Maintaining Hemostatic Balance in Treating Disseminated Intravascular Coagulation

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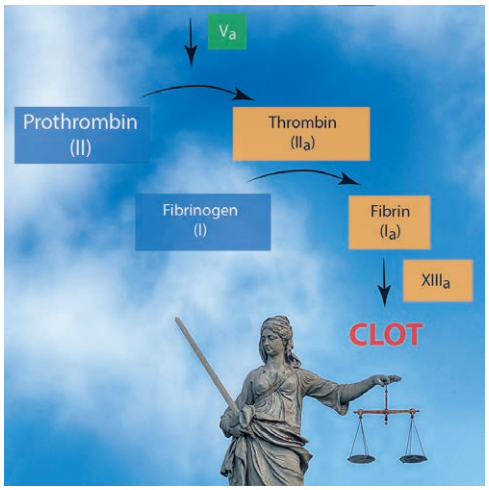
Disseminated intravascular coagulation (DIC) is a complex coagulopathic state that can present as a thromboinflammatory response to diverse causes that include septic shock, traumatic injury, pregnancy, and cancer.[1,2] The International Society on Thrombosis and Hemostasis (Carrboro, North Carolina) defines DIC as "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes that can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction."[3] In DIC, endothelial injury and microcirculatory abnormalities produced by hemostatic abnormalities cause multiorgan failure.[4] Of note is that DIC is not a primary disease state, but rather a pathophysiologic response to an underlying disease process, and is based on laboratory diagnosis. The clinical (phenotypic) manifestations can range as a spectrum of either bleeding or thrombotic manifestation due to causes that include the underlying disease process (*e.g.*, cancer-induced DIC), or the time course of diagnosis and therapy.[2] The basis of therapy for DIC is to treat the underlying disease, but also provide temporary support of the coagulation disorder and coagulopathy that depends on whether patients present with bleeding or thrombotic phenotypes. The complexity of managing DIC is to balance both the bleeding and thrombotic complications that occur.



"The complexity of managing DIC [disseminated intravascular coagulation] is to balance both the bleeding and thrombotic complications that occur."

In the current edition of the Anesthesiology, Grottke *et al.* evaluated, in a porcine trauma model, whether prothrombin complex concentrate–induced DIC could be prevented by coadministering antithrombin, a physiologic anticoagulant.[5] They evaluated multiple procoagulant and anticoagulant combinations including tranexamic acid in their multiorgan trauma model that included femur fractures, thoracic contusion, and blunt liver injury. Although prothrombin concentrates reduced bleeding, there were thromboembolic complications (pulmonary emboli) that can occur in clinical DIC. However, when antithrombin was administered in combination with prothrombin concentrate and/or fibrinogen concentrate, DIC did not occur, and there were no early deaths in the fibrinogen concentrate plus prothrombin concentrates plus antithrombin group. Collectively, these studies demonstrate that following experimental animal trauma, administration of prothrombin complex concentrates, either alone or in combination with fibrinogen concentrate, can potentially induce hypercoagulability, but coadministration of antithrombin mitigated this effect.

What can we learn from this model of coagulopathy when there are multiple causes of bleeding and thrombosis that have been extensively characterized and have many of the similar characteristics of DIC? European trauma guidelines are increasingly considering prothrombin concentrates as part of a multimodal approach to managing bleeding compared to fresh frozen plasma for rapid factor administration due to their availability without the need for cross-matching.[6,7] In a bleeding coagulopathic patient, the critical management strategy is to administer products that create a thrombotic milieu; the question is how to balance the risk of thrombotic complications, consumptive coagulopathy, or potentially DIC.

Image: J. P. Rathmell.

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Four-component prothrombin concentrates are approved in the United States for warfarin reversal, but there are increasing reports about their use for major bleeding.[6] The potential risk of thromboembolic complications with prothrombin concentrates appears low when used for warfarin reversal. Importantly, the results presented by Grottke *et al.* suggest the thrombotic potential of prothrombin concentrates or any procoagulant therapy should be considered. Nonetheless, in life threatening hemorrhage, stopping bleeding is critical to survival. They also noted supplementing antithrombin levels balanced the thrombotic potential of prothrombin concentrates; however, rapid determination of antithrombin levels is not readily available as point-of-care testing or in most hospitals. Viscoelastic testing for hypercoagulability offers a potential method for monitoring and individualizing bleeding management, however, its sensitivity to antithrombin levels is unlikely to facilitate monitoring of thrombotic potential. Although monitoring and repleting antithrombin levels during treatment with prothrombin concentrates could mitigate potential thrombotic complications, it is currently unclear how to effectively achieve this in a clinical setting.

Anticoagulation in patients with sepsis-associated DIC has been previously reported.[1] This therapeutic approach, administering the physiologic anticoagulants antithrombin or thrombomodulin, is similar to the once used anticoagulation therapy of administering activated protein C in sepsis. In sepsis-associated DIC, physiologic fibrinolysis is suppressed, and prothrombotic effects can occur depending on the time course of the disease.[2] Animal models have been developed to mimic the complications of DIC.[7] However, these models do not fully capture the complexity of the clinical manifestations of DIC, therefore, there is a need for the characterization of new pre-clinical models as reported by Grottke *et al.*

In clinical practice, when prothrombin concentrates are used off label to treat bleeding in trauma or surgical patients, they are often used as multimodal therapy in combination with fresh frozen plasma. Perhaps when shifting to the use of only factor concentrates as a therapeutic approach, clinicians should consider what factors are not being repleted when fresh frozen plasma is not administered. Fresh frozen plasma contains critical serine protease inhibitors including antithrombin, C1 esterase inhibitor, alpha-2 antiplasmin, protein C, and protein S, all important proteins for providing both anticoagulant and potentially antiinflammatory effects. Because thrombin and thrombin activation are linked to proinflammatory states, antithrombin—with its multiplicity of potential antiinflammatory effects—may be important. Although fresh frozen plasma is widely used in perioperative bleeding, the clinical effectiveness for reducing bleeding is unproven; however, in trauma patients it is thought to preserve endothelial function.[8] Perhaps the antithrombin in plasma is the critical component responsible for regulating thromboinflammatory responses in a spectrum of pathologic responses.[9]

When treating patients with major bleeding, our clinical goal is to focus on restoring hemostasis. As part of hemostatic resuscitative strategies, we may transiently produce hypercoagulability to stop bleeding. However, when using factor concentrates clinicians should consider what factors are not being repleted when restoring hemostatic balance.

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Competing Interests

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References

1. Levi M, Scully M: How I treat disseminated intravascular coagulation. Blood 2018; 131:845–54
2. Iba T, Levy JH, Wada H, Thachil J, Warkentin TE, Levi M; Subcommittee on Disseminated Intravascular Coagulation: Differential diagnoses for sepsis-induced disseminated intravascular coagulation: Communication from the SSC of the ISTH. J Thromb Haemost 2019; 17:415–9
3. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M; Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH): Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327–30
4. Iba T, Levy JH: Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost 2018; 16:231–41
5. Grottke O, Honickel M, Braunschweig T, Reichel A, Schöchl H, Rossaint R: Prothrombin complex concentrate-induced disseminated intravascular coagulation can be prevented by coadministering antithrombin in a porcine trauma model. Anesthesiology 2019; 131:543–54

6. Levy JH, Douketis J, Steiner T, Goldstein JN, Milling TJ: Prothrombin complex concentrates for perioperative vitamin K antagonist and non-vitamin K anticoagulant reversal. Anesthesiology 2018; 129:1171–84
7. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina, R, Maegele, M, Nardi, G, Riddez, L, Samama, C, Vincent, J, Rossaint, R: The European guideline on management of major bleeding and coagulopathy following trauma: Fifth edition. Crit Care 2019;23(1):98
8. Levy JH, Grottke O, Fries D, Kozek-Langenecker S: Therapeutic plasma transfusion in bleeding patients: A systematic review. Anesth Analg 2017; 124:1268–76
9. Levy JH, Sniecinski RM, Welsby IJ, Levi M: Antithrombin: Anti-inflammatory properties and clinical applications. Thromb Haemost 2016; 115:712–28

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