Transfusión en pacientes con sangrado agudo mayor: evidencia de cuándo, a quién y qué producto es mejor

Transfusion in patients with acute major blood loss: evidence when, for whom and what products are best

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Introduction

Major blood loss (MBL) requires an immediate response to stop the bleeding and optimization of hemo-dynamics by so-called damage control resuscitation (DCR) protocols(1). However, the additional presence of and compliance(2) to massive transfusion protocols (MTP)(3) ensuring the fastest possible availability of blood products also influence mortality. Validated clinical scoring systems should already identify the patients that likely progress to MBL and thus will need fast initiation of massive transfusion support. For trauma patients in particular, a subsequent and timely switch from dilution with intravenous fluids as hemodynamic support, to evidence-based ratios of plasma and red blood cells (RBC) is critical. Of particular importance in bleeding, and besides their role as oxygen carrier, RBC also optimize blood platelet dependent primary haemostasis, while plasma derived coagulation factors enforce the haemostatic plug. The here presented evidence about whom, what (ratio of) blood products, with what timing(4) are most effective in patients with acute major blood loss is of clear relevance(5). Indeed, for trauma patients, exsanguination still accounts for 30% to 40% of mostly early (within 3 hours) deaths(6); also for postpartum haemorrhage -in 3 to 8% of all deliveries- blood loss accounts for almost one fifth of maternal deaths(7).

How to identify patients at risk for massive transfusion?

Even by experts(8), estimation of MBL appears unreliable and post-hoc identification of patients that
received major transfusion support is not of use to prevent such\(^9\). Practical scores like the Critical Administration Threshold (CAT)\(^{10}\), the shock index\(^{11}\) and the Assessment of Blood Consumption (ABC)\(^{12}\), help to predict the need for massive transfusion (MT) and justify the start of MTP. Important in on-going bleeding, these scores are based on immediate available clinical (like heart rate, systolic blood pressure, penetrating injury, hemoperitoneum etc.) parameters. For such scores to remain actual, they should logically be repeated (e.g. hourly like in CAT) but in our opinion, also include the rates and total volume of the initiated fluid support as a measure of ‘pre-dilution’\(^{10}\). As soon as intrinsically-delayed laboratory (like Hb, Hb drop, INR, fibrinogen) show (trends towards) stabilization or when validated point of care parameters (i.e. TEG and ROTEM) become available, ‘goal-directed transfusion and coagulation’ therapy becomes warranted\(^5\).

What blood product (ratios) to transfuse?

RBC, plasma and coagulation factors
Notwithstanding the valued concept of ‘permissive hypotension’, both in trauma as well as in non-trauma patients with MBL, hemodynamic support starts with administration of more or less large amounts of intravenous fluids. This strategy obligatorily dilutes the haemostatic potential, and likely also outcome. Even in the absence of Acute Coagulopathy of Trauma (ACoT)\(^{13}\), especially colloid fluids increase fibrinolysis, impair platelet function, fibrin polymerization and lower von Willebrand levels\(^{14,15}\).

Both retrospective as well as prospective cohort studies like PROMMTT already showed that DCR incorporating plasma and RBC in ratios of 1:1 or 1:2 improved short (6 and 24 hrs.) as well as longer (30 days) term survival with a decrease in overall need for blood products. However, because higher ratios are likely to involve patients that live longer anyway and hence are more prone to receive more plasma, RCT derived proof had to be awaited\(^{16-18}\).

In the landmark PROPPR trial, 680 of more than 11000 on ABC scores screened patients were randomized between more liberal plasma use vs. RBC in the 1:1 ratio versus a 1:2 ratio. While no significant difference in 30 days mortality was detected, hemostasis was achieved in more patients and less 24 hrs.-deaths by bleeding occurred in the 1:1 group\(^{19}\).

Very important to first realize is, that the overall mortality of PROPPR patients, irrespective of the study arm, was already reduced by their participation to the trial. As iterated in more detail in the following paragraph, the very early start of the MTP and thus plasma availability by the rigorous study logistics explain this and automatically result in less differences than the studied ratios could have had in normal life. Second, the added hemostatic potential calculated as clotting factors of the 1:1 ratio is only slightly superior to the 1:2 ratio\(^{20}\) and will likely make less difference in more diluted and thus patients with a higher risk to die\(^{21}\). Third, a risk score based MTP initiation -as is standard in such trials- will also involve patients that don’t need an MTP. One can never know this beforehand, but the better outcome of such patients will neither be influenced by different plasma-RBC ratios. Finally, although not a limitation of the PROPPR results, in real life, only 10 % of MTP involve trauma patients. In this respect, only for the ‘more prediluted’ trauma patient, early plasma administration in MTP will be of specific importance\(^{22}\). Indeed, although in a retrospective study design, the received plasma: RBC ratio did not differ between 30 days surviving and non-surviving non-trauma patients\(^{22}\).

Notwithstanding the fact that 1:1 plasma, RBC ratios are nowadays default in MTP guidelines\(^{23}\), it seems logical that more disturbed hemostasis e.g. by ACoT or dilution by iv. fluids might not benefit enough by optimized ratios of blood products. In such conditions or when plasma is not available, several trials have or are attempting to show feasibility\(^{24}\) and effectivity of early administration of fibrinogen without\(^{25}\) or with on TEG/ ROTEM results titrated other purified coagulation factors\(^{5, 26-29}\). Such strategies obviously should show reduced mortality and with it less need for blood products.

Platelets

While several recent reports indicate that platelet administration could unexpectedly be detrimental\(^{30, 31}\), in most studies and similar in the study arms, platelets are given along with RBCs and plasma. Hence, their influence on hemostasis is hard to interpret. Surely, platelet counts in trauma patients will decrease by their consumption in on-going hemostasis and the dilution by iv. administered plasma or other fluids. From a hemostatic perspective,
lowering of platelet counts, however, is known to be less critical as compared to lowering of the RBC mass or hematocrit\(^{(32)}\). This is caused by the fact that platelet-dependent hemostasis is strongly dependent on the RBC-mediated margination of blood platelets towards the vascular boundary layer. Isolated lowering of blood platelet counts therefore is having a relatively small influence on the hemostatic capacity. Together with their early expiration and the more complicated storage conditions required for blood platelets, starting MTP with only RBCs and plasma might not make a big difference. The delayed versus immediate use of blood platelets should, however, be investigated together with the use of cold stored platelets. The latter namely, being intrinsically activated, might be superior in halting MBL.

**How to manage an early start of blood products?**

As shown above, trials like PROPPR\(^{(19)}\), but also those testing fibrinogen and clotting factor concentrates vs. plasma not only compare products but also differences in the timing of hemostatic support. In this respect, with the near perfect logistics as implemented in the PROPPR study\(^{(19, 33)}\), median times of MTP activation and arrival of blood products were both reduced to less than 10 minutes. More standard for normal logistics is that initiation of plasma transfusions on average takes 90 minutes\(^{(34, 35)}\). As said, although the 2 study arms did not differ much, the PROPPR logistics coincided with a 10% decrease in 30-day mortality as compared to historical conditions. Separate analysis moreover showed that every minute of delay between MTP activation and administration of blood products gave a 5% odds increase in mortality\(^{(33)}\).

While in PROPPR\(^{(33)}\) pre-thawed plasma was shipped, standard presence of thawed plasma at the emergency department can also speed up its availability\(^{(34)}\). Longer term pre-thawing, however, will lead to gradual loss of coagulation capacity, an additional risk for bacterial contamination and more plasma expiration and thus net use. The inventory could in this respect become threatened especially if -to avoid minor ABO incompatibility-, we only consider the rare AB plasma for MTP. An interesting study in this respect showed that patients with blood groups B and AB receiving minor incompatible A plasma, experienced no increase in morbidity or mortality as compared to patients receiving only ABO compatible AB plasma. While, hemolysis so far has not been actively screened for\(^{(36, 37)}\), pooled pathogen reduced plasma products with averaged antibody titers, might also reduce this seemingly acceptable risk of minor incompatibility. Maximal reduction of death by exsanguination, might further be obtained by pre-hospital or remote DMR\(^{(39)}\) with (O negative) RBC units and pre-thawed or even lyophilized plasma. In this respect, pre-hospital use of thawed plasma in the so called PAMP trial indeed resulted in decreased 30-day mortality as compared to standard care\(^{(39)}\). Similar trials will soon show if this is reproducible\(^{(40, 41)}\). Lyophilized plasma furthermore can be stored at room temperature and is reconstituted in approximately 6 minutes. Randomized against frozen plasma (FFP), lyophilized plasma (FLyP) in this respect already confirmed its potential for much faster administration\(^{(35)}\). Although other blood product’s use, and 30-day mortality were not significantly reduced in this more limited size trial, both again showed favorable trends\(^{(42)}\).

**Near future objectives**

Arranging fast implementation of effective MTP in hospitals should be our first aim\(^{(43)}\). In this respect, in the period 2009-2011 only 2% of UK trauma patients were found to receive plasma and RBCs in >= 1:2 ratios\(^{(44)}\) and even in PROMMTT centers, 70% of patients did not get 1:1 ratios within one hour\(^{(45)}\). Presence of thawed or lyophilized A or AB plasma not only at the institution’s blood bank but at the emergency ward will help in this respect\(^{(36, 37)}\). The benefit of platelet transfusions in initial MTP is still to be determined. To specifically stop bleeding, cold stored platelets could be superior and should be studied as well\(^{(45, 46)}\). However, all mentioned measures to reduce mortality from exsanguination, involve the entire transfusion chain. Only empowered multidisciplinary hospital oversight will be able to ensure their eventual success.

**Take home messages:**

- Bleeding patients at risk for death by exsanguination can be identified with simple but repeated scoring algorithms as basis for fast initiation of MTP.
- To preserve the hemostatic capacity in MBL, limiting dilution and fast addition of plasma in equal ratios with RBC are advised; in trauma patients this
will improve acute survival.

- Availability of lyophilized or thawed plasma at the emergency ward or even pre-hospital, will significantly speed up such MTP with proper plasma vs RBC ratios.

- Administration of fibrinogen with or without concentrated coagulation factors (fibrinogen) most preferably based on point of care (TEG/ROTEM) assays could be of benefit when significant ACoT and/or non-plasma induced dilution of the hemostatic capacity is present.

**Conflicts of interest**

The author has received speaker fees from Vifor pharma, Novartis, Amgen and served as temporarily scientific advisor for Bioverativ. He is furthermore employed by and received research grants of Sanquin the Dutch blood supply organization. These activities have no direct relation with and thus have not influenced the content of this article whatsoever.

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