PCC Reverses Dabigatran-Associated Bleeding in Polytrauma Model

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Four-factor prothrombin complex concentrate (PCC) rapidly reversed dabigatran-associated bleeding in a polytrauma animal model, which was enhanced with the addition of tranexamic acid (TXA) and fibrinogen (FBG). Oliver Grottke, MD, PhD, RWTH University Clinic Aachen, Aachen, Germany, presented data from a study that evaluated PCC in combination with FBG plus TXA compared with PCC monotherapy in a model of polytrauma with anticoagulation by dabigatran.

The 2013 European Heart Rhythm Association guidelines on the use of new oral anticoagulants recommend that in patients taking dabigatran or factor Xa inhibitors who experience non–life-threatening serious bleeding, TXA can be considered as an adjuvant, whereas PCC or activated PCC (aPCC) should be considered in patients with life-threatening bleeding [Heidbuchel H et al. *Eur Heart J.* 2013]. A previous study demonstrated that administration of PCC reduced blood loss in a porcine polytrauma model with dabigatran-associated bleeding [Honickel M et al. *Crit Care.* 2014]. In addition, higher levels of FBG are associated with an incremental increase in survival in patients with trauma [Schöchl H et al. *Crit Care.* 2012]. The purpose of this study was to evaluate the efficacy of PCC plus TXA and FBG in anticoagulation reversal in a polytrauma model.

In this study, a porcine model was used in which, after an infusion of dabigatran or placebo, trauma was induced that resulted in hemorrhagic shock [Grottke O et al. *Eur Heart J.* 2014 (abstr 4844)]. After 12 minutes, blood loss was assessed and blood draws were taken for laboratory analysis. At 14 minutes, animals received the following: only dabigatran; TXA plus FBG; PCC monotherapy; or TXA plus FBG and PCC. Blood loss was significantly greater in the group that received dabigatran compared with a sham infusion ($P = .002$).

Animals who received PCC or TXA plus FBG and PCC demonstrated a significant reduction in blood loss compared with placebo ($P < .001$ for both). In addition, animals that received PCC monotherapy or in combination with TXA and FBG demonstrated significantly higher rates of survival at 100% compared with control animals ($P < .001$). Animals treated with TXA and FBG without PCC demonstrated similar rates of blood loss and survival compared with control animals. In addition, although arterial blood pressure decreased after trauma was induced, treatment with PCC with or without TXA plus FBG resulted in an increase in arterial blood pressure and normalization of lactate levels that were sustained over 240 minutes. Similarly, treatment with PCC with or without TXA plus FBG increased cardiac output to near normal levels that were sustained over 240 minutes. Animals that received placebo or TXA plus FBG experienced decreasing arterial blood pressure and cardiac output and rising lactate levels over 120 minutes.

Dabigatran plasma levels steadily decreased over 240 minutes in all groups. FBG levels decreased in the control and PCC monotherapy groups; TXA plus FBG with and without PCC increased initially, but decreased rapidly in the TXA plus FBG group and decreased gradually in the PCC plus TXA and FBG group. Clotting time and clot formation time were longer in the TXA plus FBG and control groups compared with the PCC groups, which decreased after intervention administration and were sustained over 240 minutes. Clotting time, clot formation time, and maximum clot firmness were similar in the control and TXA plus FBG groups.

For coagulation tests, postintervention prothrombin time was affected, which increased in the control and TXA plus FBG groups and remained steady in the PCC groups. Thrombin-antithrombin was increased up to 60 minutes, then gradually decreased over 240 minutes, in the PCC groups compared with the control and TXA plus FBG groups, which remained steady over 240 minutes. Activated prothrombin time was not affected by any of the interventions and decreased steadily up to 60 minutes and remained steady until 240 minutes.

In conclusion, Dr Grottke stated that the data from this study suggest that TXA plus FBG failed to reverse bleeding in a polytrauma animal model that received dabigatran. In contrast, PCC rapidly reversed anticoagulation by dabigatran, which was enhanced by the addition of TXA and FBG. He indicated that clinical studies are warranted.