Bleeding news

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

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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.