

PLASMA PRODUCTS IN CRITICAL CARE MEDICINE

Paul F. W. Strengers

Introduction

Plasma from blood donors is the source for the preparation of a number of medicinal products, with a wide range of clinical indications. The purification and concentration of human proteins out of plasma started with the work of Dr. Edwin Cohn during the Second World War at Harvard University in Boston, USA. Dr. Cohn aiming for the preparation of albumin solutions for the treatment of severe blood losses of soldiers on the battlefields, developed a fractionation process of plasma by using differences in concentration of added alcohol, temperature and ion strength. This work resulted ultimately in the recovery and production of several proteins, like albumin, immunoglobulins, and serine proteases, and this fractionation process is still be used, sometimes in a adapted form. Another important discovery was made by Dr. Judith Pool at UCLA in San Francisco, who in 1968 by accident found a high concentration of coagulation factor VIII in a precipitation, which had been formed after thawing of frozen plasma. This discovery has led to the development of clotting factor concentrates like cryoprecipitate, factor VIII concentrate, factor IX concentrate, prothrombin complex concentrate in different purities and concentrations.

Plasma products are medicinal products and the production and specification have to comply with national and international directives and guidelines. In Europe, the Council of Europe, and the Committee for Proprietary Medicinal Products of the European Commission have issued Guidelines, Directives and Notes for Guidance to safeguard the quality and safety of these products. These rules apply for the whole chain from donor to recipient.

Safety

Blood, as human body material is rich with proteins. However, it may also contain viruses, bacteria, parasites and other microorganisms, which may harm the recipient of the product. To prevent the transmission of blood-borne microorganisms, mainly viruses, strict procedures are introduced. This implies the use of voluntary, non-remunerated donors, careful selection of donors to exclude donation from risk populations, screening of each donation on blood-borne viruses like HIV, HBV, HCV and others with serological and microbiological techniques, screening of plasma pools, validated viro-inactivating and/or viro-reducing procedures in the production process, the adherence to current good manufacturing practices, and pharmacovigilance (1). The result of these activities in order to bring the risk on transmission to a minimum and for some viruses to almost zero has unfortunately not only increased the price of these products but also endangered the supply. For example, the measures to prevent the theoretical risk of transmission of the agent (prion) of Transmissible Spongiforme Encephalopathies (TSE) and mainly of variant Creutzfeldt Jakob Disease (vCJD) has had a significant effect on the supply of intravenous immunoglobulin in the world, due to recalls of final products from donations of anamnestic CJD-positive donors.

Albumin

Over decades, the intravenous administration of human albumin found wide acceptance as the therapy not only for hypovolemia, but also in the treatment of severe burns, hypoalbuminemia, and ascites (2). The clinical rationale for the broad applica-

tions of albumin solutions is the restoration of deficits of a normal and rather important constituent of the human body. The main functions of albumin are first to maintain the colloid-osmotic pressure, second to transport substances such as bilirubin, metals, ions, enzymes, amino acids, hormones, free fatty acids and drugs, and third to deactivate reactive oxygen species.

The therapeutic indications of 4.5% albumin are:

1. acute blood volume loss,
2. Treatment of severe burns after the first 24 h (when saline is normally administered), 4.5 % albumin solution can be used to maintain plasma albumin near 25 g/l and a colloid osmotic pressure above 20 mmHg.
3. As an exchange fluid in therapeutic plasmapheresis.
4. In patients in which severe acute albumin losses are sustained e.g. small bowel infarction and acute pancreatitis.

The exact requirement depends on the size of the patient, the severity of trauma and on continuing losses. Particularly careful monitoring is required in the very young, very old and in patients with limited cardiac reserves. Contraindications include all conditions in which hypervolemia and its consequences, or haemodilution could represent a special risk for the patient. Examples are:

- Decompensated cardiac insufficiency
- Hypertension
- Oesophageal varices
- Pulmonary oedema
- Haemorrhagic diathesis
- Severe anaemia
- Renal and post-renal anuria

The therapeutic indications of 20% albumin are:

1. The short-term management of hypoproteinaemic patients in whom there is extravascular fluid overload and resistance to diuretics, particularly in nephrotic syndrome.
2. Patients with ascites and peripheral oedema due to hepatic failure and in whom there are a resistance to diuretic therapy.
3. The clinical management of burns in situations where plasma volume expansion is required, but it is also necessary to limit salt and water intake.

Fresh Frozen Plasma

Fresh Frozen Plasma or FFP is by many specialists in transfusion medicine considered as a blood component and not specifically as a plasma product, because it is prepared of a single unit of blood. However, the large scale production of viral inactivated FFP (SD-treated FFP) out of pools of many plasma units of one blood group have given this product an intermediate status. Fresh Frozen Plasma contains all of the coagulation factors. It can be used for patients who have had massive transfusions or patients undergoing plasma exchange.

The therapeutic indications of Fresh frozen Plasma are:

1. Bleeding, or emerging bleeding, together with combined coagulation factor deficiencies due to:
 - Dilution with crystalloids and or colloids during massive transfusions,
 - Severe hepatic failure.

For both indications, a precise laboratory diagnosis must show the coagulation factor deficiency.

2. Complex deficiencies of coagulation factors such as consumption coagulopathy (DIC), coagulopathy due to severe hepatic failure and massive transfusion or repeated large volume plasma exchange.

3. Isolated coagulation factor V deficiency.
4. Treatment of Thrombotic Thrombocytopenic Purpura (TTP).
5. Rapid reversal of the effect of fibrinolytics (rec.tissue plasminogen activator, streptokinase, urokinase).

The dosage depends on the clinical condition of the patient and the concentration of the coagulation factors in the plasma. In general, the plasma levels of these factors should be lower >30% of normal values. Administration of FFP must be based on ABO-blood group compatibility. In emergency cases, FFP blood group AB can be regarded as universal plasma since it can be given to all patients.

Cryoprecipitate

For patients with specific coagulopathies and high volumes of plasma are limiting, concentrates such as cryoprecipitate or specific coagulation concentrates of individual coagulation factors are preferred.

The therapeutic indications of cryoprecipitate are:

1. Treatment of bleeding in patients with hypofibrinogenemia.
2. Treatment of bleeding in Von Willebrand's disease, or haemophilia A.
3. Treatment of refractory bleeding in uraemia.
4. Preparation of surgical adhesive.

In patients who are bleeding, the coagulation laboratory should be used to demonstrate laboratory evidence of a coagulopathy, so specific therapy can be ordered and appropriate blood components can be selected.

Prothrombin Complex Concentrate (PCC)

Over the last decade there has been a dramatic increase in the use of oral anticoagulants (3). This is primarily as a result of the demonstration of their benefit in atrial fibrillation. Unfortunately, many studies have reported the risks of haemorrhage in patients on oral anticoagulants and have investigated the factors associated with an increased bleeding risk. In critical care medicine more and more patients are admitted to the Critical Care Unit (CCU) with a fatal, major or minor bleeding due to relative over-anticoagulation. Particularly in major and life-threatening anti-coagulant bleeding, the deficient clotting factors II, VII, IX and X should be replaced as quickly as possible. This can be achieved using Fresh Frozen Plasma (FFP) or prothrombin complex concentrate. The advantages and disadvantages of these products are compared in the following table:

Table. Comparison of FFP and PCC

Table.	Comparison of FFP and PCC	
	FFP	PCC
Volume	large	small
Availability	widespread	limited
Administration speed	slow	fast
Viral inactivated	only FFP-SD	yes
Pooled product	only FFP-SD	yes
Blood group	group specific	not group specific
Thrombogenicity	no	yes

Based on the above presented Table, PCC, if available, should be used in this indications, because the concentrations of the coagulation factors II, VII, IX, and X to be replaced is much higher in PCC than in FFP, resulting in a reversal of the anti-coagulant bleeding more quickly.

Intravenous Immunoglobulin (IVIG)

The anti-inflammatory effect of Intravenous Immunoglobulin (IVIG) has been shown in Kawasaki's disease, an idiopathic syndrome resembling toxic shock syndrome, and juvenile arthritis (4). In several randomised controlled trials, polyclonal Intravenous Immunoglobulin has been proven to be effective in the treatment of sepsis and septic shock but these findings could not be shown in other studies. IVIG seems to be more effective compared to anti-endotoxin antibodies or anti-cytokines. The product seems to be effective in both Gram-negative as Gram-positive shock, especially as the last has been caused by exotoxin producing *Streptococcus* sp. In the most recent analysis of the Cochrane Library, IVIG seems to decrease the mortality, but prospective confirmation of this finding seems to be necessary (5). Although the working mechanism is not known, the effect of IVIG may be explained inter alia by the ability to modulate the production of cytokines and cytokine antagonists and to decrease the levels of superantigens.

Other products

Recently important studies have been published regarding other less frequently used plasma products, like C I-esterase inhibitor, in sepsis and septic shock. The results of these studies have to be confirmed. Antithrombin, a natural anticoagulant that plays a pivotal role in coagulation homeostasis by inhibiting thrombin and factor Xa and to a lesser extent factor IXa and factor Xia, was considered to have potent anti-inflammatory properties. In animal models of sepsis, the product showed to be protective. Unfortunately, in large randomised clinical trials in humans, this effect could not be found (6).

Conclusion

Several plasma products play an important role in the treatment of patients in critical care medicine. In many studies, the effect and the monitoring of treatment show that these products should be given appropriately, when clearly indicated and aiming for optimal patient care. Transfusion medicine specialists can play an important role in the appropriate management of critically ill patients by consulting with clinicians about the proposed use of some of the specialised blood products that may not be routinely available or that are used infrequently.

References

1. Morgenthaler J-J. Securing viral safety for plasma derivatives. *Transf. Med. Rev.* 2001, 15,3:224-333.
2. Bell E. The dud cigar? - Cochrane collaboration and the saga of human albumin. *Adverse Drug React. Toxicol. Rev.* 1999, 18(3), 149-163.
3. Makris M., Watson HG. The management of coumarin-induced over-anticoagulation. *British J. Haematol.* 2001, 114:271-280.
4. Kazatchkine MD, Kaveri S.V. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001, 345, 10:747-755.
5. Alejandria MM, et al., Intravenous immunoglobulin for treating sepsis and septic shock. Updated Version 2, Oxford, The Cochrane Library; 2001.
6. White B, Perry D. Acquired antithrombin deficiency in sepsis. *British J Haematol.* 2001, 112:26-31.