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Perioperative Therapeutic Plasmapheresis

Sloan C. Youngblood, M.D.,* Yi Deng, M.D.,† Alice Chen, M.D.,‡ Charles D. Collard, M.D.§

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NUMEROUS disease states, including those often encountered in the perioperative setting, are mediated by excessive, deficient, or abnormal blood components. Although systemic immunosuppression has been used successfully to treat many of these, significant side effects and refractory disease often persist. Therapeutic apheresis facilitates the removal and replacement of both humoral and cellular blood elements and has found a unique niche in the treatment of these disorders.

In current practice, the terms "plasmapheresis" and "therapeutic plasma exchange" are often used interchangeably. However, plasma exchange takes the plasmapheresis procedure one step further. Plasma is separated from whole blood and discarded, whereas erythrocytes, leukocytes, and platelets are returned to the patient along with replacement fluid in a volume equal to that of the removed plasma.

Perioperative plasmapheresis poses several challenges for the anesthesiologist, including alterations in intravascular volume, serum electrolytes, the coagulation cascade, and drug pharmacokinetics. We now review the plasmapheresis procedure and its implications for perioperative care.

The Plasmapheresis Procedure

Apheresis refers to the selective removal of blood fractions and may be directed toward elimination of formed (cytapheresis) or plasma (plasmapheresis/plasma exchange) constituents. Extracorporeal processing of whole blood is used to isolate and remove blood elements, and replacement solutions of varying compositions are administered to maintain euvolemia and/or replete removed elements.

A typical goal with each plasmapheresis procedure is to eliminate a volume equal to 120% of the patient's calculated plasma volume, allowing for removal of up to 72% of most plasma components. Several plasmapheresis procedures are often necessary because many small proteins (particularly immunoglobulin G) are distributed throughout interstitial fluid and reequilibrate with the intravascular space after the procedure is completed.[1]

Two modalities of apheresis processing are possible. The more common centrifugal plasmapheresis uses a standard centrifuge to separate blood elements into their respective fractions based on variations in specific gravity (fig. 1). Profound hemoconcentration (hematocrit > 0.80) is possible, allowing efficient removal of plasma at low rates of blood flow into the device and permitting centrifugal plasmapheresis to be performed *via* peripheral venous access. To remove 120% of the predicted plasma volume, 1.5 blood volumes must be processed. Citrate is the most common anticoagulant used for this modality and, although the administered citrate is nearly completely eliminated along with plasma, citrate intoxication is possible.

Membrane filtration plasmapheresis uses a semipermeable membrane or fiber matrix with a pore size sufficient to allow removal of all plasma constituents while preserving cellular elements.[2] Compared with centrifugal plasmapheresis, higher flow rates are required for this modality because cellular elements may be damaged by contact with the membrane, thereby limiting the ability to hemoconcentrate. Membrane filtration requires processing of 3 to 4 blood volumes to achieve the goal of eliminating 120% of the predicted plasma volume and often requires central venous

*Assistant Professor, § Professor, Division of Cardiovascular Anesthesiology, Texas Heart Institute, St. Luke's Episcopal Hospital, and Department of Anesthesiology, Baylor College of Medicine, Houston, Texas. † Resident, Department of Anesthesiology, Baylor College of Medicine, Houston, Texas. ‡ Assistant Professor, Division of Pathology, Texas Heart Institute, St. Luke's Episcopal Hospital, and Department of Pathology, Baylor College of Medicine, Houston, Texas.

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Address correspondence to Dr. Youngblood: Department of Anesthesiology, Baylor College of Medicine, 1709 Dryden Road, Suite 1700, Houston, Texas 77096. sloan.youngblood@bcm.edu.

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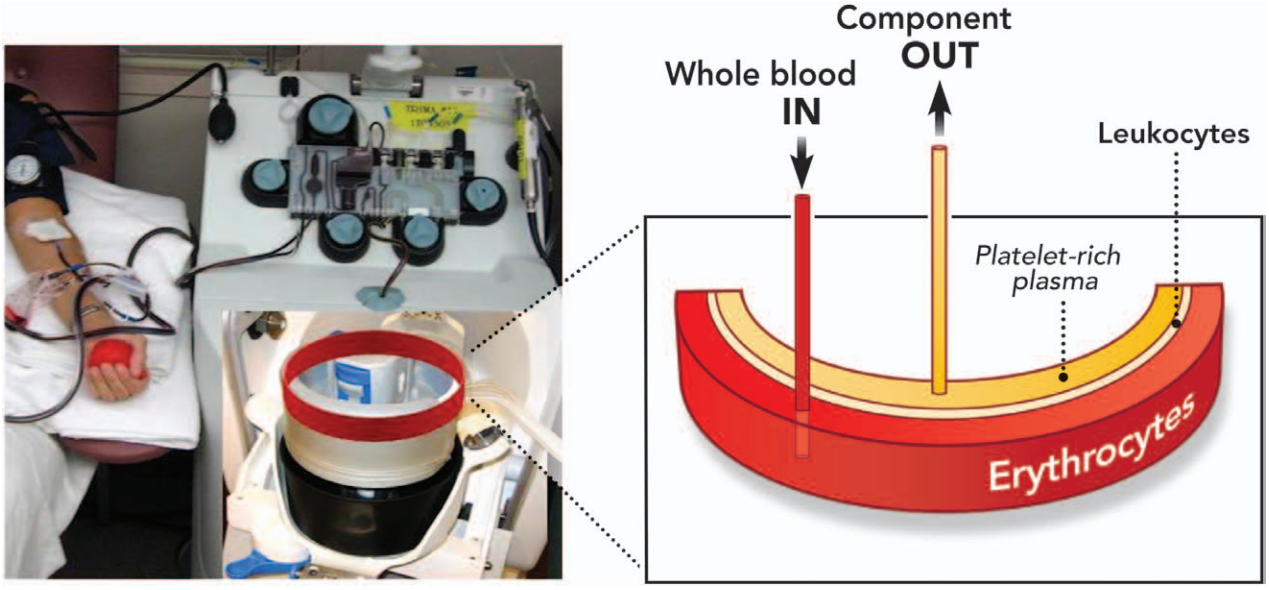

Fig. 1. Photograph of centrifugal plasmapheresis procedure and schematic of blood component separation.

access to provide adequate blood flow. Membrane filtration circuits are generally incapable of performing cytapheresis and typically require heparin anticoagulation.

Both centrifugal and membrane filtration circuits can be adapted for secondary processing of plasma and subsequent return of normal plasma components. Secondary filtration systems typically using immunoadsorption techniques may be able to specifically remove offending pathologic proteins while allowing reinfusion of normal plasma components, thus minimizing the need for replacement fluid administration and avoidance of plasmapheresis-associated coagulopathy. Erythrocytes and platelets are returned to the patient along with any residual plasma and replacement fluids.

Replacement fluid selection is determined by the indication for and planned frequency of plasmapheresis procedures, as well as the presence of underlying cardiac, renal, and hepatic dysfunction. Albumin (5%) is frequently administered alone or in combination with crystalloid solutions to maintain euvolemia and plasma oncotic pressure. Because of thermal inactivation, albumin does not pose the infectious risks associated with blood component therapy, although the potential for allergic reactions and hypocalcemia persists. Hydroxyethyl starch and dextran 40 are well tolerated and may be cost-effective alternatives to albumin.[3] Plasma replacement with albumin and modified fluid gelatin is associated with a higher risk of allergic manifestations than albumin alone.[4]

Replacement fluids devoid of clotting factors may result in coagulopathy because of clotting factor depletion, particularly if several plasmapheresis procedures are performed in rapid succession. Administration of fresh frozen plasma (FFP) eliminates this problem and is usually the preferred means of fluid replacement in the perioperative setting. FFP carries the allergic and infectious risks of blood product administration and adds to the total dose of citrate administered.

Plasmapheresis Indications

The efficacy of plasmapheresis lies in the elimination of pathologic intravascular components (*e.g.*, immunoglobulins, immune complexes, and hormones) or the replacement of abnormal or deficient proteins. Thus, plasmapheresis can only logically be used when the pathologic cause of disease seems amenable to these mechanisms. In fact, the use of plasmapheresis for treatment of autoimmune diseases such as lupus nephritis or rheumatoid arthritis has proven to be of no benefit, likely because the immune insult is localized

Table 1. Summary of the Mechanisms of Action of Therapeutic Plasmapheresis and Representative Diseases

Antibody removal
Myasthenia gravis
ABO-incompatible solid organ transplantation
TTP
Cryoglobulinemia
Heparin-induced thrombocytopenia
Restoration of normal protein
TTP
Fulminant hepatic failure
Removal of abnormal/excessive proteins
TTP
Thyroid storm
Immune complex removal
Systemic lupus erythematosus
Autoimmune hemolytic anemia

TTP = thrombotic thrombocytopenic purpura.

in peripheral tissues outside of the intravascular space. Over 100 disease states have been successfully managed with plasmapheresis using guidelines established by the American Society for Apheresis.[5] We now review those diagnoses amenable to perioperative plasmapheresis. A summary of these diseases is provided in table 1.

Solid Organ Transplantation

Humoral rejection of transplanted organs remains a major source of postoperative morbidity and mortality and is frequently associated with antibodies directed against ABO blood group antigens or human leukocyte antigen. Nonetheless, the significant shortage of organs available for transplantation in the United States has resulted in increasing use of ABO-incompatible donor organs. According to the Organ Procurement and Transplantation Network, 0.5% of all solid-organ transplants occurred in the setting of ABO incompatibility between January 2009 and May 2012. Transplantation of ABO-incompatible organs is associated with an increased risk of hyperacute rejection because of the presence of preformed recipient anti-A or anti-B antibodies. In addition to immunosuppressive therapy, perioperative plasmapheresis to remove offending anti-ABO antibodies has been shown to improve clinical outcomes after renal and cardiac transplantation, although definitive randomized controlled trials have not been performed.[6,7] Results after ABO-incompatible liver transplantation have been varied as a result of the emergent nature of these procedures and differences in immunosuppressive regimens. When compared with ABO-compatible transplants, graft survival after ABO-incompatible liver transplantation is generally worse.[7]

Anti–human leukocyte antigen antibodies are detected by the panel reactive antibody screen and are reported as the percentage of the American population against which the recipient would likely demonstrate early rejection,[8] and a panel reactive antibody screening value greater than 10% is predictive of acute rejection after lung transplantation.[9] Perioperative plasmapheresis and immunosuppression decrease the amount of circulating antibody and have been shown to significantly decrease acute rejection in seropositive patients undergoing renal transplantation.[10–12] Promising results have also been suggested for seropositive patients undergoing lung transplantation.[13]

Myasthenia Gravis

Myasthenia gravis is an autoimmune disease characterized by bulbar weakness, respiratory failure, and marked sensitivity to neuromuscular blocking agents. Over 80% of patients with myasthenia gravis have identifiable antiacetylcholine receptor antibodies, and approximately 50% of "seronegative" patients will have anti–muscle-specific receptor tyrosine kinase antibodies. The onset of action of common immunosuppressant agents is delayed, limiting their effectiveness in the acute treatment of myasthenic crisis. Plasmapheresis rapidly reverses weakness associated with myasthenic crisis by eliminating these autoantibodies and is considered by the American Society for Apheresis to be first-line therapy in conjunction with corticosteroids and respiratory support for both seropositive and seronegative myasthenic patients.[14,15] Plasmapheresis improves early outcomes (<1 week) in patients with moderate to severe myasthenia, but this beneficial effect often disappears by day 15.[16] Therefore, the utility of plasmapheresis is limited to the acute treatment of severe myasthenic weakness, and concomitant medical therapy should be instituted.

Heparin-induced Thrombocytopenia

Heparin-induced thrombocytopenia results from antibodies directed against the platelet factor 4–heparin complex (anti-HPF4) and occurs in susceptible individuals after exposure to either unfractionated or low-molecular-weight heparin.[17] Antibody binding causes platelet activation, with subsequent thrombosis and thrombocytopenia. Treatment of heparin-induced thrombocytopenia includes discontinuation of heparin, administration of a nonheparin anticoagulant, monitoring platelet count, and evaluating for the presence of thrombi.

In cardiac surgery requiring cardiopulmonary bypass, elective surgery is typically deferred until anti-HPF4 titers are negative followed by a single intraoperative exposure to heparin, but urgent cases do not allow such a waiting period.[18] In a case series of 11 patients, Welsby *et al.* described the use of intraoperative plasmapheresis and heparin administration to patients with anti-HPF4 antibodies undergoing urgent cardiac surgery.[19] Anti-HPF4 antibody titers were reduced after a single treatment by as much as 84%, and no patient developed severe thrombocytopenia or thrombotic complications. Postoperative anticoagulation was only necessary in the subset of patients undergoing ventricular assist device or mechanical valve implantation. One randomized controlled trial addressed the use of plasmapheresis early and late in the course of heparin-induced thrombocytopenia. The subset undergoing plasmapheresis within 4 days of the onset of thrombocytopenia demonstrated fewer thrombotic complications, less time to platelet recovery, and shorter durations of hospitalization.[20] The use of plasmapheresis for heparin-induced thrombocytopenia is not addressed by the American Society for Apheresis.

Thyroid Storm

Thyroid storm is an extreme manifestation of thyrotoxicosis characterized by hypermetabolism, fever, tachycardia, arrhythmia, mental status changes, and coma. First-line therapy includes controlling sympathetic tone and decreasing both thyroxine release and peripheral conversion with antithyroid agents, iodine, β-blockade, and glucocorticoids. Thyroxine is bound to thyroxine-binding globulin in plasma, and elimination of bound thyroxine *via* plasmapheresis is

possible when other medical therapies are ineffective. Several case series have reported the successful use of perioperative plasmapheresis for refractory thyrotoxicosis before thyroidectomy.[21] Plasmapheresis efficiently removes amiodarone and may be particularly useful in patients with amiodarone-induced thyrotoxicosis without other thyroid abnormality.[22]

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is defined by the pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, and mental status changes. TTP is caused by deficient ADAMTS-13 enzyme activity as a result of congenital deficiency or autoantibody formation.[23,24] Plasmapheresis with FFP used as replacement fluid both removes autoantibody and restores normally functioning ADAMTS-13 enzyme.[25] Treatment of TTP requires seven or eight daily plasmapheresis procedures and has reduced TTP mortality from nearly 100% to less than 10%.[26,27] Recently, recombinant ADAMTS-13 has been studied as a potential alternative therapy for TTP; however, persistent anti–ADAMTS-13 antibody in acquired TTP may bind recombinant as well as native protease.[28] Therefore, although the need for FFP as a source of ADAMSTS-13 enzyme may be reduced, plasmapheresis will likely continue to be used to remove autoantibody.

Complications

Plasmapheresis is a relatively safe procedure, with a reported overall complication rate of less than 5%.[29] Commonly reported side effects such as rigors, chills, muscle cramps, and paresthesias are likely to be masked by general anesthesia. Other notable complications such as coagulopathy and citrate intoxication are predictable when appropriate considerations are made for the type of plasmapheresis, the replacement fluid administered, and any underlying medical condition.

Appropriate intravascular volume resuscitation is critical for patients undergoing perioperative plasmapheresis and must account for the risks of both hypervolemia and hypovolemia. Hypotension may result from inadequate volume resuscitation and has been reported in association with the development of myocardial ischemia and infarction during plasmapheresis.[30] The use of angiotensin-converting enzyme inhibitors may potentiate the hypotensive effects of plasmapheresis, and withholding these agents for 24 h is advised.[31]

Sodium citrate chelates ionized calcium and is the most common anticoagulant used during plasmapheresis. Up to 9% of procedures are complicated by citrate intoxication as a result of calcium's role in normal coagulation, myocardial contractility, vascular tone, and cardiac electrophysiology.[30] Coagulopathy associated with citrate administration has been reported and occurs most commonly in the setting of additional citrate administration with use of FFP or in patients with hepatic dysfunction and decreased metabolic capacity for citrate.[32]

Hypocalcemia is associated with prolongation of the corrected QT interval and predisposes to the development of ventricular dysrhythmias. This effect may be potentiated by hypomagnesemia in patients with compromised hepatic function.[33] Calcium also plays an important role in myocardial and smooth muscle contractility. Hypotension may result from decreased cardiac output or systemic vascular resistance and should be treated promptly with intravenous calcium salts.

Any replacement fluid is capable of causing ionized hypocalcemia because of citrate (FFP), direct sequestration (albumin), or dilution (crystalloid). Hepatic metabolism of citrate yields bicarbonate ion that is subsequently eliminated in urine. Patients with compromised renal function may develop metabolic alkalosis with the administration of citrate, causing increased calcium sequestration by plasma proteins in exchange for hydrogen ions. Prophylactic use of a 10% calcium chloride infusion has been demonstrated to decrease the rate of citrate-related complications to 1%.[34]

Plasmapheresis-associated coagulopathy is a significant perioperative concern that is often multifactorial in nature. Coagulation factors and fibrinogen are removed along with discarded plasma and become depleted if albumin or crystalloid solutions are used for replacement.[35,36] Most are restored to baseline levels within 24–48 h after the procedure, although fibrinogen levels may require up to 4 days to normalize.[30] Activated partial thromboplastin time and prothrombin time typically return to baseline at 4 and 24 h, respectively. FFP and the use of secondary plasma processing may mitigate this complication. Antithrombin depletion occurs with plasmapheresis but is not believed to contribute to hypercoagulability because of concomitant hypofibrinogenemia.[30]

Centrifugal plasmapheresis may decrease platelet counts by greater than 30%. Technical adjustments of the apheresis instrument can minimize platelet loss. Membrane filtration plasmapheresis minimizes this complication, although rare bleeding complications have been reported, caused by the requirement for heparin anticoagulation with membrane filtration.[37]

Hypogammaglobulinemia has been described in the setting of plasmapheresis and may predispose patients to perioperative infections, mandating strict adherence to aseptic technique.[35] Appropriate administration of perioperative antibiotics should be ensured. Either FFP or IV immunoglobulin (IVIG) may be administered to supplement deficient immunoglobulin if deemed clinically necessary.

FFP use during plasmapheresis presents the inherent allergic, inflammatory, hemolytic, infectious, and immune risks of allogeneic blood product administration. Transfusion-related acute lung injury deserves particular consideration, as FFP is the blood product most often associated with this complication. This diagnosis should be considered if idiopathic pulmonary dysfunction develops with a temporal relationship to FFP infusion.[38]

Perioperative Management

Anesthetic planning for patients undergoing plasmapheresis should first take into account the type, timing, and dose of plasmapheresis administered. The risk of depletion coagulopathy increases with increased dose and frequency of plasmapheresis, and centrifugal plasmapheresis can cause thrombocytopenia. Information regarding transfusion of blood products should be reviewed, and a current ABO/Rh type and antibody screen should be available if intraoperative plasmapheresis is planned or if significant intraoperative bleeding is possible.

Adequate vascular access should be planned in collaboration with the apheresis team. Plasmapheresis can be performed using peripheral venous access, but this may be impractical in the perioperative setting. Central venous catheterization may be necessary to provide adequate flow rates or for patients that will require several plasmapheresis procedures. Access *via* the cardiopulmonary bypass circuit is an uncommon but efficient approach, providing high flow rates and eliminating the need for additional central venous access in appropriate operations.[39]

An accurate patient height and weight along with determination of the serum hematocrit should be determined to assist in calculating the patient's predicted plasma volume. Because the priming solution of the apheresis circuit is devoid of cellular elements, significant anemia may develop in patients with small estimated blood volumes. Assessment of the serum hematocrit may help predict the severity of this hemodilution and prompt addition of erythrocytes to the priming solution.

Prothrombin time, activated partial thromboplastin time, and fibrinogen levels should be assessed if the patient has undergone several plasmapheresis procedures without FFP, and a platelet count should be performed if centrifugal plasmapheresis is planned. The presence of coagulopathy may alter anesthetic management, particularly if a neuraxial anesthetic is planned.

Drug elimination resulting from plasmapheresis is difficult to predict because of the various and inconsistent modalities with which it has been described.[40] Data regarding most anesthetic agents are lacking. In general, because the plasma phase of blood is removed, hydrophilic agents with significant protein binding and a small volume of distribution are readily removed.

Depletion of pseudocholinesterase and prolonged duration of action of both succinylcholine and mivacurium have been described.[41] The effect of plasmapheresis on other neuromuscular blocking agents has not been studied, but these agents may be eliminated more quickly than expected, and monitoring of neuromuscular transmission should guide their administration.

Little effect would be expected for the lipid-soluble volatile anesthetics, propofol, or benzodiazepines, although variations in protein binding make broad generalizations difficult. Little is known about the effect of plasmapheresis on opioid pharmacokinetics, but each individual agent's lipid solubility and protein binding should be considered when attempting to predict effects on drug concentration. One case report described normal emergence from a remifentanil-based anesthetic after several cycles of plasmapheresis.[42]

The highly charged anticoagulant heparin is readily removed by plasmapheresis, perhaps necessitating frequent readministration if therapeutic anticoagulation is necessary. Plasmapheresis-mediated decreases in antithrombin could cause heparin resistance; therefore, careful monitoring of anticoagulation *via* activated clotting time or other equivalent measures is necessary. Ampicillin, ceftriaxone, gentamicin, and tobramycin are cleared by plasmapheresis, although cefepime is not.[43] Reports of vancomycin pharmacokinetics during plasmapheresis have yielded mixed results, although some have suggested as much as a 49% decrease in plasma concentration.[44] Consideration should be given to redosing most antibiotics after the termination of plasmapheresis.[45] Basiliximab, Thymoglobulin (Genzyme, Lyon, France), IVIG, and other monoclonal antibodies are predictably removed by plasmapheresis and should be administered after the completion of the procedure.[46]

Plasmapheresis *versus* IVIG

IVIG, through inhibition of circulating antibody and lymphocytes, possesses immunomodulatory properties beneficial for the treatment of many immunologic diseases. In fact, IVIG and plasmapheresis share many of the same indications. Few studies comparing the efficacy of IVIG and plasmapheresis exist, and their results have been inconsistent. IVIG for the treatment of myasthenia gravis may be as efficacious as plasmapheresis and results in fewer complications.[47] Plasmapheresis may be superior to IVIG for the treatment of renal transplant recipients with donor-specific antibody positivity, and the combination of IVIG and plasmapheresis improves survival after ABO-incompatible liver transplantation.[48,49] IVIG may be associated with aseptic meningitis and malaise and is approximately twice as expensive as five plasmapheresis procedures.[1] Because of the cost, risk, and paucity of evidence comparing plasmapheresis to IVIG, local expertise tends to determine which modality is used.

Future Directions

Although significant advances in the field of apheresis have been achieved, much remains to be learned about the use and conduct of the plasmapheresis procedure. The optimal timing and dose of perioperative plasmapheresis has yet to be determined. Complications associated with the administration of replacement fluids remain a significant obstacle, and the concept of plasma regeneration to mitigate the need for fluid replacement continues to be explored. Technological advances such as immunoadsorption and selective filtration continue to be developed. Most evidence for the use of

plasmapheresis is derived from small case series, and definitive randomized trials are needed to best address these issues.

Conclusions

Plasmapheresis is a safe therapy for multiple immunologic, endocrine, and hematologic diseases. Because of the cost of alternative therapies such as IVIG, the popularity of plasmapheresis has increased. Perioperative plasmapheresis poses several challenges for the anesthesiologist, including fluid management, alterations in serum electrolytes, modulation of the coagulation cascade, and poorly defined alterations in the pharmacokinetics of perioperative medications. A multidisciplinary approach involving surgeons, anesthesiologists, and clinical pathologists should be used for the successful management of patients requiring perioperative plasmapheresis.

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