Massive bleeding - Section 2

Transfusion in patients with massive blood loss: Evidence when, for whom and what products are best

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Take Home Messages
- Bleeding patients at risk for death by exsanguination should promptly be identified with simple scoring systems.
- To preserve the hemostatic capacity in massive bleeding, fast addition of plasma or fibrinogen and platelets in equal ratios with PRBC is advised; in trauma this will moreover improve acute survival.
- Additional administration of concentrated coagulation or factors (fibrinogen) should be considered when significant ACoT and/or non-plasma fluid induced dilution of the hemostatic capacity is suspected.

Introduction

Massive blood loss (MBL) requires an immediate response to stop the bleeding and optimization of hemodynamics by so-called damage control resuscitation (DCR) protocols. However, the additional presence of and compliance to massive blood transfusion protocols (MBTP) ensuring the fastest possible availability of blood products also influence mortality. Validated clinical scoring systems identify the patients that progress to massive blood transfusion (MBT). For trauma patients in particular, a subsequent and timely switch from dilution with intravenous fluids, to evidence-based ratios of fresh frozen plasma (FFP), platelet concentrates (PC) and packet red blood cells (PRBC) is critical. Of particular importance in bleeding, PRBC optimize blood platelet dependent primary hemostasis while plasma derived coagulation factors enforce the hemostatic plug. The presented evidence about whom, what (ratio of) blood products, with what timing are most effective in patients with MBL is of clear relevance. Indeed, for trauma patients, MBL still accounts for 30-40% of early (within 3 hours) deaths. In postpartum hemorrhage (3-8% of all deliveries) MBL accounts for almost 1/5 of maternal deaths.

What blood product (ratios) to transfuse?

Both in trauma and in non-trauma patients with MBL, administration of more or less large amounts of intravenous fluids together with only PRBC is initiated. Although safeguarding hemodynamics, this strategy dilutes the hemostatic potential with deficient hemostatic control and inferior outcome. Additionally, even in the absence of Acute Coagulopathy of Trauma (ACoT), colloid fluids increase fibrinolysis, impair platelet function, fibrin polymerization and lower von Willebrand factor (VWF) levels. While both retrospective and prospective cohort studies like PROMMTT already showed that DCR incorporating FFP, PC and PRBC in ratios of 1:1:1 or 1:1:2 improved short (6-24 hrs) and longer (30 days) term survival with a decrease in overall need for blood products, aRCT derived proof had to be awaited. In the landmark PROPPR trial, 680 of 11000 on ABC scores screened patients were randomized between somewhat more restricted FFP:PC vs PRBC use in a 1:1:2 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 1:1:1 group. The added hemostatic potential, measured as platelet numbers and clotting factors, however, is not very different between the 1:1:1 versus the 1:1:2 ratio. In less hemostatically defective patients these small differences between 1:1:1 and 1:1:2 ratios might be less important. Indeed, a retrospective study in predominantly non-trauma patients indeed found no different FFP:PRBC ratios between 30 days survivors and non-survivors. Notwithstanding the fact that 1:1:1 FFP, PC, PRBC...
How to manage an early start of blood products?

With near perfect logistics as implemented in the PROPPR study, median times of protocol activation and arrival of blood products can be reduced to less than 10 min. Although the 2 study arms did not differ, versus historical conditions, the PROPPR logistics coincided with a 10% decrease in 30-day mortality. Separate analysis moreover showed that every minute of delay between MTP activation and administration of blood products gave a 5% odd increase in mortality.24 While in PROPPR prethawed FFP was shipped, standard presence of thawed FFP at the emergency areas might further reduce mortality.25 Pre-thawing, however, will lead to some loss of coagulation capacity and additional risk for bacterial contamination. The inventory could become threatened especially if, to avoid minor ABO incompatibility, we only consider the rare AB-FFP for MTBP. An interesting study in this respect showed that patients with blood groups B and AB receiving minor incompatible A-FFP, experienced no significant increase in morbidity or mortality as compared to patients receiving only ABO compatible FFP. Although, hemolysis was not actively screened for,26 pooled pathogen reduced FFP products with averaged antibody titers, might even reduce this seemingly acceptable risk of minor incompatibility. Maximal reduction of death by MBL can further be obtained by pre-hospital or remote DMR27 for which (O negative) PRBC units and AB plasma can be considered. In this so-called Pre-Hospital Blood, however, Product (PHBP) administration, lyophilized plasma (FLyP)28 allows ABO compatibility at all time. Moreover, it can be stored at room temperature and is reconstituted in approximately 6 min. Randomized against FFP, FLyP in this respect enabled much faster administration. In the coming years, many new and ongoing studies29,30 will show the cost-benefit analyses for PHBP administration.

Future perspectives

Notwithstanding the latter future possibilities, proper in hospital logistics are far from being implemented. In this respect, only 2% of UK trauma patients received plasma and RBCs in >=1:2 ratios31 and in PROMMTT centers geared up to deliver 1:1:1 ratios, even for FFP this was not achieved in 70% of cases within one hour.3 Therefore, our first focus should be in hospital identification of patients at risk for massive transfusion together with as early as possible administration of prethawed FFP or FLyP and PC together with O-negative PRBC in equal ratios. Multidisciplinary hospital oversight groups are needed to ensure the best management of patients with MBL/MBT.

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