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COMMENTARY

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Prothrombin complex concentrates for DOAC-associated bleeding, global coagulation assays, and assessments of clinical hemostasis: How to gauge the impact?

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Direct oral anticoagulants (DOACs) account for an increasing proportion of oral anticoagulant medication use for venous thromboembolism and atrial fibrillation. Bleeding, the major complication of anticoagulation, will be increasingly encountered due to expanding indications and increased eligibility for DOAC use. Although routine monitoring of DOAC anticoagulant effect is not required, laboratory assessment of the coagulation system is desirable for DOAC-related emergencies such as major bleeding, which has reported case fatality rates of 8%-15%.[2] Laboratory testing may facilitate the judicious use of DOAC reversal agents and hemostatic therapies and provide information about the ability of such treatments to correct coagulopathy. However, conventional coagulation assays such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) do not provide reliable quantitative assessments of DOAC anticoagulant effect and specific DOAC assays (eg, calibrated anti-Xa activity assays, dilute thrombin time) are not readily available. Global coagulation assays such as thrombin generation assays (TGAs) are a promising methodology for measuring anticoagulant effect and changes in coagulation parameters following treatment for DOAC bleeds. Unlike routine coagulation tests, TGAs can also measure prothrombotic potential to help address concerns regarding incremental prothrombotic effects of reversal agents and hemostatic therapies used for DOAC-related bleeding.

In a recent issue, Bavalia and colleagues provide data on clinical and laboratory outcomes from a cohort of patients with DOAC-associated bleeding (n = 101) or patients requiring urgent surgery (n = 21) at 5 hospitals in the Netherlands (reference). A majority of patients with major bleeding were on rivaroxaban (54%) and presented with intracranial hemorrhage (59%), whereas only 27% presented with gastrointestinal (GI) bleeding. Prothrombin complex concentrate (PCC; median dose, 50 IU/kg) was administered to 67% of patients treated with oral direct factor XA (FXa) inhibitors. Clinical hemostasis was assessed by local study coordinators using ISTH/Sarode criteria,[3,4] and TGAs were used to measure the effect of PCC on coagulation status. Effective hemostasis was reported to be 70% (95% confidence interval [CI], 55%-81%) among PCC recipients as compared to 64% (95% CI, 45%-80%) among patients who did not receive PCCs. The mortality rate among patients who did not receive PCC was substantially higher, a finding that could be attributable to prognostic differences between the groups at baseline and selection bias.

Bavalia and colleagues build on published data from 2 observational studies on the use of PCCs for the management of FXa inhibitor-associated bleeding.[5,6] In a cohort study by Majeed and colleagues,[5] 84 patients received PCC for management of rivaroxaban- or apixaban-associated bleeding. Hemostasis, adjudicated using ISTH criteria, was rated effective in 69% of cases, whereas 32% of patients died within 30 days of the major bleeding event. Schulman and colleagues[6] similarly evaluated clinical hemostatic outcomes among 66 patients following PCC administration for bleeding on FXa inhibitors using a modified version of the criteria published by Sarode et al. Hemostatic efficacy was rated as good in 65% of cases, moderate in 20% of cases, and poor in 15%, with a 30-day mortality rate of 14%. As with all non-randomized treatment studies, these studies should be interpreted with caution as treatments were not randomly assigned and there is a high likelihood of

baseline confounding. Moreover, direct comparisons between studies are problematic due to differences in population demographics, recruitment procedures and inclusion criteria, PCC dosing, bleeding sites, and definitions of "effective" hemostasis.

What is common to these all studies, however, is the high mortality rates reported despite moderate to high rates of adjudicated clinical hemostatic efficacy. This raises the possibility that existing clinical criteria for hemostasis may not be sufficiently sensitive to detect ongoing bleeding or, more concerningly, that major DOAC-related bleeding leads to a cascade of illness in elderly comorbid patients despite cessation of bleeding. Reliable assessments of hemostatic efficacy are needed not only for guidance and harmonization of clinical management but also for developing effective and safe treatments. Establishing the biochemical effects of reversal or hemostatic therapies may help support the biological plausibility, development, and use of such therapies including PCC.

Evidence of a biochemical effect of PCC on DOAC anticoagulant effect is drawn primarily from in vitro and animal studies, as well as studies in human volunteers, which showed variable and modest corrections of conventional coagulation assays such as the PT.[7-13] Several groups have also evaluated the impact of PCCs on global coagulation assays such as TGAs, which measure both kinetic (lag time, time to peak [TTP]) and quantitative (peak, endogenous thrombin potential [ETP]) parameters of thrombin generation.[14] Whereas conventional coagulation assays provide only the time to initiation of fibrin formation, TGAs provide in-depth data on the speed and amount of thrombin generated by a patient's plasma. PCCs have been shown to reliably correct quantitative TGA parameters[7]. However, data regarding the impact of PCCs on kinetic TGA parameters is sparse. Several groups were unable to demonstrate an impact of PCCs on the lag time.[10,11] This is particularly relevant since early DOAC pharmacodynamic studies revealed that DOACs exert a profound impact on the kinetics of thrombin generation.[15] Blockade of FXa delays initial thrombin production, which in turn delays the amplification and propagation phases of coagulation and the resulting "thrombin burst." DOAC levels are best correlated with kinetic parameters, rather than quantitative.[15,16] The clinical effect of correcting 1 or both aspects of thrombin generation has not been established.

Bavalia and colleagues report thrombin generation parameters in DOAC-treated bleeding patients at baseline and after receiving PCC (reference RTH212336 as above). Compared to a population of healthy volunteers, patients on DOACs had significantly prolonged lag time values, up to 700% of normal. The difference in ETP between DOAC-treated patients and healthy volunteers did not reach statistical significance (P = .06 for FXa inhibitors and P = .09 for dabigatran). Post-PCC ETP values were available for a minority of patients (13/51 FXa-treated patients receiving PCC for major bleeding) and demonstrated a significant correction to levels exceeding normal reference values (P = .001, mean 1108 nM/min^{-1} to 2275 nM/min^{-1}). Similar results were observed with respect to peak thrombin generation.

Global coagulation assays such as TGAs represent a potential strategy for quantifying changes in hemostatic parameters following therapies such as PCC in patients with DOAC-related bleeding. However, several challenges remain including uncertainty about which TGA parameter best reflects hemostatic integrity in this setting. Studies to date have largely focused on the measurement of ETP (TGA area under the curve) as a measure of total hemostatic output. In contrast to conventional coagulation assays (PT, aPTT), the effect of PCC may be better captured by the rise in ETP as observed in in vitro and animal studies. Few studies have evaluated TGA kinetics (lag time, TTP), and it would be important to assess the effect of PCC on thrombin kinetics. In addition to uncertainty about the relationship between TGA parameters and clinical outcomes in this setting, the clinical use of TGAs is constrained by limited availability; the requirement for specialized expertise and equipment; and a lack of standardized methodology, reporting, and reference ranges.

The report by Bavalia and colleagues supports the findings of previous studies suggesting that patients with DOAC-associated major bleeding have substantial short-term mortality risk and further emphasizes the need to understand how treatments such as PCC may impact clinical and laboratory outcomes. These findings also lend further support to the notion that the definitions of effective clinical hemostasis may not adequately assess the clinical sequelae of acute bleeding. Importantly, these definitions include subjective criteria and rely heavily on assessments of nonspecific indices such as hemoglobin level, which is affected by factors other than active bleeding. This is particularly problematic for nonvisible sites of bleeding such as the GI tract, the most common site of DOAC-related bleeding. Given the challenges of defining clinical hemostasis, TGAs have the potential to support clinical assessments by measuring hemostatic indices and providing biochemical evidence of treatment effect, which can then be used to evaluate the incremental benefits and harms of treatments in much-needed randomized trials.

RELATIONSHIP DISCLOSURE

Dr. Siegal has received honoraria for attending advisory board meetings for Aspen Pharma, BMSPfizer, Leo Pharma, Novartis, Portola Pharmaceuticals. JRS declares nothing to report.

AUTHOR CONTRIBUTIONS

JRS drafted the manuscript and wrote the final version of the manuscript. DS provided critical revisions to the drafted manuscript and approved the final version of the manuscript.

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