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Theoretical Modeling of Coagulation Management With Therapeutic Plasma or Prothrombin Complex Concentrate

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Prothrombin complex concentrates (PCCs) have been associated with a possible risk of thromboembolic complications, potentially attributable to an increased ratio of the plasma concentration of factor II (FII) to antithrombin (AT). We developed a mathematical model to examine the relationship between amounts of PCC or therapeutic plasma administered, and plasma levels of FII and AT. The model showed that PCC produces substantial increases in plasma levels of FII but only small changes in AT, increasing the FII:AT ratio. Therapeutic plasma was shown to have only modest effects on levels of FII or AT, unless high doses are used. (Anesth Analg 2017;125:1471–4)

Prothrombin complex concentrates (PCCs) are recommended internationally for emergency reversal of vitamin K antagonists, with recent data indicating superior efficacy versus therapeutic plasma.[1] The use of PCCs for reversal of direct oral anticoagulants has also been investigated.

In Europe, PCCs may be used to treat excessive bleeding that is unrelated to anticoagulant therapy, where the pathophysiology of bleeding is entirely different from patients requiring reversal of anticoagulant therapy. Patients taking oral anticoagulant therapy have reductions in a limited number of specific proteins.[2] In contrast, trauma/perioperative bleeding patients have generalized reductions of all procoagulants and anticoagulants. Administration of procoagulant therapy without cosupplementation of anticoagulants may therefore introduce an imbalance in the coagulation system, increasing the risk of thromboembolic complications.[3,4] Monitoring and, if necessary, supplementing plasma levels of antithrombin (AT) has been suggested as 1 approach to improving the safety of PCCs.[3,4] Administration of PCC for perioperative bleeding may be guided by clotting time in the thromboelastometric EXTEM assay or the international normalized ratio. However, neither of these measures is sensitive to AT levels.

Our group previously developed a mathematical model to show theoretical relationships between amounts of therapeutic plasma/cryoprecipitate/fibrinogen concentrate and plasma fibrinogen level.[5] Using a similar approach, we designed a theoretical, educational tool to answer the question "What would be the resultant factor II (FII) level, AT level, and FII:AT ratio when administering a specified amount of therapeutic plasma or PCC?"

METHODS

A mathematical model was constructed to examine relationships between the amount of hemostatic agent (PCC or therapeutic plasma) and plasma levels of FII and AT. Details of the assumptions for developing the model are shown in Supplemental Digital Content 1 (http://links.lww.com/AA/B954). Briefly, they were as follows:

1. The patient starts with a certain plasma volume, FII level, and AT level.
2. Hemostatic agent is added 1 unit at a time.
3. Volume resuscitation with crystalloid or colloid may be coadministered.
4. Immediately before adding each unit of hemostatic agent, the volume of the unit plus the volume of crystalloid or colloid is removed from circulation.
5. On adding each unit of hemostatic agent plus crystalloid or colloid, plasma volume is restored to the "baseline" volume.
6. After adding each unit of hemostatic agent, new values for FII level, AT level, and FII:AT ratio are calculated.
7. If hematocrit decreases below a defined threshold, 1 unit red blood cells (RBC) is added to the simulation at the same time as the next unit of hemostatic agent.

Using literature-based values for key parameters, the model was initially developed with mathematical consideration of blood plasma and the constituents of interest (please see Supplemental Digital Content 1, http://links.lww.com/AA/B954).

Several refinements were then incorporated, using similar methodology to that described for the fibrinogen concentration simulator (Supplemental Digital Content 1, http://links.lww.com/AA/B954).[5] In vivo recovery was added and the model was modified to keep circulatory volume constant. The addition of RBC when hematocrit falls below a defined threshold was also added to the model.

RESULTS

Initial results from the finalized tool, with bodyweight 70 kg, baseline hematocrit 40%, FII 100%, and AT 100% are shown in the Figure. PCC (2000 IU) elicited considerable increase in the plasma level of FII but little change in AT. Therapeutic plasma (4 U) had little impact on levels of either FII or AT. Thus, PCC increased the FII:AT ratio to 1.89, whereas this ratio remained at 1.00 with therapeutic plasma. When baseline levels of FII and AT were reduced to 40%, PCC still increased the FII level above normal (130%) while plasma increased it only to 56%. AT changed little in response to PCC, and increased to 56% with therapeutic plasma. The FII:AT ratio remained at 1.00 with therapeutic plasma but increased with PCC to 3.15.

A new set of baseline parameters was then used: bodyweight 120 kg, hematocrit 50%, FII 40%, and AT 60%. Six units of therapeutic plasma and 3000 IU of PCC were modeled (12.5 mL/kg and 25 IU/kg, respectively). Volume resuscitation was also included: 150 mL per unit of PCC (zero with therapeutic plasma). The simulator showed that PCC produced almost a 3-fold increase in FII, to 115%, and there was a decrease in AT to 50%. Thus, the FII:AT ratio was increased to 2.31 (Supplemental Digital Content 2, http://links.lww.com/AA/B955). With therapeutic plasma, modest increases in FII and AT were observed (resultant levels of 56% and 71%), so the FII:AT ratio was increased from 0.67 to 0.80.

The original scenario was then reassessed, with a low baseline hematocrit (22%). This resulted in a unit of RBC being added along with the second unit of therapeutic plasma, reducing the levels of FII and AT in circulation without affecting the FII:AT ratio (Supplemental Digital Content 2, http://links.lww.com/AA/B955). The unit of RBC was successful in increasing hematocrit above the 21% threshold.

The tool was applied to simulate situations described in cardiovascular surgery, trauma and vitamin K antagonist reversal (Supplemental Digital Content 2, http://links.lww.com/AA/B955).

DISCUSSION

This theoretical tool indicates that, under most conditions, addition of PCC increases the FII:AT ratio. In contrast, therapeutic plasma has only modest effects on levels of FII or AT, with little effect on the FII:AT ratio. Due to dilutional effects, plasma levels of FII and AT do not necessarily increase linearly with increasing dose of therapeutic plasma. In comparison, infusion volumes of PCC are relatively small, meaning that increases in plasma levels of FII and AT are generally linear. Our results also indicate that a small amount of PCC can be far more effective than a moderate or large dose of therapeutic plasma in increasing thrombin generation potential. This can be explained by the relatively low concentrations of coagulation factors in therapeutic plasma.

The pathophysiology of bleeding differs greatly between clinical settings. For emergency reversal of anticoagulation relating to vitamin K antagonist therapy, the risk of thromboembolic complications caused by PCC appears low.[6] This may be related to normal levels of AT[2]; consequently, patients may have an FII:AT ratio close to 1 after treatment with PCC (see Supplemental Digital Content 2, http://links.lww.com/AA/B955). However, in trauma and perioperative bleeding, generalized depletion of both pro- and anticoagulants is common, and PCC therapy is likely to increase the FII:AT ratio above 1. Therefore, a cautious approach when administering PCC appears warranted in trauma and perioperative bleeding. It has been suggested that adequate levels of fibrinogen should be ensured before PCC therapy in such settings.[7] A treatment strategy with combined use of fibrinogen supplementation and PCC with AT has been supported by data obtained from kinetic modeling of thrombin generation.[8] Our tool does not include AT concentrate. However, the effects of using PCC plus AT could be modeled by increasing the quantity of AT and the volume per unit of PCC.

Limitations of the tool we designed include a lack of accounting for clinical realities such as ongoing bleeding, loss/consumption of coagulation factors, administration of additional therapies such as platelets, or the timing of events such as administration of PCC or therapeutic plasma. Therefore, clinical validation of the tool in patients with perioperative bleeding is not possible. The clinical risk of thromboembolism is affected by many factors apart from the FII:AT ratio, and the clinical implications of a change in the FII:AT ratio are poorly defined. Therefore, the extent to which our tool reflects patients' risk of thromboembolism is uncertain.

Despite the limitations, there is good evidence that FII:AT ratio may affect the risk of thromboembolic events. First, an in vitro study implicated FII as the primary cause of thrombogenic potential with PCCs, and suggested that the ratio between FII and AT must be restored to reduce thrombin generation to normal levels.[3] Second, a porcine trauma model showed that PCC (35 IU/kg) was well tolerated and effective in improving coagulation.[7] However, 50 IU/kg PCC was associated with thromboembolism and signs of disseminated intravascular coagulation. Supplementation of factors II, IX, and X after hemodilution has been shown in computational modeling to increase thrombin generation, but with coadministration of AT thrombin generation was restored to baseline (predilution) levels.[9] Finally, a study using blood samples from cardiac surgery patients supports the likelihood of excessive thrombin generation capacity after PCC therapy without AT supplementation.[10]

In conclusion, PCC may be a valuable treatment for increasing thrombin generation capacity in patients with coagulopathy and life-threatening bleeding. We developed a theoretical tool to examine the effects of PCC on the patient's FII:AT ratio, and the results highlight important differences between patients requiring reversal of oral
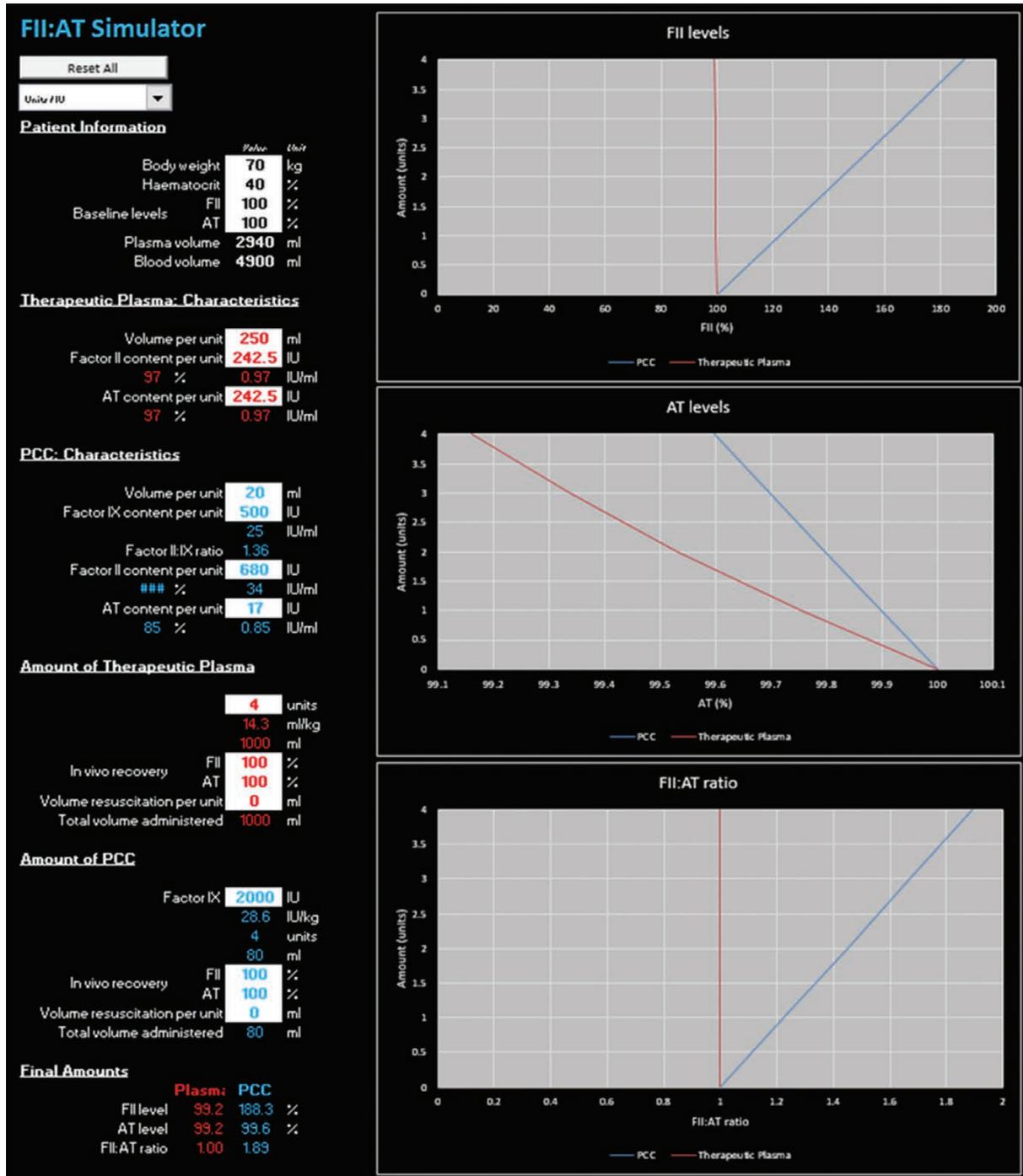
Figure. Results obtained with the finalized, theoretical FII-AT concentration simulator. Seventy-kilogram patient with 40% hematocrit, baseline plasma levels of FII and AT of 100%, and addition of 4 units of PCC and therapeutic plasma. AT indicates antithrombin; FII, factor II; PCC, prothrombin complex concentrate.

anticoagulant therapy and those with trauma/perioperative bleeding. Caution may be required with regard to the potential for PCC to produce a prothrombotic imbalance, particularly in patients with bleeding unrelated to anticoagulant therapy. A strategy of supplementing AT among recipients of PCC could be considered. ▪

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