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Plasmapheresis and Vasculitis Affecting the Kidney

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Since the first recorded plasmapheresis in 1914, the process of removing a patient's plasma as a therapeutic treatment has expanded to multiple fields in medicine. Plasmapheresis, the isolated removal of blood plasma (the extracellular component of blood), was originally developed for patients with Waldenstrom's disease to reduce serum viscosity. Shortly thereafter, therapeutic plasma exchange (TPE) was developed. In TPE the removed plasma is replaced with either a colloid (fresh frozen plasma, cryoprecipitate) or a combination of crystalloid and colloid (5% albumin) solutions. TPE was utilized during World War II, resuscitating soldiers that underwent traumatic injuries, allowing replacement of coagulation factors while maintaining an isovolemic status. In 1959, Dr. Michael Rubinstein utilized fresh blood exchange transfusion to treat thrombotic thrombocytopenic purpura (TTP) an immune-related disorder characterized by anti-ADAMTS13 antibodies and associated loss of ADAMTS13 activity.[1] The loss of functional ADAMTS13 results in the formation of unusually large von Willebrand factor remaining expressed on the endothelial cell leading to platelet clumping and activation, microthrombi formation, and hemolytic anemia. Ultimately, it was discovered that the isolated removal of plasma removed the ADAMTS13 antibody and the replacement with fresh frozen plasma provided the patient with functional ADAMTS13 stopping the disease process. In addition to TTP treatment, plasmapheresis and TPE can be used to treat other immune-related disorders. TPE should be utilized if there is a potential therapeutic benefit of removing intravascular substances such as harmful antibodies, complement components, other proteins, or toxins/poisons. The choice of fluid to simultaneous replace the volume of the removed plasma depends on the therapeutic goal of the replacement fluid. If a functional enzyme or coagulation factor needs to be replaced then exchange with FFP is most appropriate, otherwise 5% albumin to prevent circulatory collapse is usually appropriate.

MECHANISM AND DETAILS OF PLASMAPHERESIS

To accomplish plasmapheresis, there are two commonly used modalities - *centrifugation* and *filtration*.[2] In centrifugation plasmapheresis, whole blood is spun into four separate components of blood based on their **densities** (red blood cells, white blood cells, platelets and plasma). In filtration plasmapheresis, the whole blood is passed through a filter and separated based on their **size**. Generally, the extracorporeal blood volume is limited to 15% of total blood volume to limit hypovolemia and circulatory collapse. Assuming no equilibration with extravascular stores and no further production of plasma, approximately 37% of the previous plasma remains at the end of 1 plasma volume exchange. Subsequently, 22% remains after 1.5 plasma volume exchange and 14% of previous plasma remains after a 2 plasma volume exchange. Anticoagulant agents such as citrate are used to inhibit the coagulation cascade, maintaining patency of the extracorporeal system during the procedure.

The clinical application of plasmapheresis in treatment can be divided in two general categories – (1) in acute settings where an active immune-mediated process is causing rapid clinical deterioration, and (2) in chronic diseases where there are ongoing pathogenic autoantibodies being produced. As plasmapheresis does not directly treat the underlying pathology, therefore its role in the management of chronic diseases is often controversial.

Potential clinical sequelae must be considered when evaluating the addition of plasmapheresis as a treatment option. Despite best efforts to prevent complications, plasmapheresis is not without risk. The use of regional citrate anticoagulation to maintain circuit patency can cause citrate-induced hypocalcaemia and metabolic alkalosis. It depletes coagulation factors and immunoglobulins. Furthermore, plasmapheresis can remove prescribed drugs- affecting a drug's pharmacokinetics/dynamics, and potentially compromising its therapeutic benefit. If the replacement fluid is with FFP or another blood product, reactions such as hives, transfusion-related acute lung injury (TRALI) and rarely anaphylaxis can occur.

CLINICAL QUESTION

Plasmapheresis is a viable treatment option for many complex illnesses with a wide array of presentations and cellular variability. Plasmapheresis for immune-mediated, small-vessel vasculitis affecting the kidneys has been reported to be a successful therapy. However, outcomes have been variable and there is evolving concern in the interpretation of the clinical studies due to the lack of consistency in treatment patterns. Therefore clinicians continue to individualize care as no evidence based treatment guidelines have been developed. This chapter presents the current data supporting plasmapheresis/TPE for vasculitis affecting the kidneys.

PHYSIOLOGY

Small-vessel vasculitides are caused by inflammation of arterioles, capillaries, and venules, and include the following diseases: Granulomatosis with Polyangiitis (formerly, Wegner's), Churg-Strauss syndrome, Microscopic polyangiitis, and Henoch-Schonlein Purpura. The three former conditions are also referred to as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. The pathophysiology of these conditions is not completely understood though ANCA is documented to play a role in activating cytokine-primed neutrophils and monocytes to target vessel walls. Additionally, it is thought that cell-mediated immune responses play a vital role in granulomatosis with Polyangiitis and Churg-Strauss syndrome due to findings of increased T-cell numbers and the presence of granulomas.

TREATMENT

Multiple randomized controlled studies examined the efficacy of plasmapheresis in treating ANCA-mediated renal injury. Jayne et al., conducted a global study comparing plasma exchange to high-dose methylprednisolone as adjunctive therapy for severe renal vasculitides.[3]

Their study consisted of adult patients who presented with a serum creatinine greater than 5.8mg/dL and a new diagnosis of ANCA-associated systemic vasculitis. Out of 137 patients, 70 individuals received seven plasma exchanges while the remaining 67 individuals received intravenous methylprednisolone. Both groups received oral cyclophosphamide and oral prednisolone. The study illustrated that at 3 months, 33 of 67 (49%) individuals that received IV methylprednisolone compared with 48 of 70 (69%) individuals that received plasmapheresis were alive and independent of dialysis (their primary end point). Additionally, there was a 24% difference in progression to ESRD between the two subsets of patients (43% in methylprednisolone group patients versus 19% in plasmapheresis group). Furthermore, a meta-analysis by Walsh et al. identified 9 trials with a total of 387 patients.[4] The pooled relative risk of end-stage renal disease or death was 0.80 for patients treated with adjunctive plasma exchange compared to the standard therapy alone (95% confidence interval 0.65 to 0.99; p=0.04). In a retrospective review of patients with diffuse alveolar hemorrhage (DAH) associated with ANCA-associated small-vessel vasculitis, DAH resolved with apheresis in 20 of 20 patients with average of 6.4 treatments.[5]

Daily exchanges should only be considered in fulminant cases or with pulmonary hemorrhages to balance the risks of treatment as noted above. Lastly, standard replacement fluid should be with albumin unless pulmonary hemorrhage is present, or if there are concerns for coagulopathy.

CONCLUSION

In summary, the pioneering studies for plasmapheresis in the treatment of small-vessel vasculitides support plasma exchange as an adjunctive treatment if the patient is ANCA positive. By using plasmapheresis with the standard therapy such as cyclophosphamide and prednisolone, studies have shown a decrease in the development of end-stage renal disease.[6-8] Although there is a small risk of morbidity and mortality (0.3% severe events, mostly associated

with cardiac or respiratory etiology). The current data support plasmapheresis in certain circumstances (acute severe deterioration of kidney function; DAH). However, further studies are needed to formulate if plasmapheresis is therapeutic for all patients with ANCA positive vasculitis. As well as define the most appropriate pattern and duration of plasmapheresis. The results from the PEXIVAS- Plasma Exchange and Glucocorticoid Dosing in the Treatment of anti-Neutrophil Cytoplasm Antibody Associated Vasculitis a randomized controlled trial are eagerly awaited with results expected before 2019. Finally, there is very limited information utilizing TPE for small vessel vasculitides that are ANCA negative. As a result, further studies are needed for patients with acute renal failure secondary to non-ANCA vasculitis.

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