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Plasma exchange therapy for thrombotic microangiopathies

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Thrombotic microangiopathies (TMAs) are syndromes associated with thrombocytopenia and multiple organ failure. Plasma exchange is a proven therapy for primary TMA, such as thrombotic thrombocytopenic purpura (TTP). There is growing evidence that plasma exchange therapy might also facilitate resolution of organ dysfunction and improve outcomes for secondary TMAs, such as disseminated intravascular coagulation (DIC) and systemic inflammation-induced TTP. In this review, we survey the current available evidence and practice of plasma exchange therapy for TMAs.

Introduction

During the times of Hippocrates and Galen, ancient physicians embraced the concept that human illness and disease emerged from an imbalance of four bodily components, or "humors"—blood, phlegm, black bile and yellow bile. Interventions such as phlebotomy or leech therapy were frequently performed in an effort to "remove evil humors" and restore humoral balance.[1] Although such beliefs and practices might now seem rather primitive and archaic as viewed through the lens of modern scientific and medical principles, in one, somewhat ironic sense, perhaps our physician predecessors were not entirely incorrect with their notion of humoral balance. In fact, if we were to direct this concept to the hematologic and endothelial systems and utilize contemporary tools of investigation, we find that many aspects of thrombotic microangiopathy (TMA) can be better understood through this "old view with a modern twist."

In this regard, there are four major components in whole blood: red blood cells, white blood cells, platelets and plasma. The normal homeostatic maintenance and functioning of these four components are essential for the host's survival. However, under pathological conditions, these four blood components interact with themselves and/or others to the detriment of the host. In this review, we will discuss the hypotheses of (1) how the failing plasma contributes to coagulopathy in TMA and (2) whether removing and/or replenishing plasma constituents could reverse the coagulopathy in TMA.

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"Classic" Thrombotic Microangiopathies—Thrombotic Thrombocytopenic Purpura (TTP) and Disseminated Intravascular Coagulation (DIC)

The thrombotic microangiopathies (TMA) are considered a family of related syndromes recognized clinically by the development of new onset thrombocytopenia and multiple organ failure (MOF) and are characterized pathologically by widespread microvascular thromboses in multiple vascular beds and organs.[2,3] Classically, two distinct pathogenic and histological forms of TMA have been described. The first classic form, thrombotic thrombocytopenic purpura (TTP), is categorized as a primary TMA since its development has historically been regarded as being idiopathic in nature, while the second classic form, disseminated intravascular coagulation (DIC), is considered a secondary TMA because its development can often be attributed to an underlying trigger, such as sepsis, cancer, trauma or other insult.[3] Histologic examination of tissue specimens obtained from patients with TTP typically reveals platelet-rich and von Willebrand factor (VWF)-rich microthrombi in all organs,[4-8] whereas, in contrast, fibrin-rich microthrombi predominate in patients with DIC. Other non-classic forms of TMA have been more difficult to delineate because they share pathological similarities and overlap with both TTP and DIC. However, it is through our evolving mechanistic knowledge of these two classic forms of TMA that we can better understand other non-classic TMA forms. Namely, we can begin to appreciate that the pathogenesis of all forms of TMA emanates from a perturbation of homeostatic processes that regulate the complex interactions among the soluble plasma molecules, white blood cells, platelets and endothelium.

TTP Pathophysiology

In 1924, Dr. Moschowitz described the first case of TTP in a girl who abruptly succumbed with petechiae, paralysis and coma. On autopsy her terminal arterioles and capillaries were found to be occluded with hyaline thrombi. Dr. Moschowitz postulated that a "powerful poison which had both agglutinative and hemolytic properties" had existed in the bloodstream of this girl.[9] In 1982, Dr. Moake proposed that this "powerful poison" with the

hyper-adhesive property in the blood was ultra-large von-Willebrand factor (ULVWF), a multimeric, high molecular weight form of von-Willebrand factor (VWF) that is not typically seen under normal conditions.[10] VWF is the largest multimeric glycoprotein in human plasma, with molecular masses ranging from 500–20,000 kD.[11] The intrinsic role of VWF itself is to assist platelets in clot formation in order to minimize blood loss and regain hemostasis caused by blood vessel disruption or damage. VWF augments platelet adhesiveness by bridging the platelet receptor glycoprotein Ib-IX-V complex to exposed subendothelial collagen of damaged vessels, helping to form a platelet plug. VWF is initially synthesized by the endothelial cells and megakaryocytes in monomeric form, which then multimerizes before being released into the bloodstream.[12,13] Upon synthesis, VWF is secreted by either the constitutive pathway of lower molecular mass (~500 kDa) dimers or the inducible pathway of the larger and ULVWF multimers. The inducible pathway is primarily triggered by inflammatory processes.[14-17] The "adhesiveness" of VWF is proportional to the size of VWF multimers, with the larger multimers having the ability to cause spontaneous platelet aggregation. The normal host counter-regulates this hyper-adhesiveness of ULVWF by cleaving them into smaller sizes that remain hemostatically active but are considerably less prothrombogenic. In 1998 Furlan et al. and Tsai et al. independently identified a VWF-cleaving protease that is now known as ADAMTS-13, an acronym for A Disintegrin And Metalloprotease with ThromboSpondin motifs-13.[18-20] Discovery of ADAMTS-13 was critical in delineating the pathophysiologic mechanism of TTP, as it is now known to be caused by an underlying deficiency in ADAMTS-13 activity. In the chronic relapsing form of TTP, a genetic abnormality in the ADAMTS-13 gene leads to a congenital deficiency of ADAMTS-13 activity,[19] while in the acquired idiopathic form of TTP, there is the presence of inhibitors or proteolytic inactivators of ADAMTS-13, such as autoantibodies, IL-6, plasma-free hemoglobin, VWF proteolytic fragments, thrombin, plasmin and granulocyte elastase.[14,20-24] With either form of TTP, the absent or reduced activity of ADAMTS-13 impairs the removal of ULVWF, the "powerful poison" originally postulated by Dr. Moschowitz and Moake, leading to spontaneous formation and dissemination of microthrombi and the classic clinical "pentad" of TTP that includes thrombocytopenia, hemolytic anemia, fever, central nervous system abnormality and renal dysfunction.[25] New onset thrombocytopenia in TTP heralds the progression of MOF and death if left untreated. On autopsy, patients who died with TTP have VWF-rich and platelet-rich microthrombi in all organs.[4-8]

DIC Pathophysiology

In 2001, the Scientific Subcommittee on DIC of the International Society of Thrombosis and Haemostasis proposed the consensus definition of DIC as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[26] In DIC, investigators have observed pathologic consumption and exhaustion of coagulation proteins and platelets, caused by excessive, systemic release of tissue factor.[3] Tissue factor is a transmembrane glycoprotein that is expressed in numerous tissues, including the vascular endothelium and leukocytes, and plays a pivotal role in the initiation and propagation of the coagulation cascade. Local tissue injury or inflammation induces the release of tissue factor into the bloodstream,[27] which complexes with factor VIIa to enhances its procoagulant property. The tissue factor-factor VIIa complex activates factors IX and X, eventually leading to thrombin generation and, finally, fibrin clot formation. Local clot formation during a focal infection lends a teleological survival advantage to the host by immobilizing bacteria and limiting their spread. Hence, with limited local release, tissue factor activation is thought to be beneficial. However, under the conditions of vigorous systemic injury and inflammation, excessive release of tissue factor can cause deleterious hyperactivation of the coagulation system, leading to disseminated microvascular thrombosis as well as simultaneous consumption and depletion of coagulation proteins, often leading to increased bleeding. To further aggravate the prothrombotic state in DIC, the level of anti-fibrinolytic plasminogen activator inhibitor type-1 (PAI-1) is elevated, and the levels of anticoagulants antithrombin III and protein C are diminished. In contrast to TTP, histological studies in DIC have shown that there are extensive fibrin-rich microthrombi in small and mid-size vessels of all organs.[4,6,8]

Biologic Plausibility Supporting the Role of Plasma Exchange Therapy in TMA

Through our ever expanding understanding of TTP and DIC, we have begun to recognize that a potential common pathogenic mechanism for the development of TMA points to the abnormal interactions among the soluble plasma molecules, platelets, white cells and endothelium. While many soluble proteins and cellular components are elevated and activated in the blood, others are deficient or depleted as a result of consumptive coagulopathy. This provides us with the biological plausibility supporting the role of plasma exchange therapy for TMA. The goals of plasma exchange in TMA are to remove excessively thrombogenic and anti-fibrinolytic molecules and to replenish the deficient anticoagulants and profibrinolytic molecules in order to regain a normal homeostatic milieu. In TTP, plasma exchange is hypothesized to replenish ADAMTS-13 and to remove the ULVWF and ADAMTS-13 inhibitors/proteolytic inactivators, such as ADAMTS-13 autoantibodies, IL-6, plasma-free hemoglobin, plasmin, thrombin and granulocyte elastase.[25] In DIC, plasma exchange is hypothesized to remove tissue factors, PAI-1 and replenish antithrombin III, protein C and S and tissue plasminogen activator inhibitor.[28-32] In essence, plasma exchange attempts to bring the patient's plasma from dysregulated prothrombotic and antifibrinolytic states back to its homeostatic milieu.

Different Techniques of Plasma Exchange Therapy

Plasmapheresis is the process of separating plasma component from whole blood. It can be done by two different techniques—

centrifugation or membrane filtration. The pros and cons of these techniques have been vigorously debated.[33-36] Centrifugation has the advantage of (1) removing all sizes of soluble plasma components and (2) no interaction of blood components to a membrane filter. The centrifugation machine spins the blood, separates the blood components by gravity and density and removes the desired component according to its sedimentation characteristic during the spin. This technique is commonly utilized by blood banks and hematologists. The filtration technique has the advantage of being easily accessible by intensivists and nephrologists, as a membrane filter can be added to a continuous extracorporeal veno-venous circuit. However, compared to centrifugation, the filtration technique can potentially activate platelets and the complement cascade.[37,38] Furthermore, the pore size rating of the filter can potentially limit the size of the soluble molecules being removed. For example, it might not be expected that a membrane filter with a pore size rating of 1,000 kDa can remove ULVWF that approaches 20,000 kD in size. Despite this theoretical limitation and somewhat unexpectedly, experimental data have actually shown that ULVWF can still be removed by current existing plasmapheresis membrane filters,[39] postulated, perhaps, through protein adsorption rather than actual filtration. With the help of modern technology, filters with larger membrane pores and less contact activation properties are continuously being developed.[40-42]

Current Practices with Plasma Exchange Therapy for TMA

Patients with TMA have a high risk of mortality if the coagulopathy is not addressed. For primary TMA, plasma exchange is recommended as soon as the diagnosis of TTP is suspected. This recommendation is supported by Rock et al. who in 1991 reported in a randomized control trial that plasma exchange therapy significantly reduced mortality compared to plasma infusion alone for patients with acute TTP.[43] In this study, the plasma exchange therapy group experienced a mortality rate of 3.9% compared to 15.7% for the plasma infusion group by the end of the first treatment cycle (day 9). This beneficial effect on mortality remained statistically significant six months after the trial, as 21.6% of the patients treated with plasma exchange therapy had died compared to 37.3% of the patients who had received plasma infusion. Plasma exchange therapy has since become a standard therapy for documented TTP.

There have been many studies appraising the potential role of plasma exchange therapy for patients with secondary TMA.[22,28,29,31,32,44-51] For example, Stegmayr et al. reported in a large case series that adults with DIC and MOF who received plasma exchange had an 82% survival compared to <20% observed survival in historical controls.[31] Pene et al. reported that plasma exchange in adults with TMA triggered by infections was independently associated with lower mortality, regardless of disease severity [Hazard Ratio = 0.234 (Confidence Interval 95%: 0.095–0.573), p = 0.001].[49] And Darmon et al. reported that plasma exchange for adult patients with secondary TMA is associated with significantly lower organ failure scores from days 3 to 9 and improved outcome.[47] Despite such studies reporting positive benefits of plasma exchange therapy for certain secondary TMA, unlike for primary TMA, the strength of these data has been more limited. Still, this has not negated a growing interest in attempting to alter plasma components in patients with systemic inflammation, especially in patients with sepsis-induced MOF.

In our own single-center study, we identified a subset of critically ill pediatric patients with Thrombocytopenia-Associated Multiple Organ Failure (TAMOF) (defined clinically as platelet counts <100,000/mm^3 and ≥3 failing organs) and found that they had similar pathophysiologic process to those with TTP.[22] These patients had the presence of ULVWF, were deficient in ADAMTS-13 activity and inhibitors to ADAMTS-13. Autopsies in TAMOF patients had microvascular thrombosis in the lungs, kidneys and brain. We randomized patients with TAMOF to either receive plasma exchange or standard therapy. Patients randomized to plasma exchange received a 1.5x plasma volume exchange on day 1 followed by 1x volume exchange for 14 days or until the resolution to less than 3 failing organs for 48 hours. Plasma exchange was initiated within 30 hours of the diagnosis of TAMOF. Plasma exchange reversed the coagulopathy, facilitated organ failure resolution and improved outcome in patients with TAMOF. Currently, there is an ongoing collaborative study composed of a network of twelve pediatric intensive care units in the US enrolling children meeting criteria for TAMOF. The network is comparing biochemical markers and outcome in patients receiving standard therapy versus plasma exchange (NCT 00118664, clinicaltrials.gov).

There are currently no consensus recommendations regarding indication, patient selection, method, timing and duration of plasma exchange therapy for secondary TMA. Some clinical applications of plasma exchange therapy for patients with secondary TMA have included (1) overt DIC, (2) TAMOF (thrombocytopenia and ≥3 failing organs), (3) persistent TMA with progressive of MOF or (3) significant coagulopathy with progressive MOF. Patient selection is probably the most important criterion in determining the success of the therapy. Because plasma exchange has been shown to significantly reduce mortality in patients with TTP, it would be reasonable to hypothesize that patients with secondary TMA, who share similar pathophysiologic biochemical markers to TTP, would respond to the plasma exchange. However, the laboratory tests for ADAMTS-13 activity, VWF activity and detection of ULVWF are still difficult to obtain in a timely manner to make clinical decisions. We are still relying on simple lab tests to suggest the presence of TMA such as (1) blood smear to detect the presence of schistocytes and (2) elevation of lactate dehydrogenase (LDH) and clinical data such coagulopathy and MOF to make decision for plasma exchange.

Conclusions

There is growing evidence that plasma exchange therapy may improve outcome in patients with secondary TMA. With further understanding of the pathophysiologic mechanism of TMA,

we should have a better understanding regarding how plasma exchange therapy might beneficially alter course of TMA outcome in these patients. There are still many unanswered questions in using plasma exchange for patients with TMA. Studies of plasma exchange comparing the different methods, timing, duration and patient population are needed.

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