Review

Role therapeutic plasma exchange in critical care

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Therapeutic plasma exchange (TPE) or therapeutic plasmapheresis are the terms used interchangeably and involve extracorporeal separation of plasma from cellular elements using centrifugal or membrane-based device. The remaining cellular element is mixed with replacement fluid, which is then reinfused back to the patient. The main objective of TPE is to remove pathologic antibodies, cytokines and immune complexes involved in pathogenesis of wide variety of diseases.[1] The American Society for Apheresis (ASFA) periodically summarizes the evidence-based approach in grading and categorization the use of TPE in various medical conditions. The eight editions of ASFA guidelines provides the evidence of therapeutic apheresis for 157 clinical situations in 84 diseases, which include variety of neurological, hematological, nephrological and rheumatological disorders. Some of the category 1 (accepted as first line therapy, either alone or in conjunction with other modes of treatment) indications of TPE recommended by ASFA are[2]:

Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre Syndrome)

ANCA associated vasculitis/Anti-glomerular basement membrane disease

Antibody mediated rejection in ABO compatible renal transplant

Catastrophic antiphospholipid syndrome (CAPS)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Hyper viscosity in hypergammaglobulinemia (symptomatic)

Myasthenia Gravis (Acute, short-term treatment)

N-methyl-D-aspartate receptor antibody encephalitis

Paraproteinemic demyelinating neuropathies.

Thrombotic thrombocytopenic purpura (TTP)

Wilson disease, Fulminant

Applications of TPE

TPE is a rational choice in clinical situations, where the implicated substance for removal has high molecular weight (> 15000 Da), long half-life or has low turnover rate. Some examples of successful use of TPE in clinical practice include removal of monoclonal IgM antibodies in Waldenstrom macroglobulinemia, acetyl choline receptor antibodies in myasthenia gravis and GQ1b antibodies in Miller Fisher variant of Guillain-Barre syndrome. Other postulated mechanisms of TPE include replacement of missing plasma components (ADAMTS13 in thrombotic thrombocytopenic purpura), sensitization of antibody producing cells to immunosuppressant agents and alteration in lymphocyte activity.[1,3,4]

During TPE, there is non-selective removal of normal and pathological plasma constituents. There is a significant decline in coagulation factor activity following TPE, particularly when albumin is used as replacement fluid. Most of the coagulation abnormalities return to baseline 24-48 hours post TPE.[5] In addition, TPE may also remove medications, including antibiotics. The data on drug dosing for medications during TPE is scarce , however it is important to consider pk/pd of various anti-microbials while considering supplementary dosing.[6]

Technical aspects of Plasmapheresis (Machine and devices)

The devices used to perform TPE can be divided into two types: centrifugation based, or membrane based. Membrane based TPE system contains pores or filter that allow the passage of plasma proteins but not the cellular components. Centrifugal systems separate blood components based on the density of individual elements, with most dense elements

(RBCs) settling furthest from axis of rotation and least dense elements (plasma) layering closest to the axis of rotation. In both the systems, the plasma layer is discarded, and cellular elements are returned to patient along with replacement fluid. Membrane based TPE can be performed with multifunctional RRT machines and is the preferred method in most ICUs/nephrology units. Hematology or transfusion medicine-based apheresis units prefer to use centrifugal method for plasma exchange. The two methods of TPE are similar with respect to therapeutic efficacy, although plasma removal efficiency is significantly higher with centrifugal system.[7,8] There is requirement for vascular access to achieve adequate blood flow to centrifugal or membrane-based filtration device. Centrifugation based devices require blood flow of 50-120 ml/min, whereas membrane based TPE requires a higher blood flow ranging from 150-200 ml/min. Central venous access is usually necessary for membrane based TPE to achieve higher blood flow. On the other hand, Centrifugation TPE can also be performed with peripheral venous access, as this method requires lower blood flow, thus avoiding the complications related to placement of central venous catheters.[9]

Dose of plasmapheresis

The usual prescription for TPE is 1.0 to 1.5 times plasma volume, which results in removal of approximately 60-70% of plasma constituents. One plasma volume in an adult roughly approximates 50 ml/kg. Targeting TPE dose beyond 1.5 times plasma volume removes only small amount of additional pathological molecules, while exposing the patient to more anti-coagulation, replacement fluid and increased risk of complications.[1,10] Multiple sessions of plasmapheresis are required as the concentration of pathogenic molecules usually rebound due to equilibrium achieved between interstitial space and intravascular compartment following a TPE session. The frequency of TPE sessions required depend on underlying disease, time required for pathological molecules to re-equilibrate in intravascular space and need to minimize complications, particularly bleeding due to depletion of coagulation factors. ASFA guidelines describe the rationale of TPE for individual diseases and provide guidance regarding the technical aspects like number of sessions to be performed. [2,7]

Anticoagulation

The goal of anticoagulation during TPE is to maintain circuit patency and to prevent clotting of extracorporeal circuit, while minimizing the systemic effects. Commonly, the anticoagulants used during TPE are unfractionated heparin, low molecular weight heparin or regional citrate. The choice of anticoagulation depends on patient's underlying medical condition (thrombocytopenia, risk of bleeding, hepatic or renal disease) and type of machine used for TPE (centrifugal vs membrane filtration). The anti-coagulation effect of citrate is mediated through reversible chelation with Ca^{2+} ions. Citrate acts as a regional anticoagulant in the extracorporeal circuit and is a preferred choice because of its less systemic bleeding risks. However, the use of citrate can lead to various metabolic complications including hypocalcemia, hypomagnesemia and metabolic alkalosis. Depending on the baseline status of metabolic parameters, it is important to initiate calcium replacement in the return line during citrate anti-coagulation. The use of heparin as anticoagulation leads to increased risk of systemic bleeding and heparin induced thrombocytopenia. Heparin based anti-coagulation is preferred in membrane based TPE or used in combination with citrate to reduce citrate load. [11,12]

Replacement Fluid

The plasma removed during TPE is replaced with frozen plasma (FFP) or albumin. It is reasonable to combine replacement fluid with 0.9% saline solution to minimize the cost. The main considerations while choosing the replacement fluid are availability, risk of bleeding, underlying medical condition and cost. Albumin 5% is commonly used as the replacement fluid for majority of TPE indications, as it is not associated with viral transmission or transfusion related adverse events. However, plasma exchange with albumin leads to increased cost, coagulation abnormalities and risk of bleeding. Use of FFP as replacement fluid is associated with increased risks of allergic events and transfusion reactions. FFP is the preferred replacement fluid in patients with active bleeding, coagulopathies, those requiring invasive procedure and in management of TTP. In the management of TTP, FFP replacement during plasma exchange provides the source of deficient enzyme ADAMTS13.[13,14]

Complications

TPE is associated with mostly minor complications, which can be managed easily and include[15]:

Vascular access related complications (pneumothorax, arterial puncture, bleeding, and infections).

a. Fever, chills or urticaria occur more frequently when FFP is used as the replacement fluid. On the other hand, hypotension is more commonly seen with albumin-saline replacement.

b. The use of albumin as replacement fluid leads to transient depletion of coagulation factors. Most of the coagulation abnormalities return to baseline within 24-48 hours after TPE.

c. Related to anti-coagulant use during TPE:

- The use of citrate can result in various metabolic complications including hypocalcemia, metabolic alkalosis and other electrolyte derangements. The most common manifestations of citrate toxicity are tingling or paresthesia secondary to mild hypocalcemia. Tetany and cardiac arrhythmias can occur with more severe hypocalcemia. To prevent symptomatic hypocalcemia, it is a common practice to replace IV calcium in return line and regularly monitor the electrolyte levels during TPE.
- Use of heparin as anti-coagulant can result in systemic bleeding and heparin induced thrombocytopenia.

In conclusion, therapeutic plasma exchange (TPE) is used to treat a diverse group of disorders in critical care through bulk removal of pathogenic antibodies circulating in plasma. The procedure can be carried out with centrifugation or membrane-based filtration device. The American Society for Apheresis (ASFA) regularly publishes evidence-based guidelines to assist the medical practitioners for the appropriate use of plasma exchange in various medical conditions. The choice of replacement fluid and anti-coagulation during plasma exchange depends on patient related factors, underlying medical condition, availability, and cost. Most of the complications seen with TPE are minor and can be easily treated.

Conflict of interest: Nil

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