Bleeding news

Comparison of 4-factor prothrombin complex concentrate and andexanet alfa for reversal of apixaban and rivaroxaban in the setting of intracranial hemorrhage

Michelle Lipski, Stacy Pasciolla, Kevin Wojcik, Brian Jankowitz, Lauren A Igneri

J Thromb Thrombolysis. 2023 Apr;55(3):519-526. doi: 10.1007/s11239-022-02752-z.

Four-factor prothrombin complex concentrate for the treatment of oral factor Xa inhibitor-associated bleeding: a meta-analysis of fixed versus variable dosing

Thita Chiasakul, Mark Crowther, Adam Cuker

Res Pract Thromb Haemost. 2023 Mar 10;7(2):100-107. doi: 10.1016/j.rpth.2023.100107

Author of the comment: *Dra. Raquel Ferrandis Comes.* *Anesthesiology and Resuscitation. Hospital Universitari i Politècnic La Fe, Valencia. Member of the SEDAR-COVID working group.*

Urgent management of direct anti-Xa anticoagulant drugs (xabans) is still a controverted issue, given the absence of a specific reversal agent approved in our field, since andexanet alfa is not yet available, although approved by the FDA in May 2018, based on ANNEXA-A study. Andexanet alfa, unlike idarucizumab (reversal agent of dabigatran), is a modified Xa factor that removes the drug following a competitive mechanism, thus achieving–according to several authors–a hemostatic efficiency close to 80%.

In this context, the authors of our first article present a retrospective study on 70 patients with intracerebral hemorrhage, 47 of which are treated with 4-factor prothrombin complex (4F-PCC), and 23 with andexanet alfa. The assessment of hemostatic efficiency was defined according to the increase of hematoma in control CT after 12 hours. Efficiency was deemed excellent if the increase was less than 20%, and good if between 20 and 35%. Following this criterion, both groups achieved excellent or good hemostatic efficiency in 70% of the cases, similarly to what is described in the literature. No differences were either observed in secondary outcomes approached as efficacy (need for re-operation, use of other hemostatic agents, prognosis or neurological recovery scales). It must be noted that the number of recorded thrombotic events, even though not achieving statistical significance, was higher in the andexanet (22%) group than the 4F-PCC group (17%).

Therefore, in our field, urgent management of bleeding in xaban-anticoagulated patients is based on provision of hemostatic agents, such as 4F-PCC. However, the originally recommended dose in the main guides was 50 UI/kg, a value which, apparently, is progressively decreasing, although it is not yet established.

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The second article we would like to discuss this month provides a systematic literature review, comprising 25 studies with over 1,700 patients. These studies are grouped together based on whether variable—on average, 38 UI/kg—or fixed—on average, 38 UI/kg—4F-PCC doses have been used. Although criteria assessing hemostatic efficacy differ, the overview provided by the meta-analysis is that hemostatic efficacy is achieved in 74-79% of the cases. Furthermore, recorded thrombotic events were on average 4 and 3%.

A conclusion can be drawn from this study that the doses derived from a weigh-based strategy are higher and way more variable than fixed doses. Nevertheless, in a logistic regression analysis of the data, no benefit is observed from that dose increase. These results are similar to the ones described for AVK reversion with 4F-PCC.

All in all, and still with a significant lack of evidence, the use of 4F-PCC with doses of 25-30 UI/kg, as a hemostatic agent in xaban-anticoagulated bleeding patients, might be effective and safe.

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Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion: The PROCOAG Randomized Clinical Trial

Pierre Bouzat, Jonathan Charbit, Paer-Selim Abback, Delphine Huet-Garrigue, Nathalie Delhaye, Marc Leone, Guillaume Marcotte, Jean-Stéphane David, Albrice Levrat, Karim Asehnoune, Julien Pottecher, Jacques Duranteau, Elie Courvalin, Anais Adolle, Dimitri Sourd, Jean-Luc Bosson, Bruno Riou, Tobias Gauss, Jean-François Payen; PROCOAG Study Group

JAMA. 2023 Apr 25;329(16):1367-1375. doi: 10.1001/jama.2023.4080.

Author of the comment: *Dra. Pilar Marcos.* *Intensive Care Medicine. Hospital Germans Trias i Pujol, Badalona, Barcelona.*

Introduction

The treatment for **massive hemorrhage in trauma** is still a challenge, with a high mortality in spite of strategies such as using tranexamic acid (TXA), reducing resuscitation with volume, and high transfusion ratios. Protocols for massive transfusion differ between hospitals, depending on their resources. Thus, some of them use fixed transfusion ratios, others use viscoelastic tests (VET) to guide transfusion, and others mix both strategies. *However, no strategy has proven superior to others, and this is partly due to the difficulty of performing randomized clinical trials (RCTs) in this situation and how concepts are defined. For instance, when we say that a patient is at risk of suffering from a massive hemorrhage (MH), what is a MH?, what is massive transfusion (MT)?, how is acute coagulopathy defined in trauma patients?*

Recently, **observational studies** have been published suggesting that the administration of frozen fresh plasma (FFP) together with a 4-factor prothrombin complex concentrate (4F-PCC) could decrease the mortality of trauma patients due to hemorrhage, with no increase in thrombotic events. Hence the **RCT** here discussed.

MATERIAL AND METHODS of the discussed RCT

Randomized, placebo-controlled, double-blind superiority study carried out in 12 trauma-centers in France (29 December 2017 – 4 August 2021). Randomization was performed within one hour after admission to hospital. *It would seem like the right approach, and a very ambitious one.*

Inclusion criteria: Patients ≥ 18, at risk of MH within one hour after trauma.

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Definition of MH risk: Transfusion of ≥ 1 packed red blood cells (PRBC) within one hour after trauma + assessment of blood consumption (ABC) ≥ 2, or an assessment by the physician in charge of a MT risk. *The first methodologic issue emerges here, since the definition of MT could be very subjective, since it includes clínical assessment.*

Definition of MT: Administration of ≥ 3 PRBC within one hour after trauma or ≥ 10 PRBC within 24 hours after trauma. *Second issue, since randomization is performed within one hour, but the second part of the definition assesses MT within 24 hours.*

Definition of acute coagulopathy: PT >1.2, and severe when PT >1.5.

Resuscitation performed: According to the European guides on resuscitation after trauma: Restrictive fluid therapy, high transfusion ratios (1:1 or 2:1), TXA 1+1 g within 3 hours, fibrinogen in case of values <1,5 g/L or functional deficiency according to VET, and platelets to achieve values > 50x10^9/L. *This would entail the third methodological problem, since ROTEM-guided treatment is combined with conventional coagulation.*

Hypothesis: The administration of 4F-PCC reduces the need for blood products within 24 hours after trauma.

Study outcomes:

Primary: Difference between total number of blood products (PRBC, FFP, and platelets) administered within 24 hours after trauma in treatment and placebo groups. **Secondary:** Time to achieve PT <1.5, mortality after 24 hours and 28 days, days in hospital outside of ICU, days without MV, thrombotic events after 28 days, among others.

Intervention:

Treatment group: 25 UI factor IX / Kg (1 mL//Kg). Dose in recommended range (20-35 UI/Kg). **Placebo group:** 1 mL/Kg of 0.9% saline solution.

A sample size of 350 patients between both groups was appropriately calculated.

Statistical analysis and results:

The **primary outcome** is the absolute estimation of the difference in blood products (U-Mann-Whitney), without considering variables that may have been confounders. Table 1 of the article shows that treatment and control groups are not comparable, since the ratio of patients receiving TXA and the amount of fibrinogen administered were significantly higher in the placebo group. The authors did not obtain significant differences in the absolute number of blood products

administered, without considering this important difference between the groups. *Therefore, would the administration of 4C-PCC have achieved a reduction in the number of blood products received if the control group had not been given a significantly higher amount of TXA and fibrinogen?*

As for **secondary outcomes**, the authors strongly stress the time it takes to normalize PT in both groups, and in this case they use multivariate regression analysis, with no superiority found in the 4F-PCC group. *However, they do not include in the analysis whether VET or conventional coagulation has been used to guide the transfusion, whereas this should have been taken into account.*

The **safety profile** of the treatment is also analyzed with 4F-PCC through a bivariate analysis. The results obtained show that the group treated with 4F-PCC presents a significantly higher number of thrombotic events than the placebo group, even though the latter received higher doses of TXA and fibrinogen.

Conclusions

The authors conclude that the administration of 4F-PCC does not reduce the number of transfused blood products, does not shorten the time it takes to normalize PT, and increases prothrombotic events, all within 24 hours after trauma.

Based on the above discussion:

- *We cannot prove that 4F-CCC does not reduce the number of transfused blood products, since we should take into account that the control group receives more TXA and fibrinogen.*
- *Neither can we say that the administration of 4F-PCC does not reduce the time it takes to normalize PT, since the RCT includes patients whose treatment of coagulopathy has been guided by VET, and others by conventional coagulation, and this has not been taken into account.*
- *We can "suspect" that the administration of 4F-PCC increases thrombotic events, since that is observed to a significant extent in the RCT, although the group treated with 4F-PCC receives less TXA and fibrinogen. However, further RCTs should address that.*

Therefore, I do not believe this study can categorically advise against the use of 4F-PCC in trauma patients at risk of MT.

Given how hard it is to carry out this kind of RCTs, definitions and inclusion criteria should be more restrictive, and the analysis should take confounders into consideration. Confusion is not always removed by randomization, as can be seen in this study.

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Prothrombin complex concentrate in cardiac surgery for the treatment of coagulopathic bleeding

Katia Hayes, Malindra C Fernando, Vanessa Jordan

Cochrane Database Syst Rev. 2022 Nov 21;11(11):CD013551. doi: 10.1002/14651858.CD013551.pub2.

Author of the comment: *Dra. Sonia María Veiras.* *Hospital Clínico Universitario de Santiago de Compostela. Head of Section at the Anesthesia and Resuscitation Department. A Coruña Province.*

Coagulopathy following cardiac surgery is associated with a significant transfusion of blood products and a high morbidity and mortality.

This review includes 18 studies (4993 patients). Two randomized clinical trials (151 participants) and 16 non-randomized studies, 14 of which retrospective, one prospective and one case report.

The review establishes two comparisons:

1- PCC versus standard therapy

2- PCC versus activated recombinant factor VII

They found that PCC seems to reduce the number of transfused red blood cell units. This fact is supported by moderate-quality evidence emerging from randomized clinical trials, as well as low-quality evidence based on non-randomized studies.

PCC can result in little to no difference in the incidence of post-oeprative bleeding, in the incidence of thrombotic events, in mortality, in the stay in the ICU, and in the incidence of requiring renal replacement therapy, when compared to standard therapy with frozen fresh plasma.

PCC leads to a more significant decrease in the total packed red blood cells transfused, if compared to activated recombinant factor VII. The quality of this evidence is considered to be moderate.

The use of PCC has little to no effect in thrombotic events, mortality, drainage production, stay in ICU, or incidence of extrarenal purification therapy when compared to factor VII, and the quality of the evidence is very low.

All studies but one are associated with cardiac surgery, with participants representative of the general population, but not the high-risk patient category, which should probably be the target population.

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The studied pediatric population underwent surgery for high-complexity congenital conditions, and the doses applied there were higher than the ones used in studies with adult patients, with no evidence of thrombotic event increase.

IMPLICATIONS FOR THE CLINICAL PRACTICE

PCC could be an alternative to the standard therapy in coagulopathic bleeding following cardiac surgery. The optimal safe dose is still uncertain. The range in adults in the reviewed studies ranges from 12 to 28 UI/ kg. In the pediatric population, doses ranged from 25 to 57 UI/Kg.

There is a hypothetical increased risk of thrombosis with the use of 3-factor PCC, since it does not include C and S proteins.

The authors believe there is little benefit from the use of PCC in patients undergoing low-risk cardiac surgery. Patients subject to long periods of extracorporeal circulation, deep hypothermia, and prosthetic material, such as an aortic graft, are the ones who can benefit more from the use PCC.