readers from the date of publication. Obviously, not all articles can be made "Free Access" or subscribers and advertisers would be very unhappy. However, it is within editorial discretion to choose a number of articles per year that could be so designated. We have agreed at *A&A* that the Global Health Section Editor will identify articles that are important to the Global Health community and, assuming no deterring factors, will be designated as "Free Access."

The new "Infographic" is free in every edition of the journal.[2] This provides a pictorial and verbal summary of a highlighted article in each edition of *A&A*. It can be freely downloaded to a smart phone when this is used to access the journal platform.

We hope all of these efforts will improve the access to *A&A* for our readers in LMICs. We intend to keep working toward better solutions, especially in light of rapidly developing technology.

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Clinical and Practical Aspects of Restoring Thrombin Generation in Acute Coagulopathic Bleeding

To the Editor

We have read the work by Mitrophanov et al[1] with great interest. Their focus was to model the optimal use of prothrombin complex concentrate (PCC), FVIIa, or antithrombin (AT) to achieve a "balanced thrombin generation (TG) pattern" in dilutional coagulopathy. They performed an in vitro supplementation of specific factors (Factor [F] II, FVII, FIX, FX, activated FVII [FVIIa], and AT) in diluted blood samples from 10 healthy subjects and tested for the recovery of TG. Subsequently, they did extensive computer simulation of TG to determine a best fit modeling by randomizing kinetic parameters using the above data. They concluded that (1) PCC in combination with AT would be more desirable than FVIIa in normalizing TG and (2) PCC without FVII should be preferred because the function of FVII is uncertain. However, we have noted several major discrepancies between their in vitro dilutional model and trauma-induced coagulopathy in vivo. First, severe AT deficiency (mean, 37%)[1] is only observed in extremely severe trauma; AT activity in the majority of trauma cases (n = 377, Injury Severity Score [ISS] of 18) is generally close to normal (mean, 68%–79%).[2] Further increasing AT may reduce endogenous procoagulant activity as demonstrated in the prolonged lag time of TG by Mitrophanov et al[1] (Figure 5B). In vivo activation of protein C and exogenous AT would further reduce TG. Second, the activity of FVII or FVIIa is likely underestimated in the relatively mild FVII deficiency (mean, 39%)[1] and moderate TF level (5 pM) on TG assay.[3] Hypothermia and acidosis in trauma patients may reduce the rate of procoagulant reactions after PCC [4]; thus, there may be a role for FVIIa to increase TG rate. Third, the authors mentioned the static nature of TG assay/simulation as a major limitation of their study. Indeed, lack of blood flow keeps all "generated thrombin" locally, but blood flow itself provides efficient removal of active enzymes from the vascular injury site. Finally, coadministration of PCC and AT concentrates in their model can be costly because roughly 30 international units (IU) per kilogram of PCC ($1.84 per IU) and AT ($4.43 per IU) would be required to increase factors from 40% to 100%. For an 80-kg patient, the total cost amounts to $15,000. A lower dose of 10 to 15 IU per kg of PCC without AT is less costly ($1500–$2200 per dose) and may be sufficient to increase TG in dilutional coagulopathy.[5] In conclusion, there is limited clinical evidence to support the addition of AT to PCC in active bleeding situations. The role of AT supplementation for postoperative thromboprophylaxis may be substantiated but requires further investigation.

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In Response

We thank the correspondents for their interest and comments on our article.[1] They are correct in stating that our study aimed to shed new light on the optimal use of prothrombin complex concentrates (PCCs). However, it is necessary to emphasize and reiterate our main conclusions[1]: (1) a combination of the clotting factors (F)II, FIX, FX, and antithrombin (AT) improved thrombin generation in diluted plasma in a more balanced way than did recombinant (r)FVIIa or a combination of FII, FVII, FIX, and FX (designated CCF-FVII) and (2) our computational modeling approach could capture the effects of plasma dilution and factor supplementation on thrombin generation. The suggestion that PCCs without FVII (ie, 3-factor PCCs) should be used preferentially over 4-factor PCCs that contain FVII was only mentioned in the Discussion[1] as a possibility; it was not claimed to be a conclusion of our study.

We agree that our experimental work, being a proof-of-principle in vitro investigation, did not fully reproduce the numerous factors that may contribute to coagulopathy in vivo. Likewise, practical aspects of PCC and AT administration, such as dosage and associated costs, are important but were not the focus of our work. Notwithstanding these limitations, our study was designed to investigate the main problem that arises from the in vivo use of PCCs and rFVIIa—the possibility of thromboembolic complications. In our in vitro experiments, supplementation of diluted plasma with rFVIIa resulted in an abnormally accelerated onset of thrombin generation (Figure 4A and Figure 5, B–C), and supplementation with CCF-FVII gave abnormally large values of thrombin peak height and of endogenous thrombin potential (Figure 4B and Figure 5, E–F).[1] Our computational modeling yielded similar results (Figure 6, C and E),[1] demonstrating that these effects could be predicted solely on the basis of the definitions of the 2 supplementation strategies. These findings suggest that rFVIIa and CCF-FVII may trigger excessive clotting in vivo, which is consistent with recorded occurrences of thromboembolism after rFVIIa[2] or PCC[3] administration. In contrast, a combination of procoagulant PCC components and AT resulted in an overall more balanced restoration of thrombin generation in vitro (Figures 4–6).[1] Therefore, we posit that thromboembolic complications may be alleviated by coordinating PCC administration with AT administration in coagulopathic patients. We tested the performance of this strategy in the case of 3-fold dilution,[1] which mimicked critical clotting factor deficiencies detected in coagulopathy studies.[4] Additional evidence supporting the need for coordinated PCC and AT administration comes from a recent clinical investigation of PCC supplementation, which was associated with a reduction in AT levels up to 50% and with a significant endogenous thrombin potential increase in trauma patients.[5]

Our work was intended to provide insights into the coagulopathic state, rather than into the conditions of active bleeding. Accordingly, we regarded the considered combination of procoagulants and AT as a potential means of restoring the normal ability of blood to coagulate rather than one of emergency hemorrhage control. In conclusion, we fully agree with the correspondents that the role of AT administration requires further investigation.

Disclaimer

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Army or the US Department of Defense. This correspondence has been approved for public release with unlimited distribution.

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