COMMENT & RESPONSE

Four-Factor Prothrombin Complex Concentrate for Patients With Trauma

To the Editor We have some concerns about the recent study[1] that showed that early administration of 4-factor prothrombin complex concentrate (4F-PCC) had no significant benefit in reduction of 24-hour blood product consumption in patients with severe trauma who were at risk of massive transfusion.

First, it is important to consider the timing of 4F-PCC administration as a potentially significant confounding factor. This study's results pertain only to the early administration of 4F-PCC and cannot be generalized to other administration methods, such as subsequent administration after resuscitation. Although the title of the article mentioned early administration, it seemed that the conclusion of the study lacked a clear description about the time point of administration.

Second, we have concerns about the baseline patient characteristics of the 2 groups, shown in the article's Table 1.[1] Despite randomization, there were some differences in the median systolic arterial blood pressure between patients who received 4F-PCC and placebo. Specifically, the median systolic artery blood pressure in the 4F-PCC group decreased from a prehospital value of 101 mm Hg to 89 mm Hg at admission, while the median systolic artery blood pressure in the placebo group was 90 mm Hg for the prehospital value and at admission. Furthermore, the reduction in blood pressure could have weakened the potential effect of the 4F-PCC group in reducing the amount of blood transfusion.

Third, we have concerns about the patient population included in this trial. The proportion of patients with prehospital arterial systolic blood pressure of less than 90 mm Hg was higher compared with a previous trial of patients with trauma-induced coagulopathy.[2] This difference is important because volume replenishment may be more critical than coagulation factor replenishment in patient who are in shock. Shock also causes peripheral vasoconstriction, which may increase the risk of thromboembolic events. Although there is no concrete evidence, we speculate that it may be reasonable to administer 4F-PCC after basic volume resuscitation and restoration of blood pressure.

In addition, some 4F-PCC products may contain small amounts of heparin, added to prevent the activation of the clotting proteins.[3] Consequently, 4F-PCC is contraindicated in patients with a history of heparin-induced thrombocytopenia,[4] and the risk of thrombosis needs to be considered against the benefit of hemorrhage control. Moreover, approved indications for use of 4F-PCC are currently limited in many countries.

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To the Editor The PROCOAG trial[1] showed that 4F-PCC administration did not reduce 24-hour blood product consumption in patients with trauma at risk of massive transfusion, in contrast with previous studies that revealed a benefit of 4F-PCC over fresh frozen plasma.[2] We have concerns about this study.[1]

First, the sensitivity of the Assessment of Blood Consumption (ABC) score in this trial was approximately 54%, calculated by the number of eligible patients who underwent transfusion whose ABC scores were greater than or equal to 2 or less than 2 with the clinical need for transfusion, which is much lower than the originally reported sensitivity of 75%.[3] The FAST (focused assessment with sonography for trauma) scan, one of the components for ABC scoring, is highly operator dependent, which may have caused the low predictive ability of the ABC score in this study.[1] A previous retrospective study[4] reported that the sensitivity of clinical gestalt for risk prediction of massive transfusion was 66% and that false-negative results among the gestalt-negative patients with trauma who did not receive massive transfusion were 3 times more likely to have bleeding in the pelvis and more hemodynamic instability. Therefore, combined use of the ABC score and gestalt in this trial[1] seems unsuitable for screening and may have led to undertriage by excluding patients with trauma who had internal bleeding but not external bleeding. Because a reduction in undertriaged patients should be prioritized in the trauma setting, it seems reasonable for centers with the highest trauma level activation to adopt scoring systems with higher sensitivity, such as the Trauma Associated Severe Hemorrhage score.

Second, the incidence of thromboembolic events was lower in placebo-treated patients with coagulopathy (22%) compared with those without coagulopathy (33%). In contrast, there was no difference in thromboembolic events between patients receiving 4F-PCC with and without coagulopathy or between patients without coagulopathy treated with 4F-PCC and placebo. These results may suggest possible protocol violations, such as liberal fluid therapy in placebo-treated patients with coagulopathy.

Third, the hemostatic effect of 4F-PCC may have been overridden by fibrinogen concentrate, which was administered in more than 80% of trial patients (Table 1 in the article). In the

RETIC trial,[5] patients with trauma who had coagulopathy benefited more from fibrinogen supplementation than fresh frozen plasma administration. Only 16% of fibrinogen-treated patients received administration of 4F-PCC for reversal of trauma-induced coagulopathy, limiting the role of 4F-PCC in these patients who were treated appropriately with fibrinogen concentrate supplementation.

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In Reply We appreciate the Letters to the Editor about the PROCOAG trial.[1] Regarding the comments by Dr Hsu and colleagues about the timing of administration of 4F-PCC, the design of our study stated without ambiguity that *early* corresponded to administration within the hour of admission to the resuscitation room. The per-protocol population analyzed patients within this time frame.

We acknowledge differences between the 2 groups of patients in the prehospital field, such as systolic arterial blood pressure. However, at hospital admission, no difference in systolic blood pressure was observed. Second, prehospital measurements are often imprecise, and the observed difference can be explained by this systemic imprecision. Third, the difference between prehospital and admission systolic blood pressure indicated in Table 1 in the article pertained to the median and not individual differences. A potential effect of a decrease should be assessed with individual data.

With regard to the amount of fluid resuscitation, both groups received low-volume fluid resuscitation according to European guidelines,[2] without any difference between the 2 groups. Any effect on the pathophysiology of thromboembolic events is unlikely. We agree that 4F-PCC containing heparin is contraindicated in patients with known heparin-induced thrombocytopenia as indicated in the study protocol. No higher rate of thrombocytopenia was observed in the 4F-PCC group.

We agree with Dr Sato and colleagues that clinical decision rules, such as the ABC score,[3] show lower predictive performance in real life than in their initial description. The observed sensitivity of ABC is comparable with the PROPPR trial.[4] Clinical gestalt can be superior to decision rules, which is why the discretion of the attending physician could override the ABC score in our study.[1]

We disagree with Sato and colleagues that fibrinogen substitution renders 4F-PCC administration useless, because these products do not target the same step in the coagulation cascade. 4F-PCC is thought to boost generation of thrombin. However, we acknowledge that systematic administration of 4F-PCC in combination with fibrinogen may have increased the thromboembolic risk in patients with unimpaired thrombin-generation capacity.[5]

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US Hepatitis C Elimination Plan

To the Editor A recent Viewpoint[1] identified American Indian and Alaska Native persons and non-Hispanic Black persons as groups disproportionately affected by hepatitis C virus. We consider this a problematic classification.

When considering that American Indian and Alaska Native persons and non-Hispanic Black persons are also represented in the other named groups disproportionately affected by hepatitis C virus, it would be more appropriate to identify the