

EDITORIAL

The PROPPR transfusion ratio in severe traumatic haemorrhage

C. Boer

Department of Anesthesiology VU University Medical Center, Amsterdam, the Netherlands

Correspondence

C. Boer – c.boer@vumc.nl

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Trauma-related severe haemorrhage requires damage-control resuscitation with blood products in order to rapidly encounter coagulopathy and shock. While there is broad consensus regarding the prompt initiation of resuscitation following severe haemorrhage, the optimal ratio between transfused fresh frozen plasma (FFP), platelets and red blood cells (RBC) is still under debate. While an FFP:RBC transfusion ratio of 1:1 apparently seemed advantageous for patient outcome, most studies on this topic are ambiguous due to a survivorship bias phenomenon^[1]. In particular, patients who die in the first 30-60 minutes following hospital admission frequently do not receive plasma due to the time-consuming process of thawing the FFPs. As a consequence, survivors will receive higher FFP:RBC ratios than deceased patients, which confounds the conclusion that higher FFP transfusion rates are associated with a favourable outcome^[2-4].

The Prospective Observational Multicentre Major Trauma Transfusion (PROMTTT) study^[5] previously showed that early FFP transfusion, i.e. immediately after emergency room admission, was associated with increased survival. Moreover, patients with FFP:RBC or platelets: RBC ratios less than 1:2 were 3 to 4 times more likely to die than patients receiving ratios of 1:1 or higher. These observations resulted in the design of the recently published Pragmatic, Randomised Optimal Platelet and Plasma Ratios (PROPPR) trial, which is a challenging investigation that addresses the transfusion ratio pursuit in trauma patients in a randomised controlled fashion^[6]. All participating hospitals in the PROPPR trial were logistically prepared to activate a massive transfusion protocol with prompt availability of thawed FFP. It was concluded that 24-hour and 30-day mortality rates following trauma with severe bleeding were not different when FFP, platelets and RBCs were transfused in a 1:1:1 or 1:1:2 ratio, and in both groups similar complications rates were reported. However, in the 1:1:1 ratio

group the PROPPR investigators found a reduced number of fatalities due to exsanguination, suggesting that the high transfusion ratio was more effective in breaking the downward spiral of coagulopathy and blood loss.

There are two aspects that stand out from the PROPPR study design. First, blood products were delivered in fixed quantities using containers, frequently within 10 minutes after they were ordered^[7]. Interestingly, the investigators choose for a specific order in the containers delivered to treat patients randomised in the 1:1:2 dosing ratio group, with no platelet concentrates in the first container. As a consequence, some patients in the 1:1:2 dosing ratio group received FFP and/or platelet concentrates with delay. Whether this might have contributed to a higher mortality rate due to exsanguination in the 1:1:2 ratio group is, however, unclear. Moreover, a large part of the transfused platelet concentrates was administered after the primary intervention period, which resulted in a final transfusion ratio of 1:1.7:1.3 versus a 1:1.2:1.8 ratio for the 1:1:1 and 1:1:2 dosing ratio groups, respectively, based on the median numbers reported in the supplemental file. These data suggest that some patients received relatively more platelets than the transfusion protocol primarily defined, although it is difficult to elucidate how these ratios were affected by a survivorship bias. A second striking aspect of the PROPPR trial is the lower observed mortality rates than assumed in the sample size calculation. The sample size of the PROPPR trial was based on a predicted 24-hour mortality rate of 21% versus 11% in the 1:1:2 and 1:1:1 ratio groups, respectively. The observed 24-hour mortality rates in the PROPPR trial were 17% and 12.7%, respectively, which consequently resulted in a smaller effect size than expected. The authors report this as limitation, and suggest that the sample size should have been quadrupled to detect the observed difference in 24-hour mortality.

It should be noted that the mortality rates in the PROPPR trial are difficult to compare with other studies. Borgman et al. previously suggested that the use of a predictive model for massive transfusion upon hospital admission, such as the transfusion-associated severe bleeding (TASH) score, is a prerequisite to start transfusion of high FFP:RBC ratios, thereby avoiding the inclusion of nonmassively bleeding patients and overtransfusion^[8]. The PROPPR trial indeed included a priori selected patients with a high risk for transfusion based on a positive blood transfusion prediction score with shock parameters as scoring items. Moreover, the small time window to randomisation as observed in the PROPPR trial, which was less than an hour, makes a comparison with large trauma data registries such as the CRASH-2 trial not justified^[9]. Furthermore, the observations in the PROPPR trial can only be compared with studies that used a prompt activation of a massive transfusion protocol using previously thawed units of FFP as treatment of trauma-related haemorrhage. Due to the unique entities of the PROPPR study design, the study findings are difficult to put into the perspective of the available literature. The generalisability of the PROPPR results to European practice is in part limited by the irregular use of tranexamic acid as treatment modality, and the limited number of patients receiving products such as fibrinogen and prothrombin concentrate. However, the study shows that with the application of a massive transfusion protocol, a high transfusion ratio may be beneficial in avoiding exsanguination, and pleads for the availability of thawed blood products for the treatment of severe traumatic haemorrhage in patients with excessive bleeding in combination with signs of shock. Implementation of this requires a change in the chain of healthcare for severely injured patients, at the cost of specific efforts of transfusion services for the timely delivery of thawed FFP and the possible waste of unused blood products. However, the additional costs are negligible if these strategies are lifesaving in patients with a high risk of death due to haemorrhage.

Disclosure

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