geq$0.95 at a blood flow rate of 100 mL/min. In addition to the filtration properties of membrane plasma filters, their surface area has also been studied.[48] A porcine experiment showed that larger surface area plasma filters were not more effective than smaller-sized ones in clearing specific measured solutes. This is of practical importance. Other synthetic materials used in membrane plasma filters include polysulphone and polyethylene, the latter in Plasmaflo OP (Asahi Medical, Tokyo, Japan).[49] Besides plasma filtration, another potential mechanism of solute clearance during membrane plasma exchange may be adsorption. Animal and clinical studies of CVVH in sepsis have shown that

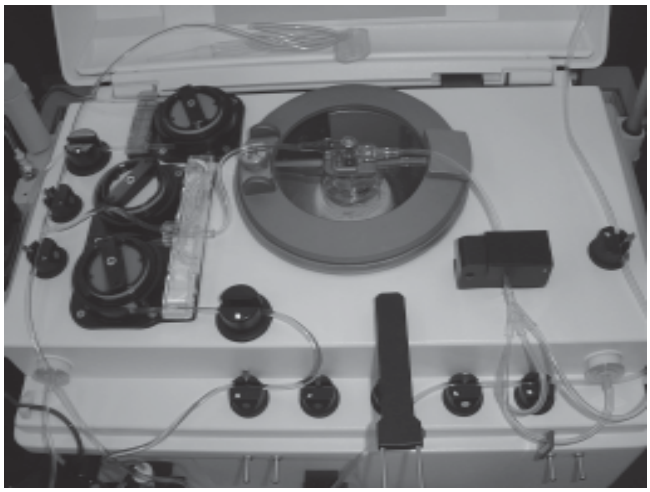

Fig. 1. Device for centrifugation (CF) therapeutic plasma exchange (TPE). PCS² (Haemonetics, Minneapolis, Minnesota) unit.

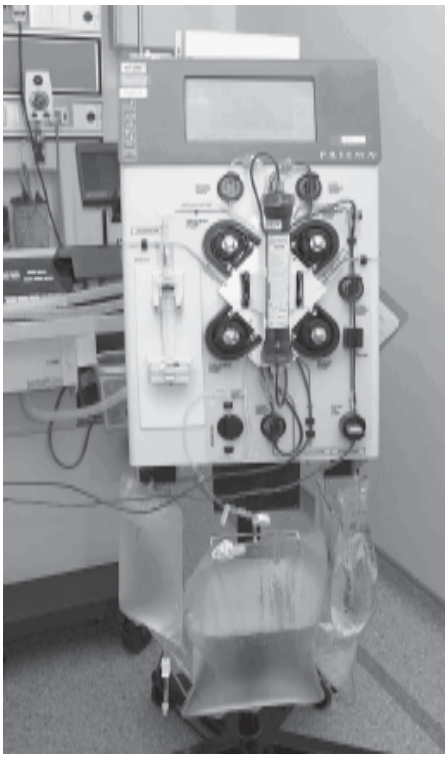

Fig. 2. Continuous renal replacement therapy (CRRT) machine capable of performing membrane plasma filtration (PF) therapeutic plasma exchange (TPE). Prisma (Hospal, Lyon, France) fluid bag-based CRRT platform.

cytokine adsorption onto polyacrylonitrile haemofilter occurs and observes saturation kinetics.[50,51] It may be that plasma membrane adsorptive removal of various humoral disease mediators also plays a role in the overall elimination of plasma-borne disease mediators. Such a role, however, remains to be further elucidated.

The principles and practice of TPE and its complications have been described by Kaplan.[52,53] Citrate anticoagulation is the anticoagulant of choice when performing CF-TPE whereas heparin is the conventional anticoagulant used in PF-TPE. A recommended dose of heparin (in the absence of overt bleeding diatheses) is 2000 IU to 5000 IU initially (40 IU/kg to 60 IU/kg) followed by 1000 IU/h to 2000 IU/h or 500 IU/h to 1000 IU/h every hour for the duration of TPE. Lower doses of anticoagulant should be used or omitted altogether if there is a very high risk of bleeding. Anticoagulant is administered pre-plasma filter (Fig. 3). Citrate toxicity can occur even if citrate anticoagulant is not used given the relatively high content of citrate (up to 14% by volume) in fresh frozen plasma (FFP), especially if there is significant concomitant renal and/or hepatic dysfunction. Human albumin (5%) is also used in combination with FFP as fluids for plasma replacement to maintain isovolaemia. However, transmission of infectious diseases and/or anaphylaxis can occur with the use of such blood products. Plasma substitution fluids are administered post-plasma filter (Fig. 3). It is advisable to use a 2- or 3-way tap to administer plasma replacement fluids so that each unit of FFP can be infused one bag at a time to facilitate subsequent identification of the specific product that may be the cause of anaphylaxis should it occur. The ratio of FFP to albumin used is dependent on disease biology and bleeding diatheses. More FFP is used if known specific disease inhibitor(s) is/are present in it and/or there are bleeding diatheses. Synthetic fluids used for plasma replacement have also been studied. One such fluid is HES. Haltern et al[54] compared normal saline with HES in an experiment involving porcine blood circuits and plasma filters. HES was found to be associated with increased haemolysis and adversely affected the filtration properties of the plasma membrane studied.

Blood flow rate in PF-TPE can range from 100 to 200 mL/min. All commercial plasma filters have product specifications stating the specific relationship between blood flow and plasma flux or filtration under standard ex vivo conditions using bovine blood with haematocrit of 45% at a pre-determined temperature. For example, the Asahi Plasmaflo plasma filter at a blood flow rate of 150 mL/min yields a plasma flux of close to 60 mL/min. This information can be used to decide if a membrane in use is failing or suboptimal in function if it fails to deliver the predicted plasma flux at a given blood flow rate. Plasma exchange can be performed intermittently: either daily or on alternate days. Duration of treatment can range from 3 h to 6 h. The volume of plasma exchanged determines the intensity of immunomodulation. A larger volume of plasma removed during each session clears a larger amount of plasma-borne humoral disease mediators than a smaller

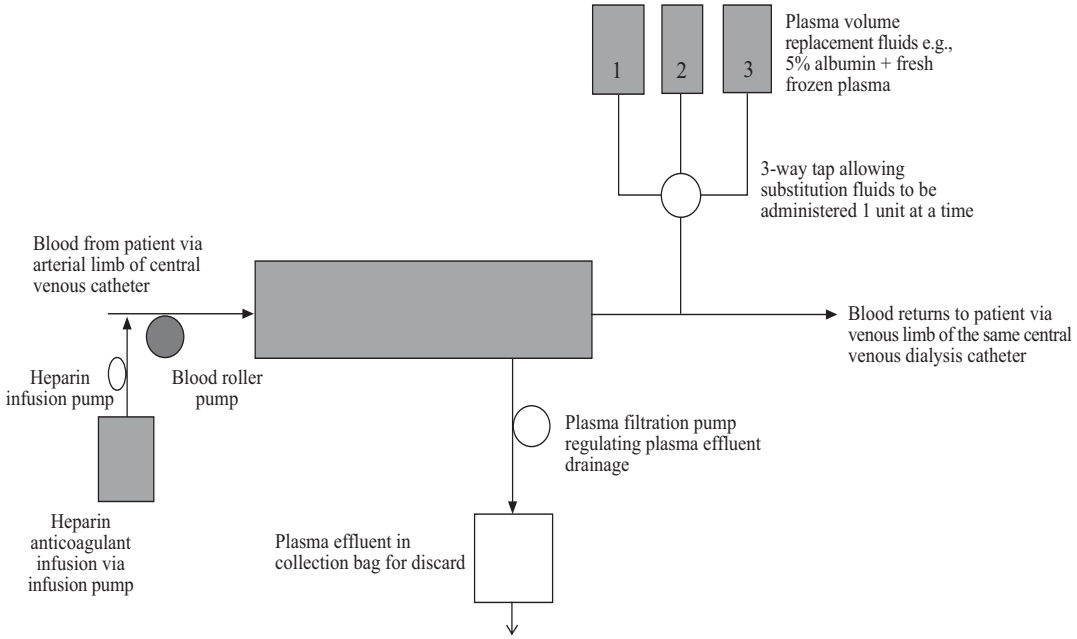

Fig. 3. Diagrammatic representation of standard membrane plasma filtration (PF) extracorporeal blood circuit.

volume of plasma. Removal of a larger quantity of disease mediators would be expected to be more intensely immunomodulatory. However, the amount of plasma exchanged per treatment is also affected by the haemodynamic status of the patient. Those with unstable haemodynamic status would need to either have lower volumes of plasma exchanged and/or lower blood flow rates used. The same immunomodulatory effect of TPE can potentially increase patients' susceptibility to sepsis. One possible explanation for this is the removal of protective immunoglobulins. However, this increased susceptibility to infections following TPE was not substantiated in one early study.[55] Hypokalaemia may occur in some patients following plasma exchange, especially if there is already baseline hypokalaemia. One reason is the absence of potassium in standard albumin solution. This complication can be avoided through potassium supplementation. The volume of plasma to be exchanged per treatment is calculated as follows:

$$EPV = (0.065 \times BW) \times (1 - Hct)$$

where EPV = estimated plasma volume, BW = body weight in kg and Hct = haematocrit.

It is estimated that it takes 5 separate plasma exchange sessions over a 7- to 10-day period to remove 90% of a patient's original total body burden of blood-borne humoral mediators, assuming negligible ongoing production of these mediators during this time. For many diseases, the optimal duration of plasma exchange treatment is empirical. In many instances, plasma exchange is instituted for as long as it remains clinically indicated, for example, failure of the disease to go into remission or disease relapse following initial remission.

Plasma Filtration Coupled with Sorbents

A major shortcoming of standard membrane plasma filtration is the need for plasma substitution fluids. Among the complications associated with their use is the increased risk of transmission of infectious diseases. Moreover, humoral mediator removal is non-specific and non-discriminatory. The use of activated charcoal sorbent cartridge placed in series with but downstream of the plasma filter is termed coupled plasma filtration adsorption (CPFA) (Fig. 4a). Filtered plasma is pumped through a charcoal cartridge such as Adsorba 150C and Adsorba 300C (Gambro, Lund, Sweden), respectively containing 150 g and 300 g of cellulose-coated, haemoperfusion-grade activated charcoal. The smaller 150-g cartridge also contains polypropylene balls as filler material. These are the same activated charcoal cartridges used for haemoperfusion. Another type of cartridge made from resins (Amberlite and Amberchrome) has been shown to adsorb large quantities of tumour necrosis factor, interleukin 1-beta and interleukin-8 through hydrophobic interaction.[56] Ronco and co-workers[57] have shown that CPFA may be useful in the treatment of severe sepsis in critically ill patients. Another kind of sorbent cartridge is an

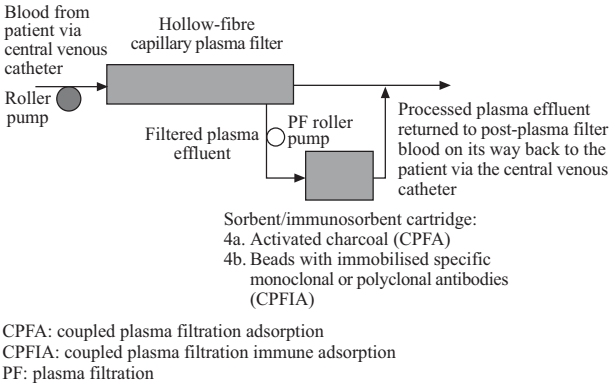

Fig. 4. Diagrammatic representation of (a) coupled plasma filtration adsorption (CPFA), and (b) coupled plasma filtration immunoadsorption (CPFIA) extracorporeal blood circuits.

immunosorbent column with mono- or polyclonal antibody-coated resin through which filtered plasma is pumped. This set-up is called coupled plasma filtration immunoadsorption (CPFIA) (Fig. 4b).

One study involved a small subset of patients with congestive cardiac failure secondary to dilated cardiomyopathy who were seropositive for a pathogenic antibody.[58] This work by a German group documented definite echocardiographic improvement in the cardiac function as evidenced by a sustained rise in left ventricular ejection fraction compared to baseline cardiac function after a few sessions of CPFA therapy. There were no additional pharmacological interventions during the period of follow-up.

Unanswered Questions

There are still many as yet unanswered questions on the use of TPE or plasmapheresis. TPE is effective in only a few conditions. In many others, its adjuvant role is still uncertain. One possible reason is the need for concomitant pharmacological immunosuppression, which masks the separate immunomodulatory effect of plasma exchange. Another reason is the lack of sensitive and specific biomarkers that parallel disease activity. For all these reasons, it is difficult to titrate plasma exchange precisely in accordance with disease status. Comparative data on the therapeutic efficacy of TPE is distorted by the lack of standardisation of plasma exchange initiation criteria and treatment intensity/dose for different diseases. Moreover, disease presentation and severity usually span a continuum from the mildest form through to the most severe and even fulminant form. Thus, a series may have more favourable treatment response with TPE for a particular disease merely because more patients with early and less aggressive diseases were included in the study. Alternatively, for the same disease, other series may report a worse outcome if plasma exchange was instituted very late, when the disease is already far advanced. At the technical level, there is little information about whether membrane plasma filters are themselves more pro-inflammatory than centrifugation technique. Without this information, the choice of plasma separation technique is based purely on logistical considerations. Ultimately, large multi-centre trials using protocol-driven plasma exchange with standardised initiation criteria and treatment intensity schedules, are needed to clarify if plasma exchange has a significant disease-modifying effect in the treatment of different diseases at different activity levels. Last but not least, the use of PF-based, sorbent-enabled blood purification techniques have added to the therapeutic options available for the treatment of severe sepsis and dilated cardiomyopathy. More clinical data are, however, needed before these tools can be widely used in clinical practice.

Conclusion

Membrane plasma filtration is a technique of plasma separation complementing traditional centrifugation TPE or plasmapheresis. Plasma exchange is clinically effective in only a few conditions. Its clinical efficacy in other conditions remains unproven. Moreover, the biocompatibility of modern capillary plasma filters is uncertain. Optimal timing of initiation and dose or intensity of plasma exchange to treat different diseases of different severities are also uncertain. Part of the problem is a lack of good biomarkers with which to monitor disease activity and treatment response. Another confounding factor is the frequent need for concomitant pharmacological immunosuppression. It is thus difficult to titrate TPE precisely. Newer techniques being developed attempt to circumvent the need for blood products as plasma replacement fluid as well as increase the specificity of mediator removal. More data on these aspects of plasma exchange in general and of membrane plasma separation, in particular, will provide a more scientific and rational basis for its use in future.

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