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Resuscitative adjuncts and alternative products when blood supplies are limited

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There are several scenarios where blood product availability may be limited. Due to the short half-life of platelets, most rural hospitals do not have them available, and the amount of red blood cell and plasma products may also be limited with one massive transfusion depleting the entire blood bank. It is estimated that during the COVID-19 pandemic, there was an almost 20% decline in available donors across the USA severely limiting blood product availability. A survey performed across 51 US institutions revealed that 92% experienced a red blood cell shortage and 84% experienced shortages of platelets (figure 1).[1] Battlefield scenarios requiring prolonged field care also require innovative blood product replacement strategies. Although blood conservation strategies can partially mitigate these challenges, alternatives and adjuncts that limit the need for blood products are strongly needed. This article will focus on factor concentrates, lyophilized plasma, tranexamic acid (TXA), and novel platelet solutions.

Prothrombin complex concentrate (PCC) is Food and Drug Administration (FDA)-approved for urgent reversal of Coumadin in bleeding patients and those who require emergency procedures. It is a concentrate made from the plasma of thousands of people, and it contains a balance of vitamin K-dependent coagulation factors as well as anticoagulant proteins, including proteins C and S and anti-thrombin III. A typical dose is 25–50 units/kg, and it has also been used to reverse the direct thrombin inhibitors and anti-Xa inhibitors. In a prospective randomized trial comparing PCC to plasma in bleeding patients and patients needing emergent procedures, 70% of patients receiving PCC achieved a normalized international normalized ratio (INR) within 1 hour, whereas only 60% of patients in the plasma group achieved a normal INR at 12 hours.[2] Although PCC is approved only for patients taking Coumadin, it has also been used in the general trauma population. Zeeshan performed a 2-year propensity score-matched retrospective analysis of the Trauma Quality Improvement Project (TQIP) in 486 patients who sustained trauma (trauma patients), half of whom received plasma alone and the other half received plasma and PCC.[3] This study revealed a reduction in red blood cell (RBC) and plasma use as well as a reduction in hospital mortality, acute kidney injury rates and acute respiratory distress syndrome rates without increases in deep vein thrombosis or pulmonary embolus in patients receiving PCC.[3]

Fibrinogen concentrate is a lyophilized powder stored at room temperature. It is rapidly reconstituted in water at a concentration of around 1 g in 50 mL, which is very similar to the amount of fibrinogen found in cryoprecipitate pools. For comparison, plasma contains about 2.5 g of fibrinogen in 1 L. Fibrinogen concentrate is inactivated by pasteurization and additional purification removes antigens and antibodies decreasing the risk of adverse reactions. The RETIC trial was a single-center randomized trial comparing 15 mL/kg of plasma to 50 mg/kg of fibrinogen concentrate in trauma patients with abnormal rotational thromboelastometry (ROTEM) values.[4] After treatment, the ROTEM was repeated, and patients were redosed within their treatment arm. If the ROTEM still did not correct, crossover salvage occurred. The trial was stopped early because the plasma group required more frequent dosing and salvage. Coagulopathy was much more likely to be corrected after one or two doses of fibrinogen concentrate compared with plasma.

Ditillo *et al* performed a 2-year retrospective review of the TQIP evaluating trauma patients who received four or more units of RBCs.[5] The authors compared patients who received cryoprecipitate to those who did not. On multivariable logistic regression analysis both 24-hour and in-hospital mortality were lower in patients who received cryoprecipitate. Fibrinogen concentrate is approved for use in the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

There is a longstanding practice in parts of Europe of using factor concentrates like PCC and fibrinogen concentrate in place of blood products utilizing ROTEM variables as a guide for administration. Schöchl published their experience of using the FIBTEM maximum clot firmness to guide fibrinogen and platelet administration and the EXTEM clotting time to guide PCC administration.[6] Utilizing this technique, the majority of patients were successfully treated with RBCs, fibrinogen concentrate and PCC and many less required plasma and platelets (figure 2).[6] In this retrospective review, patients treated primarily with concentrates achieved an observed mortality lower than predicted by standardized scoring systems.[6]

Dried plasma is another possible strategy that can be used to make plasma available in austere conditions or if supplies are exhausted in the hospital setting. Lyophilized plasma was used by the US military as a primary resuscitation product during World War II (WWII).[7] The product was a multi-donor product, and donors were not screened for infectious diseases. It was common for recipients to

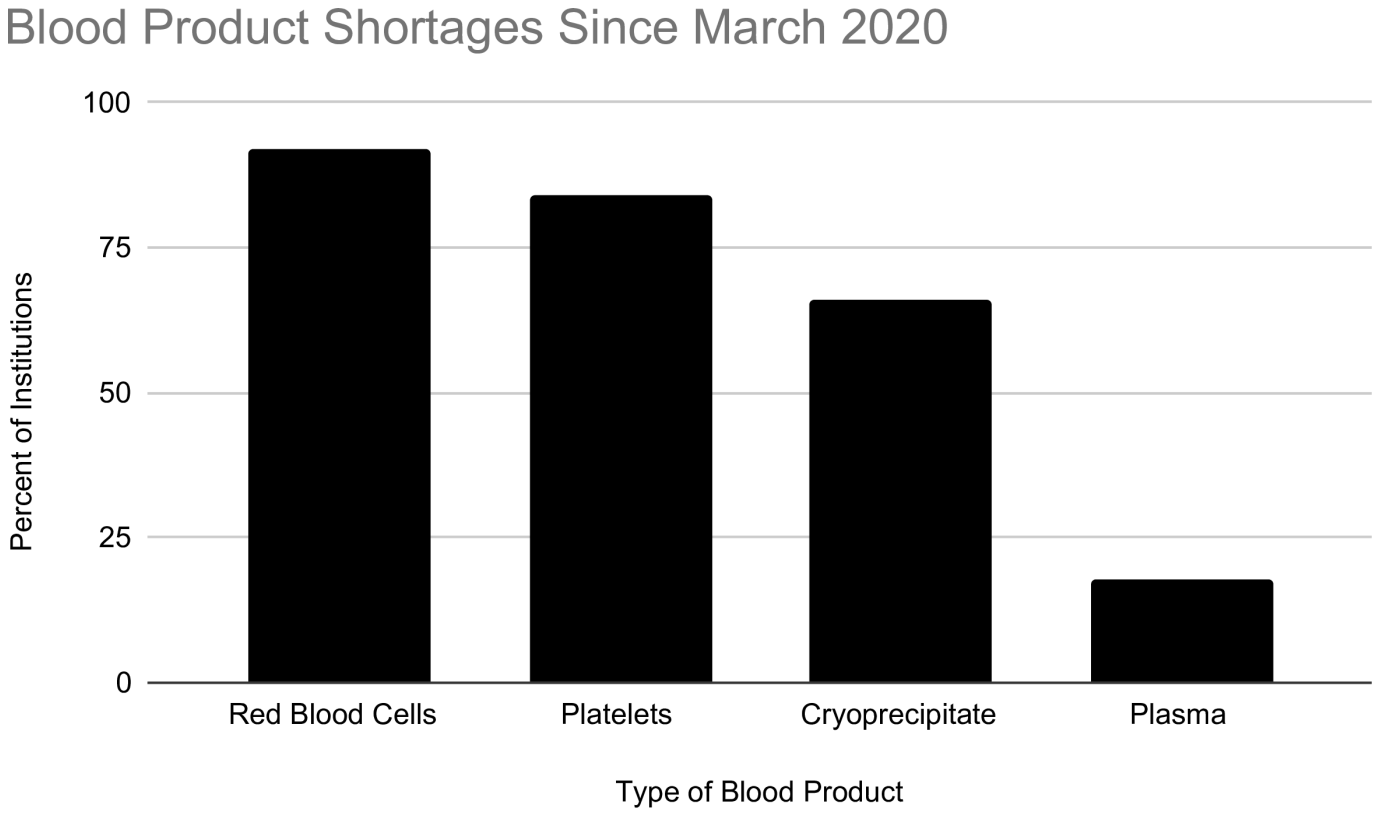

Figure 1 Percentages of shortages by blood product at 41 US institutions during COVID.

develop hepatitis, so lyophilized plasma has not been used in the USA since WWII. In general, dried plasma is logistically superior to other plasma products because it can be stored in powder form at room temperature for over 1 year. German LyoPlas is a single donor product requiring blood type compatibility. It can be stored for up to 15 months. The product is used routinely in Germany and has been given to hundreds of thousands of recipients with a complication rate similar to standard plasma.

A single unit of the French lyophilized plasma (FLyP) comes from up to 11 donors. This product is pathogen reduced to avoid infectious risks, and it can be stored for up to 24 months. It is used via Institutional Review Board (IRB) protocol by US special forces combat medics in austere conditions. It has been transfused to thousands of patients without adverse events. Garrigue *et al* performed an open-label randomized trial comparing 4 units of fresh frozen plasma (FFP) to 4 units of FLyP in trauma patients with trauma-induced coagulopathy.[8] They found that FLyP could be transfused earlier than FFP and resulted in a higher fibrinogen concentration than FFP 45 min after randomization. Dried plasma products are being used around the world, including in Africa and the Middle East. There are several companies in the USA that are producing these dried plasma products, but none have an FDA indication yet.

Tranexamic Acid (TXA) is being used with increasing frequency as an adjunct to blood products in bleeding patients. The STAAMP trial was a prospective, randomized multicenter trial that enrolled 927 patients with hypotensive trauma.[9] Patients were randomized to 1 g of TXA in the field versus a placebo. After arrival to the hospital, patients were further randomized to no additional TXA, 1 g over 8 hours, or a 1 g bolus and a 1 g infusion. Multivariate analysis revealed a survival advantage in patients who received TXA less than or equal to 1 hour after injury and in patients with a systolic blood pressure <70 mm Hg. There was no difference in blood product requirement, and patients receiving TXA did not have increased complications rates, including thromboembolic complications. TXA is FDA-approved for menorrhagia and short-term prophylaxis in patients with hemophilia in the setting of tooth extraction or menorrhagia.

	Total Administered Until Arrival at ICU		Total Administered During 24 Hours After Admission to the ER	
	Number of Patients Treated	*Dose*	*Number of Patients Treated*	*Dose*
Fibrinogen Concentrate (grams)	123	6 (4,9)	128	7 (5,11)
PCC (units)	83	1800 (1650, 3100)	101	2400 (1800, 3600)
FFP (units)	6	10 (7,10)	12	10 (9.75, 11.25)
PC (units)	22	2 (1,2)	29	2 (2,3)
RBC (units)	125	6 (4,10)	131	10 (6,13)

Figure 2 Number of trauma patients requiring Fibrinogen concentrate, PCC, plasma, platelets and RBCs guided by ROTEM on arrival to ICU and at 24 hours after admission. ER, emergency room; FFP, fresh frozen plasma; ICU, intensive care unit; PCC, prothrombin complex concentrate; RBC, red blood cell.

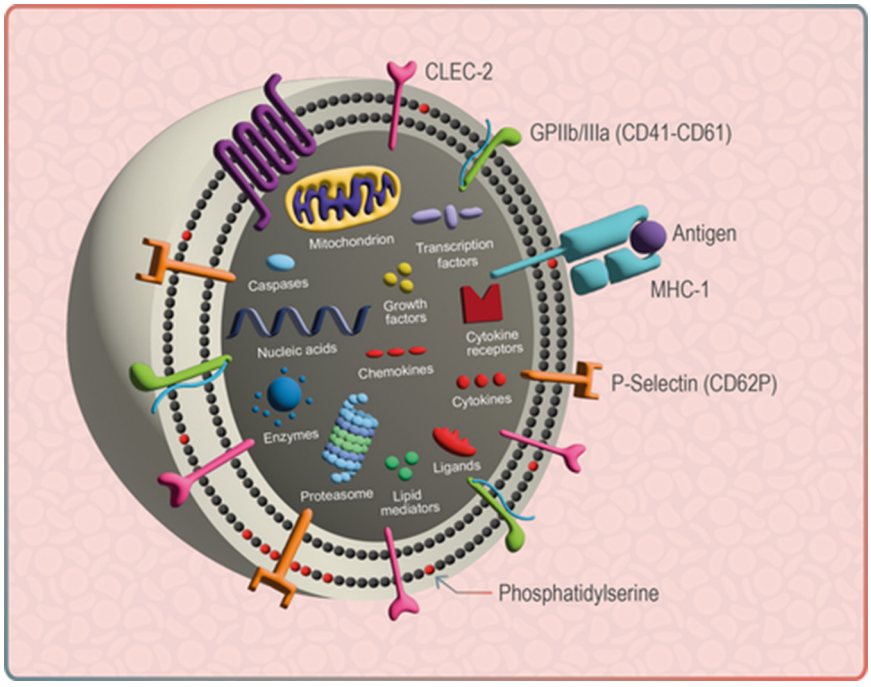

Figure 3 Diagram showing receptors expressed on the surface of platelet extracellular vesicles.

The most problematic blood component in rural and austere conditions is platelets. Platelets are stored at room temperature with a shelf-life of 5 days. They are not available in most rural hospitals, and their availability rapidly becomes limited during shortages. Novel solutions for platelet products that can be stored for prolonged periods are being developed. Thrombosomes are freeze-dried group O platelets. They are stable for 3 years at room temperature, and they are pooled from up to 10 donors. They are heat treated for viral infections and cultured prior to use for bacteria. They are rehydrated in 100 cc of sterile water, and there are ongoing studies on human subjects. Theoretical benefits of thrombosomes include that they can be stockpiled in large quantities, pooled donors reduce variability, and the platelets are fully activated when reconstituted. Since they are reconstituted as needed, there should be minimal to no waste. Thrombosomes were granted orphan drug designation by the FDA in 2020 for the treatment of acute radiation syndrome. They do not yet have FDA approval for use in humans. Platelet extracellular vesicles (PEVs) are particles secreted from platelets. They express surface receptors to include procoagulant GPIIb/IIIa, tissue factor and P-selectin (figure 3). PEVs range in size from 10 to 1000 nm and they have a prolonged shelf-life in a broad range of temperatures. They are rehydrated in 10 cc of sterile water. PEVs have shown improved survival in rat models of hemorrhagic shock.[10] PEVs do not have an FDA indication and have not been studied in humans.

Traditional therapies for traumatic blood loss have focused on controlling hemorrhage, fluid resuscitation, and blood products. This includes a variety of fluids as well as aiming to replace blood volume in a 1:1:1 ratio of red blood cells, platelets, and plasma in addition to the newer previously mentioned blood product adjuncts. However, novel studies such as the AVERT trial are attempting to change this dogma with the addition of the use of vasopressin in initial trauma resuscitations.[11] Arginine vasopressin (AVP) is released rapidly during hemorrhage or hypotension, but the secretion diminishes over time. It acts as a vasoconstrictor, shunts blood to the heart and brain preferentially, and has been theorized to improve platelet function. The AVERT trial found that the supplementation of AVP decreased the need for blood products in resuscitation when compared with traditional volume-focused resuscitation.[11] This double-blinded randomized trial had very promising results that AVP administration resulted in not only decreased blood product administration, but resulted in no difference in complications (other than decreased deep vein thrombosis in the AVP group) or overall mortality. This is timely given the need for novel resuscitation interventions given our continued limited blood supply and ever-evolving understanding of trauma physiology.

CONCLUSIONS

Many novel solutions are being developed to mitigate blood shortages and to provide equivalent hemostasis and resuscitation when standard blood products are not available. For the most part these solutions involve powdered products that can be stored at room temperature for over a year. The ultimate solution may be the equivalent of whole blood on the shelf that simply needs to be reconstituted. Based on the current level of technology, the most limiting factor is the development of an oxygen carrier because a practical replacement for red blood cells has not been found to date.

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