Precision Correction of Coagulopathy or Prothrombin Complex Concentrates?

Reversal Options for Dabigatran following Trauma

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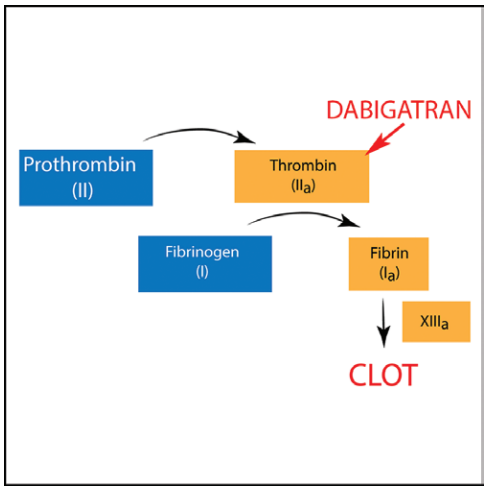
EMERGENCY care providers need to have therapies for the acutely bleeding patient, especially for trauma patients and those requiring emergency surgery. Trauma is a leading cause of mortality worldwide with hemorrhage as the leading cause of preventable death. As many as 30% of severely injured trauma patients will present with a unique, endogenous coagulopathy referred to as trauma-induced coagulopathy. In addition to this problem, the number of trauma patients on direct-acting oral anticoagulants is growing. These drugs are increasingly used for the prevention of cerebrovascular embolic stroke in patients with atrial fibrillation, the treatment of venous thromboembolism, and thromboprophylaxis in patients undergoing surgery.[1–3]

Strategies to combat trauma-related coagulopathy have centered around component-based therapy to replace clotting factors, platelets, and other adjuncts, such as tranexamic acid, to limit blood loss. To reverse direct-acting oral anticoagulants in trauma, prothrombin complex concentrates and activated prothrombin complex concentrates are being increasingly utilized and studied, with many reports of successful reversal of pharmacologic anticoagulation for both direct thrombin and factor Xa inhibitors by prothrombin complex concentrates.[4,5] In the current issue of Anesthesiology, Honickel *et al.*[6] have provided high-level preclinical data to assess the effect of multimodal therapy, including the specific antidote, idarucizumab, for the emergency reversal of dabigatran anticoagulation.

Recent availability of idarucizumab and evaluation by the U.S. Food and Drug Administration of andexanet, as a reversal agent for Xa inhibitors, raises the question of how and when to use these drugs for patients taking anticoagulation before injury.[7] This is particularly important due to evolving experience with prothrombin complex concentrates for reversing direct oral anticoagulants, as well as the simultaneous need to combat underlying trauma-related coagulopathy in severely injured patients. If prothrombin complex concentrates are effective for direct oral anticoagulant reversal, are specific reversal therapies necessary? Will targeted reversal of direct oral anticoagulants after trauma be sufficient? Honickel *et al.* attempt to shed light on the complex problem of dabigatran reversal in the polytrauma setting.



"Prothrombin complex concentrate may...correct the anticoagulation achieved by dabigatran while also correcting at least a component of trauma-induced coagulopathy."

Utilizing a swine model of polytrauma and hemorrhage, the authors convincingly show that both idarucizumab and prothrombin complex concentrate reduce blood loss, while the reduction in blood loss associated with prothrombin complex concentrate occurred at the expense of markedly enhanced thrombin generation. While this raises the theoretical concern of a prothrombotic state, the authors found no evidence of macro- or microvascular thrombi within the limited confines of their investigation. Interestingly, even lower dose prothrombin complex concentrate showed an effect on subgroup analysis, with perhaps an even greater ability to reverse clinically relevant levels of dabigatran. The authors combined their reversal with tranexamic acid and fibrinogen concentrate to attempt to replicate the multimodal therapy utilized in severely injured patients.

Although the authors conclude that idarucizumab is superior to prothrombin complex concentrate in so much as the improved hemostasis did not require extensive thrombin generation, they opine that the similar effects on bleeding between prothrombin complex concentrate and

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idarucizumab argue that prothrombin complex concentrate may be an alternative when idarucizumab is not available or when resuscitating a patient who presents on an unknown direct-acting oral anticoagulant. However, perhaps the most important reason for the enthusiasm for prothrombin complex concentrate as a reversal agent for direct-acting oral anticoagulants was underemphasized in the discussion. Prothrombin complex concentrate has recently been utilized for the resuscitation of trauma-induced coagulopathy in patients with multiple injuries and those with traumatic brain injury not taking prehospital anticoagulation.[8,9] Use of prothrombin complex concentrate as a specific resuscitation tool in addition to, or as a partial replacement for, component therapy is an evolving area of interest for the management of trauma-induced coagulopathy. The complexity of managing coagulopathy in a polytrauma patient is daunting at baseline, while the addition of prehospital anticoagulation to the mix makes a cloudy picture nearly completely opaque. Idarucizumab is a valuable agent that has proven efficacy for the specific reversal of dabigatran. However, for the polytrauma patient with trauma-induced coagulopathy who is also taking dabigatran, idarucizumab is of no value in the correction of endogenous coagulopathy. The finding by Honickel *et al.* that prothrombin complex concentrate provides similar reversal of bleeding presents a highly intriguing possibility—prothrombin complex concentrate may, in fact, pull double duty to correct the anticoagulation achieved by dabigatran while also correcting at least a component of trauma-induced coagulopathy.

A number of important limitations and concerns exist in the current work. In addition to the limits associated with translating preclinical models to practice, the study was not designed nor powered to thoroughly analyze the safety of prothrombin complex concentrate in the setting of markedly enhanced thrombin generation. Whether therapy with prothrombin complex concentrate increases the risk for thrombotic complications in the polytrauma patient is unknown, although early observational data do not report this effect. To their credit, the authors modeled a "worst case scenario" with higher than usual levels of dabigatran and lower than standard dosing of idarucizumab. Rebound of dabigatran remains a clinical concern that was also observed in this model, although dosing strategies for reversal in polytrauma are not fully explored. Finally, although the authors claim that co-administration of tranexamic acid and fibrinogen concentrate in combination with prothrombin complex concentrate led to reduced mortality and lower blood loss, these data are compared to a historical control (albeit with the same model), limiting the decisiveness of these conclusions.

In summary, idarucizumab, while the preferred agent for dabigatran reversal, is subject to potential limitations that include potential availability in some clinical centers or countries where it may not be available. The well-conducted, high-level, preclinical study by Honickel *et al.* highlights that while idarucizumab may play a role in dabigatran reversal in the polytrauma patient, the use of prothrombin complex concentrate results in similar effect and could be a potential substitute worth studying in human patients for situations where idarucizumab is unavailable. Furthermore, this work highlights the critically important observation that multimodal reversal of trauma-induced coagulopathy in polytrauma is mandatory, and it raises the intriguing question as to whether prothrombin complex concentrate may play a dual role in both reversal of direct-acting oral anticoagulant therapy and treatment of trauma-induced coagulopathy, especially in patients who have previously bled and present with low hemostatic factor levels. The optimal management of traumatic bleeding remains a leading priority for clinical trials in trauma, where the evolving frequency of direct-acting oral anticoagulant use in the population mandates a thorough and robust understanding of treatment options by acute care providers faced with the need to manage bleeding.

Competing Interests

Dr. Neal receives research funding from and has served as a consultant for Janssen Pharmaceuticals (Beerse, Belgium). Dr. Levy has served or serves on research steering committees, data safety monitoring boards, or advisory boards for Boehringer-Ingelheim (Ingelheim am Rhein, Germany), CSL Behring (King of Prussia, Pennsylvania), Grifols (Barcelona, Spain), Instrumentation Laboratories (Bedford, Massachusetts), Janssen, Leading Biosciences (Solana Beach, California), and Pfizer (New York, New York).

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Awnings before Yawnings: Advertising Anesthetic Stupor at "the Cooper"

An "albumen print" is glued crookedly to the obverse of this trade card (*above*) selected from the Wood Library-Museum's Ben Z. Swanson Collection. The print depicts Manhattan's Cooper Institute, a tuition-free school founded in 1859 as "Cooper Union" by philanthropist Peter Cooper. The original caption read: "*Presented by* COLTON DENTAL ASSOCIATION. 16 COOPER INSTITUTE." Horrified by the numerical misprint, dental anesthetist Gardner Q. Colton (1814 to 1898) demanded the darker overprinting: "COOPER INSTITUTE, NEW YORK CITY / 19." Besides directing patients to Room No. 19 for dental extraction while "yawning" under the anesthetic "stupor" of nitrous oxide, the overprinting helped non-Manhattanites localize "the Cooper" to New York City during the celebrations of 1876, America's centennial year. Centered over the broad first-floor awning was a pair of second-floor awnings, each of whose sides advertised "COLTON / DENTAL," and looming over those awnings was a banner sign reading, "COLTON'S." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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