Fresh frozen plasma, cryoprecipitate and platelets: Evidence and risks

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Administration of fresh frozen plasma (FFP) in trauma patients has historic origin. With the introduction of synthetic colloids, indication for FFP switched from fluid therapy to prophylaxis for bleeding, therapy for coagulation disorders and improving pathological coagulation status. With the introduction of coagulation factor concentrates, indication for FFP could be further restricted to rare specific clinical situations: We really need plasma for transfusion or plasma exchange in trauma patients with hereditary deficiency in coagulation factor V, in factor XI or in vWF:CP (synonym: ADAMTS13) in order to maintain haemostatically effective factor levels of at least 15–20%, because for these deficiencies no licensed concentrates are available yet for substitution [1]. Plasma exchange in thrombotic thrombocytopenic purpura (TTP) and adult haemolytic uraemic syndrome (HUS) is another 1A-indication for plasma [1]. In trauma patients with liver dysfunction, plasma could be transfused when PT is <50% and major bleeding occurs (grade 2C) [1]. Other congenital coagulopathies are principally treated with coagulation factor concentrates e.g. haemophilia A is treated with factor VIII concentrates, also in the trauma situation. The effect of oral anticoagulants or of a severe vitamin K deficiency is recommended to be reversed rapidly by administration of prothrombin complex concentrates (PCC) [1,2]. If in such emergencies no concentrates are available in the hospital, FFP could be considered as an alternative but with lower efficacy compared to factor concentrates. The question however, is do we really need FFP for these rare indications or should other virus-inactivated preparations such as solvent-detergent (SD) plasma be preferred.

Austrian experience shows that it is feasible to run a level-1 trauma unit without FFP [3]. Most important, use of an early goal-directed TheraNostic approach (with point-of-care coagulation monitoring and physiology-driven use of potent coagulation factor concentrates) with avoidance of FFP improved trauma patient survival [3]. Early correction of bleeding may indeed be the explanation for outcome improvements. This cannot be achieved with FFP in clinical practice because of a logistic delay of 35 - 45 mins. due to ABO-identical FFP request from the blood bank/depot, thawing and warming (using licensed equipment) of FFP stored in suitable freezers and infusion of large quantities through a filter of a pore size of 170–230 µm. Accordingly, the Austria task force on Peri-operative Coagulation recommended the use of factor concentrate as a first choice, because this permits quick, effective and physiology-driven correction of relevant deficiencies in trauma-related massive bleeding [2].

Despite the short list of rare indications for FFP, the recommendations and the observed survival benefit of the factor concentrate-based coagulation management, FFP administration is still standard practice in many hospitals as prophylaxis and therapy for plasma clotting disorders in trauma-related bleeding. One myth encouraging the use of FFP is the perception that overt trauma-induced coagulopathy with microvascular bleeding can be corrected by FFP dilution. FFP is an 8.5% protein solution, the main components being water, albumin (40 - 50 g/l) and other plasma proteins, while the concentration of fibrinogen (2 - 4 g/l) and other coagulation factors is physiologically low and varies considerably (0.6 - 1.4 IU/ml) depending on the original

concentration in the particular blood donors. Evidence-based medicine shows that there is no proof for the efficacy of FFP in reversing clinically relevant clotting disorders and reducing blood loss [2,4]. If control of the efficacy of FFP transfusion by laboratory analyses would be done routinely, the misuse of 2-4 bags of FFP would be abandoned shortly. In massive bleeding >100% of blood volume when massive amounts of volume replacement fluids and plasma-poor red blood cell concentrates (RBC) have been infused, a haemostatically significant drop in the fibrinogen level to <1.5 g/L and prothrombin time values <50% with diffuse microvascular bleeding can be anticipated. In this situation, high doses of 20-30 ml/kg body weight of plasma are required for the treatment of coagulopathy [2]. Retrospective observational studies suggest that a high transfusion ratio of FFP: RBC of about 1:1 is able to improve mortality in severely injured and massively bleeding patients as compared to a low infusion rate of FFP [5,6]. The therapeutic choice of 1:1 mostly used in the US may be, at least in part, be explained by the fact that factor concentrates have not been available until recently. Although there is a considerable survival bias in these retrospective studies [7], the observation indeed supports the concept that high doses of plasma are required to substitute for acquired coagulation factor deficiencies.

It is a myth that FFP is safe with regard to triggering thromboembolic events as FFP contains all coagulation activators and inhibitors. However, such incidences have indeed been reported. Furthermore, plasma transfusion has considerable disadvantages such as citrate overload (leading to reduced myocardial function, arrhythmias, increased neuromuscular excitability), transfusion-related infections, immunomodulation (TRIM), volume overload (TACO) and acute lung injury (TRALI), the most frequent lethal side-effect of transfusion [8,9]. The latter complication can be avoided by the use of SD plasma (Octaplas®). Noteworthy, SD plasma, lyophilized human plasma and methylene-blue-photo inactivated plasma have lower coagulation factor levels (fibrinogen levels by 20-35%). Rapid transfusion of FFP during massive transfusion may aggravate hypothermia and may cause adverse events in patients with chronic cold agglutinin disease, high titres of cold antibodies. Preterm infants to adult patient may develop vasospasms when given chilled blood products. FFP is contraindicated in patients with plasma intolerance and confirmed IgA deficiency (prevalence 1:650).

It is a myth that coagulation therapy with FFP is cheaper compared with factor concentrates. True costs of allogeneic blood products and costs for transfusion-related complications from the societal perspective needs to be considered (costs of fear, ignorance, illness and damage) [10,11].

High-molecular weight plasma proteins precipitate upon slow thawing of FFP. This fraction is called cryoprecipitate and contains coagulation factor VIII, fibrinogen, fibronectin, von Willebrand factor, Factor XIII and other plasma proteins. Accordingly, cryoprecipitate shares the same problems concerning patient safety and contraindications as FFP [12]. Concerning efficacy, cryoprecipitate is less effective than fibrinogen concentrate in acquired fibrinogen deficiency [13]. The availability of cryoprecipitate in Europe is limited and in the light of alternatives with a favourable risk-benefit ratio there is no demand for this non-virus-inactivated labile allogeneic product with variable factor content.

Platelet concentrates (PC) can be prepared from pooled blood of 4-6 donations or by apheresis. PCs contain 200-400x10^9 in 200-350 ml of plasma or plasma replacement fluid. According to good manufacturing practice there are less than 3x10^9 red cells and less than 1x10^6 leucocytes per unit. According to the storage temperature at 22°C maximum storage time is 5 days and recovery rate of platelet count is around 65%. Indication for PCs is prophylaxis and correction of platelet-dependent bleeding with a target range of platelet count being dependent upon co-morbidities and bleeding symptoms [1]. In case of severe bleeding a PC-transfu-

sion trigger of 50-100 G/l has been recommended (grade 2C) (1, TIC).

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