

Solvent/detergent plasma: pharmaceutical characteristics and clinical experience

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Abstract The solvent/detergent treatment is an established virus inactivation technology that has been industrially applied for manufacturing plasma derived medicinal products for almost 30 years. Solvent/detergent plasma is a pharmaceutical product with standardised content of clotting factors, devoid of antibodies implicated in transfusion-related acute lung injury pathogenesis, and with a very high level of decontamination from transfusion-transmissible infectious agents. Many clinical studies have confirmed its safety and efficacy in the setting of congenital as well as acquired bleeding disorders. This narrative review will focus on the pharmaceutical characteristics of solvent/detergent plasma and the clinical experience with this blood product.

Keywords Viral inactivation · Solvent detergent plasma · Fresh frozen plasma · Transfusion-related acute lung injury · Clinical efficacy · Cost-effectiveness

Introduction

The solvent/detergent (S/D) pathogen inactivation method was developed in the early eighties for the inactivation of enveloped viruses in plasma-derived medicinal products [1, 2]. Actually, this technique turned out to be a tool capable

of damaging the membrane of lipid-enveloped viruses, cells and the majority of protozoa without harming the labile coagulation factors V and VIII. On the contrary, the S/D method does not have any effect on non-enveloped viruses.

Currently, S/D treatment for pathogen reduction of plasma for transfusion and plasma-derived medicinal products is the most common, validated and robust industrial method for the virucidal treatment of blood products. Although many millions of therapeutic doses of S/D inactivated products have been used to date, there is no report on transmission of viral infections caused by enveloped viruses in recipients [3].

The pharmaceutical characteristics of S/D plasma and the clinical experience on its use will be the focus of this narrative review.

Solvent detergent pathogen inactivation of fresh frozen plasma

A study conducted in the early seventies with tri-nitrobutylphosphate (TNBP) solvent substantiated its effectiveness in the disruption of lipid-enveloped viruses [4]. However, the S/D method of pathogen inactivation was patented in 1985 for the treatment of concentrates of coagulation factors [1]. Since then it has become the most widely spread industrial method for the virucidal treatment of plasma-derived medicinal products. The composition of plasma, unlike clotting factor concentrates, is extremely complex and [5], between 1986 and 1989, Bernard Horowitz implemented a modified S/D method adapted to its higher lipid content and able to ensure an effective virucidal power [6]. In 1992, the first studies describing the characteristics of inactivated plasma and the S/D industrial inactivation process were published and it was licensed [7,

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8]. However, in 1998, the robustness of this method was finally confirmed by the validation study of viral safety by Biesert and Shartono [9]. It was first introduced into clinical practice in Germany, based on observational studies demonstrating safety and efficacy [10].

The S/D treatment is preceded by filtration with a 1- μm filter to remove cells and debris. Fresh frozen plasma (FFP) is thawed rapidly and treated for 4 h with TNBP solvent and with Triton X-100 detergent, both at 1 %. The TNBP is then removed by extraction with castor (or soybean) oil and the Triton X-100 by hydrophobic chromatography. These processes are followed by sterile filtration with a 0.2- μm filter and aseptic packaging into the final product (frozen units of 200 mL or lyophilized units in glass bottles of 50 or 200 mL) [6]. According to the European Pharmacopoeia the allowed residual amounts of these substances in the final S/D-treated product are less than 2 $\mu\text{g}/\text{mL}$ for TNBP and less than 5 $\mu\text{g}/\text{mL}$ for Triton X-100 [11]; these figures are much lower than the toxicity levels for either substance or ambient environmental exposures in developed countries and, actually, the levels of these additives in most S/D plasma batches are below the detectability threshold that is 0.5 and 1 $\mu\text{g}/\text{mL}$, respectively [6, 12]. In addition, the general safety tests performed on rodents indicate that the S/D processing of plasma do not generate toxicity and do not have mutagenicity, embryo toxic, or teratogenic potential. A thrombotic thrombocytopenic purpura (TTP) patient could theoretically receive 63 L of S/D plasma or 2.7 mg/kg of Triton X-100, which is still well below the toxicity levels of this chemical compound.

Furthermore, the safety of the S/D treatment is also shown by the absence of reports of toxicity or antibodies against neoantigens after large-scale exposure of patients to several million transfused units [6].

In 2006, Thierry Burnouf and co-workers developed a process of S/D inactivation for use on single-donor plasma or mini-pools of plasma to be used in blood establishments in developing countries [13]. This newly developed treatment method is based on 1 % TNBP as solvent and 1 % Triton X-45 instead of the Triton X-100; recently, it was also used for mini pools of cryoprecipitate (400 ± 20 mL) in a newly designed integral disposable processing bag system; the products were subjected to double-stage S/D viral inactivation, followed by one oil extraction and filtration on a S/D and phthalate absorption device as well as an 0.2- μm terminal filtration step to remove bacteria and blood cell debris [14].

Very recently, a prion-depleted version of S/D plasma was introduced with an additional step involving an affinity chromatography on a ligand gel containing a specific binding agent for the abnormal isoform of the prion protein (PrP^{sc}). This plasma is totally bioequivalent to S/D plasma with respect to the recovery of clotting factors and

demonstrated comparable safety and tolerability in healthy volunteers but, due to its shortened S/D treatment, resulted in significantly higher plasmin inhibitor concentrations in vivo [15, 16].

Viral and bacterial decontamination

The decontamination of S/D plasma is guaranteed by the treatment with both the solvent and the detergent, immunological neutralisation (due to the physiological presence of neutralising antibodies in the pool of plasma for fractionation), as well as by double filtration, which removes cells, cell fragments, and bacteria. S/D treatment is highly effective in disrupting lipid membranes and, therefore, guarantees a high level of safety with regards to all viruses with a lipid envelope (including human immunodeficiency virus, hepatitis B and C virus, and emerging ones such as the West Nile virus, Chikungunya virus, new influenza strains, and severe acute respiratory syndrome Coronavirus), bacteria, protozoa and intracellular viruses, such as cytomegalovirus, Epstein-Barr virus and human T cell leukaemia virus I and II [6].

In addition, the treatment has a high reserve capacity provided by the 4-h incubation time; in fact, it reduces the virus load below detection levels in less than 2 min [6]. While the S/D process effectively destroys more than 5 logs of most enveloped viruses, the vaccinia virus is relatively resistant; this pathogen reduction technique is also less effective against non-enveloped viruses such as hepatitis A and parvovirus B19. The risk of transmitting these infectious agents is reduced by the dilution of any initial viral load, the presence of neutralising antibodies in the plasma pools, the size of plasma pools (60–380 L in comparison to 4,000–30,000 L of the pools from which plasma-derived medicinal products are produced) [6], the hydrophobic chromatography to which the product is subject, and by testing each plasma pool for the presence of genomic material [17].

The concentrations of anti-hepatitis A antibodies in S/D plasma are 30 times the prophylactic dose and should warrant an adequate protection from this infection. The concentrations of antibodies against parvovirus B19 are similar to those of intra-venous immunoglobulins used to treat chronic infections [12] but transfusion transmission of B19 has been reported with S/D plasma [18] and in the 1990s an outbreak of hepatitis A occurred with a factor VIII product [12].

In conclusion, preclinical virus validation studies, clinical safety virological assessments, and extensive post-marketing clinical experience have clearly shown that the S/D treatment achieves a rapid, irreversible, and thorough inactivation of enveloped viruses. Moreover, the efficacy of the S/D treatment is highlighted by the fact that between

1991 and 2009 approximately 10 million units of S/D plasma were transfused without any documented case of transmission of HBV, HCV or HIV [6].

Nevertheless, the “traditional” S/D pathogen inactivation has only a limited prion clearance capacity as it is able to reduce the PrPSc by only 2.5 logs whereas a further extension of this removal capacity (more than 5 logs) has been recently warranted by the above mentioned “modified” manufacturing process that includes a specific prion reduction step [6, 15, 16].

Although bacteria rarely contaminate FFP because of its storage conditions [19], the impact of S/D on bacterial growth and on the capacity of the complement to kill bacteria has been recently investigated and showed that the S/D treatment of plasma does not alter the bactericidal activity of the complement, and inactivates some gram-positive bacteria [20].

Standardisation, dilution effect and other possible benefits

The dilution and neutralisation of antibodies and allergens during the industrial process of S/D plasma pooling can reduce the incidence of allergic reactions in recipients and also result in a high level of final standardisation of the concentrations of labile and stable clotting factors and other plasma proteins, thus eliminating the biological variability between single units of FFP [9, 17, 21–23].

Neither anti-human leucocyte antigen (HLA) nor anti-human neutrophil antigen (HNA) antibodies are detectable in S/D plasma as they are diluted and neutralised by the presence of leukocytes or their fragments, which are then removed by the S/D treatment [24–26]. For this reason countries using S/D FFP have not reported any transfusion-related acute lung injury (TRALI) case due to the transfusion of plasma [27, 28].

In addition, the double filtration of S/D FFP removes residual cells and many of their fragments, thus reducing the possibility of allo-immunisation and cell-mediated adverse immunological reactions in the recipient [17].

Recently, 100 plasma samples obtained from voluntary blood donors in Germany were compared to six aliquots of different lots of S/D plasma through tandem mass spectrometry to assess the presence of drug residues. In 12 % of the analysed specimens, residues of diuretics, beta-receptor blocking agents, stimulants, or contraceptives were detected and they were all within or below levels commonly reported in cases of therapeutic usage. On the contrary, the analysis of the aliquots of S/D plasma preparations yielded no findings of drug residues. These results are attributed to the dilution and the liquid–liquid and solid-phase extraction, which are included in the industrial production process of pathogen inactivated plasma [29].

Other methods for pathogen reduction of plasma currently in use exploit different mechanisms of actions and, consequently, generate a large quantity of reactive oxygen species (ROS). ROS have a key role in the damage of red blood cells and recently fostered an approach to improving the quality and efficacy of stored red cells focused on reducing oxidative damage by removing oxygen at the beginning of storage and maintaining the anaerobic state throughout the storage period [30]. Very recently Feys et al. [31] revealed the mechanism of damage to plasma constituents by riboflavin and light and showed that generated ROS played a direct role in adversely affecting the biomolecular integrity of relevant plasma constituents such as ADAMTS13, factor VIII and fibrinogen. In this case, plasma product integrity could be maintained by applying hypoxic conditions during the pathogen inactivation process. It is important to note that the formation of singlet oxygen upon illumination is part of the mechanism of action also of the methylene blue (MB) pathogen reduction system [32] whose efficacy is indeed increased in the presence of oxygen [12].

Factor composition of solvent detergent treated plasma and possible changes related to the production process

S/D plasma deriving from FFP units prepared and frozen through optimal collection and production procedures [33] has a moderate reduction of clotting factor and inhibitor activities and a final composition similar to FFP. Moreover, thanks to the filtration process, the high molecular weight multimers of von Willebrand factor (vWF) are absent. The metalloprotease ADAMTS13, implicated in the pathogenesis of TTP, is normal and stable up to 5 h, even after thawing and storage at room temperature [17]. S/D plasma also contains normal levels of factor H [34], a plasma glycoprotein involved in the control of the complement cascade and with a pathogenic role in atypical haemolytic uremic syndrome. The percentage retention of selected factor is reported in Table 1. The content of factor VIII is about 20 % lower compared to the source FFP and the activity of protein S (PS) is reduced by about 35–40 % [6, 10]. Reductions in this order of magnitude are not clinically significant due to the wide reference range (50–200 %) for most clotting factors and inhibitors in single plasma units.

The level of plasmin inhibitor (α_2 -antiplasmin) is influenced by the duration of the S/D treatment, the size of the plasma pool and the quality of the plasma. It ranges from 20–24 to 33 % of normal values in S/D plasma deriving from pools of 200 (South Africa) to 380 (Europe) L [6, 10]; it increases up to 37–42 % in French S/D plasma, derived from pools of 60 L, approximately up to 66 % in the above mentioned prion-depleted version of S/D plasma,

Table 1 Current methods for pathogen reduction of plasma and selected factor percentage retention [10, 32, 34, 46–58]

	Solvent/detergent	Methylene blue	Amotosalen	Riboflavin
Illumination	No	Visible light	Ultraviolet A light (320–400 nm)	Ultraviolet A and B light (285–365 nm)
Mechanism of action and primary target	Damage of lipid membranes	Binding to viral nucleic acids followed by singlet oxygen-mediated destruction upon illumination	Binding to viral nucleic acids followed by covalent cross-links and block of DNA/RNA replication upon illumination	Association with nucleic acids and mediation of oxygen-independent electron transfer upon illumination
Shelf life	4 years at ≤ -18 °C	2 years at -30 °C	2 years below -25 °C 1 year between -18 and -25 °C	2 years at -30 °C
Selected factor retention (%)				
Fibrinogen	84	65	72	77
Factor V	63	77	92	73
Factor VIII	78	67	73	77
Factor XI	95	73	86	67
Protein C	97	95	94	79
Protein S	56	100	98	91
Antithrombin	96	102	97	100
Plasminogen	100	99	94	94
α_2 -antiplasmin	21	96	80	90
von Willebrand factor multimers	Reduced	Normal	Normal	Some loss
ADAMTS-13	100	100	96	96

whose S/D treatment lasts 2–3 h less, and up to 80–90 % in mini-pools of plasma, where also the activity of PS is less reduced (10–20 % of normal).

However, there is no evidence supporting a possible role of reduced levels of plasmin inhibitor in the pathogenesis of bleeding from hyperfibrinolysis in patients with altered haemostasis treated with plasma [17]. In fact, in Europe, a retrospective observational study of patients who had undergone orthotopic liver transplantation revealed a higher incidence of laboratory signs of hyperfibrinolysis in patients treated with S/D FFP than in those treated with FFP; the red cell transfusion requirements were not, however, significantly different between the two groups of patients [35]. The hyperfibrinolysis, which was initially attributed to reduced levels of α_2 -antiplasmin in S/D FFP, was subsequently correlated to the amount of bleeding. Following modifications of the surgical technique and the introduction of low doses of aprotinin no further thrombotic or haemorrhagic complications occurred [36]. In Norway 208 liver transplants were carried out between 1993 and 2001 using S/D FFP and aprotinin, with no reports of thrombotic or haemorrhagic complications [36]. Furthermore, there have been no descriptions of persistent bleeding in patients with congenital or acquired deficiency

of plasmin inhibitor treated with S/D plasma-based replacement therapy [22, 37]. Therefore, clinical studies did not confirm the initial concerns due to the low levels of α_2 -antiplasmin or antitrypsin activity in S/D plasma [6, 22].

Bleeding problems in liver transplantation case reports following the use of S/D plasma produced from USA plasma [38] may have been caused by the remarkable differences in the production process of North American plasma with much larger pool sizes and less strict quality requirements regarding separation and freezing.

Significant differences in the manufacturing processes between PLAS + SD, which was produced in the USA from 1998 to 2002, and the S/D plasma products used in Europe have been reported [17, 22]. These differences include: (i) the way plasma was obtained and the pool size; (ii) the citrate concentration; (iii) the storage time before freezing methods of source plasma, (iii) the stabilizing plasma proteins, and (iv) the oil used to extract the solvent-detergent chemicals [39].

The USA plasma derived from (much larger) pools of 650 L of plasma obtained by fractionation and not by apheresis, had a low citrate concentration that could have been insufficient to avoid coagulation activation, and was separated and frozen 15 h after collection [6, 17, 22, 40];

coagulation factors were stabilized with 2 mM calcium chloride while sodium hydrogen phosphate (5 mM) at pH 6.0–7.4 is used in the European manufacturing process; furthermore, TNBP and Triton X-100 were extracted with soybean oil while castor oil is used in Europe; finally, PLAS + SD underwent concentration and ultrafiltration passages not used in the European product.

Therefore, the North American plasma showed a greater decrease in the activities of antitrypsin, plasmin inhibitor activity, and plasmin activator inhibitor, contained residues of TNBP, and had high concentrations of lipoprotein (a), fibrin monomers and C3a des-Arg, a complement activation marker. Moreover, the American product had almost no PS activity, whereas European S/D plasma has a moderate reduction of PS activity and antigen [6, 17, 22, 40, 41].

Collectively, these differences could be responsible for the adverse effects reported after the use of S/D plasma produced in the USA [17, 40, 42], which led to its withdrawal from the market following the notification of six deaths caused by thromboembolic complications after orthotopic liver transplantation [40] and three cases of deep vein thrombosis in patients with TTP treated with plasma-exchange using S/D plasma as the replacement fluid [42]. However, in January 2013, the US Food and Drug Administration approved an S/D plasma product manufactured with plasma collected from US donors as an alternative to single-donor FFP.

By contrast, in Europe there have been no reports of thromboembolic episodes directly related to treatment with S/D plasma. In a retrospective analysis of 68 patients with TTP treated with plasma-exchange using S/D plasma produced in Europe eight thromboembolic events were found in seven patients, all of whom, however, had additional risk factors [43]. Thrombotic complications were also described after the use of standard FFP and plasma cryosupernatant [44, 45].

In conclusion, thrombosis or hyperfibrinolytic bleeding triggered by reduced protein S or low plasmin inhibitor potencies in European S/D plasma have not withstood critical review [6, 22].

Other pathogen reduced plasma products

The other pathogen reduction technologies for plasma currently in use target nucleic acids, involve the use of visible or ultraviolet light, and are designed for use in blood establishments. They exploit MB, amotosalen, and riboflavin as additives [46]. A novel system exploitable for pathogen inactivation in plasma and platelets is based on short-wave ultraviolet C without photoactive substances and is currently undergoing clinical efficacy and safety testing [32]. A detailed description of these products has been recently addressed by several review articles [32, 46–

49]. In Table 1 the mechanism of actions of the pathogen reduction systems for plasma currently in use and the main characteristics of the inactivated plasma products are summarised [10, 32, 34, 46–58].

Clinical experience on solvent detergent-treated plasma

The high level of safety towards allergic reactions, TRALI and risk of transmission of enveloped viruses and of final standardization of coagulation factor content has recently led to the wide use of S/D plasma. In Italy two products are commercially available. A number of clinical studies have analysed in the last two decades the efficacy and safety of this biological agent in various clinical settings, including congenital coagulation deficiencies, acquired coagulopathy of liver disease, coumarin-reversal and surgery [59–82], as summarized in Table 2.

Efficacy issues

As regards the clinical use of S/D plasma in congenital bleeding disorders, the most important study was published by Horowitz and Pehta [60], who described the effective use of S/D plasma in 48 patients with hereditary deficiencies of factors II, V, X, XI, and XIII treated in 137 transfusion episodes for active bleeding (51 episodes), surgical prophylaxis (47 episodes), or routine prophylaxis (39 episodes). More recently, Santagostino and colleagues reported on 17 patients with recessively inherited coagulation disorders (1 afibrinogenemia, 4 factor V, 6 combined FV and FVIII, 1 factor X, and 5 factor XI deficiencies) [61]. In 13/16 cases (81 %) S/D plasma was fully effective, while in the remaining three cases it was partially effective as the post-surgical mild bleeding was controlled by continuing or increasing treatment with S/D plasma. As was the case in recent studies [62, 63] and also recommended by international guidelines on the appropriate usage of non-inactivated FFP [64–66], this article clearly shows that also the dosages of S/D plasma to be used to ensure the effectiveness of the treatment are greater than the traditional ones of 10–15 mL per kilogram and frequently are approximately 30 mL per kilogram.

As regards the use in patients with acquired coagulation deficits, a randomized, double-blinded study assessed the ability of S/D plasma and FFP to reduce a prolonged prothrombin time (PT) to 15 s or less [67]. No differences between S/D plasma and FFP were seen with regard to the mean dose of plasma infused, percentage of patients with corrected PT to ≤ 15 s (32 % for S/D plasma vs 26 for FFP, $p = 0.67$) or percentage of patients whose bleeding stopped (27 % for S/D plasma vs 22 % for FFP). Clinical response to plasma therapy was similar between the groups. Similar results were found in another randomized

Table 2 Summary of the main studies on the clinical use of S/D FFP

First author, year (ref.)	Study design/product used ^a	Clinical setting	Patients enrolled	Main results	
				Efficacy	Safety
Inbal, 1993 [59]	Observational/Octaplas	Inherited and acquired coagulation disorders	11 (8 inherited and 3 acquired coagulation disorders)	Complete 11/11 (100 %)	2 (18 %): 1 urticaria, 1 moderate anaphylactoid reaction
Horowitz and Pehta, 1998 [60]	Observational/PLAS + SD RCT/PLAS + SD	Inherited coagulation disorders TTP	48 26 (16 S/DP vs 10 FFP)	Prevention or control of bleeding (87 %)	Adverse reactions: 26/788 (3 %) Adverse reactions: 16/163 (10 %)
Santagostino, 2006 [61]	Open-label, multicentre study/Octaplas	Inherited coagulation disorders	17	Complete 13/16 (81 %); partial 3/6 (19 %)	1 rash (6 %)
Beck, 2000 [68]	RCT/Octaplas	Severe coagulopathy	40 (17 S/DP vs 23 FFP)	No differences in clinical efficacy or haemostatic correction	NR
Lerner, 2000 [67]	RCT/PLAS + SD	Severe coagulopathy with prolonged PT	5 (22 S/DP vs 23 FFP)	No differences in PT correction (32 % S/DP vs. 26 % FFP) or control of bleeding (27 % S/DP vs. 22 % FFP)	Adverse reactions: 2 (9 %) in each group
Williamson, 1999 [69]	RCT/Octaplas	Complex coagulopathy: liver disease or transplantation	49 (24 S/DP vs 25 FFP)	No differences in clinical efficacy or haemostatic correction	1 parvovirus B19 seroconversion in FFP group
Solheim, 2006 [70, 71]	Open label/UniPlas	Liver resection	122 (81 S/DP, 41 not transfused)	Maintenance of PT, aPTT and protein C levels.	2 adverse reactions (2.5 %): 1 fever, 1 urticaria
Chekrizova, 2006 [72]	Observational/Octaplas	Obstetric/gynaecologic emergencies, critically ill neonates; liver disease	94	Improvement of laboratory indices of coagulopathy	No adverse reactions
Freeman, 1998 [73]	RCT/Octaplas	OLT	28 (12 S/DP vs 13 FFP)	S/DP and FFP showed equal correction of clotting factors, aPTT and PT	No adverse reactions
Bindi, 2013 [74]	RCT/PlasmaSafe	OLT	63 (30 S/DP vs 33 FFP)	S/DP reached the same clinical results of FFP with a reduced amount of transfusions	NR
Lepri, 2013 [75]	Case control/PlasmaSafe	Critically ill patients	80 (29 S/DP vs 51 FFP)	S/DP reached the same haemostatic efficacy of FFP with a reduced amount of transfusions	No adverse reactions
Haubelt, 2013 [76]	Prospective/Octaplas	Open heart surgery	67 (36 S/DP vs 31 FFP)	Clinical haemostasis revealed no significant differences between the two treatment regimens	No adverse reactions
Wieding, 1999 [77]	RCT/PLAS + SD	Cardiopulmonary bypass surgery	71 (35 S/DP vs 36 MBP)	No clinical differences were observed between the two treatment regimens	NR
Tollosfrud, 2003 [78]	RCT/Octaplas - UniPlas	Cardiac surgery	84 (36 UniPlas, 19 Octaplas, 29 controls)	No clinical differences between the two products	No adverse reactions
De Silvestro, 2007 [79]	Prospective/PlasmaSafe	OLT, TTP, heart surgery	18 (7 heart surgery, 8 OLT, 3 TTP)	Effectiveness in correcting coagulation defects and for treating TTP	No adverse reactions

Table 2 continued

First author, year (ref.)	Study design/product used ^a	Clinical setting	Patients enrolled	Main results	
				Efficacy	Safety
Yarranton, 2003 [43]	Retrospective/ PLAS + SD, Octaplas	TTP	68	NR	8/68 (12 %) VTE cases
McCarthy, 2006 [80]	Observational/ PLAS + SD	TTP	161 (35 S/DP, 62 FFP, 48 CPP)	90 % response with S/DP, vs 70 % with CPP and 75 % with FFP	No adverse reactions
Scully, 2007 [81]	Retrospective/ Octaplas	TTP	50 (21 Octaplas, 12 CPP, 15 CPP + Octaplas)	No differences in number of PEX to remission	32 allergic reactions: 16/172 PEX (9 %) with CPP vs 16/509 (3 %) with S/DP; 1 case of superficial vein thrombosis
Edel, 2010 [82]	Case series/ Octaplas	TTP	8	All patients responded to S/DP	No adverse reactions or thrombotic events reported

RCT randomized clinical trial, *TTP* thrombotic thrombocytopenic purpura, *PT* prothrombin time, *S/DP* solvent/detergent-treated plasma, *FFP* fresh frozen plasma, *NR* not reported, *OLT* orthotopic liver transplantation, *aPTT* activated prothrombin thromboplastin time, *MBP* methylene blue light virus-inactivated plasma, *VTE* venous thromboembolism, *CPP* cryo-poor plasma, *PEX* plasma exchange

^a Octaplas, Octapharma, Vienna, Austria; UniPlas, Octapharma, Vienna, Austria; PLAS + SD, VITEX, Watertown, MA, USA; PlasmaSafe, Kedrion SpA, Castelvecchio Pascoli, Lucca, Italy

trial conducted by Beck et al. [68] on 40 patients with severe coagulopathy. The efficacy of S/D plasma in patients with coagulation defects associated with liver disease was examined in comparison to standard FFP through a prospective randomized trial [69]. Forty-nine patients with liver disease or undergoing liver transplantation were randomly assigned to receive FFP or S/D plasma prior to procedure (liver biopsy or transplantation) or for severe coagulopathy. The dose of plasma infused was similar between the groups. Results showed that correction of clotting factor levels and prolonged activated partial thromboplastin time (aPTT) was equal with FFP and S/D plasma. The greater decrease in the International Normalized ratio (INR) seen in the S/D plasma group was attributed by the authors to the higher baseline INR of those patients compared to those in the FFP group. Notably, use of S/D plasma in patients undergoing liver transplantation did not increase the need for other blood components. Two randomized trials analysed the use of S/D plasma in patients undergoing orthotopic liver transplantation (OLT). In the first study, by Freeman and colleagues [73], 28 patients with coagulopathy following OLT showed equal correction with S/D plasma or FFP. In the second, more recent, study conducted by Bindi and colleagues on 63 OLT patients [74], the use of S/D plasma in association with the monitoring of haemostasis by means of thromboelastography gave the same therapeutic results as FFP but with a significant reduction in the amount of plasma transfused ($2,617 \pm 1,297$ mL in the FFP group vs $1,187 \pm 560.6$ mL in the S/D plasma group, $p < 0.0001$).

A similar finding (1,549 mL in the FFP group vs 503 mL in the S/D plasma group) emerged also in a case-control study conducted by our group on critically ill patients [75].

As regards the use of S/D plasma in patients with complex coagulopathy associated with cardiac surgery, a prospective trial found that 36 patients treated with 600 mL of S/D plasma showed a similar rise in factor VIII, fibrinogen, antithrombin, protein C, free PS, alpha-1 antitrypsin and plasminogen as well as a decrease in PT and aPTT as compared with 31 patients treated with 600 mL of FFP [76]. On the other hand, significant differences between these products were found for levels of total PS and plasmin inhibitor. However, clinical haemostasis evaluation revealed no significant difference between the two treatment regimens. These results were in agreement with the previous findings from a randomized clinical trial conducted by Wieding et al. [77] comparing S/D plasma and MB light virus-inactivated plasma in 71 patients undergoing cardiopulmonary bypass surgery. A prospective randomized study by Tollofrsud et al. [78] also reported positive experience on the use of S/D plasma in open-heart surgery. Finally, on the basis of the finding that S/D plasma lacks the highest molecular weight vWF multimers [56], which have been involved in the pathogenesis of TTP, some investigators have assessed S/D plasma in the treatment of patients with acute TTP with reported rates of remission between 90 and 100 % [43, 79–82]. Furthermore, these studies documented that S/D plasma dramatically reduces [81] or even eliminates [80] allergic reactions.

Safety issues and haemovigilance

While S/D plasma was withdrawn from the US market more than 10 years ago and only recently has been reintroduced, in Europe it continued to be widely utilized after the laboratory evidence of a markedly different composition from the US product and studies that failed to detect thrombotic complications in similar patient groups [40]. Indeed, haemovigilance national programs clearly demonstrate the safety of S/D plasma in all clinical settings [6]. Clinical experience from France, after the transfusion of more than 1.9 million units of S/D plasma since 1994, and from Finland, after more than 150,000 units since 2005, show a significant reduction in the rate of serious adverse events (approximately 85 %) as compared with standard FFP [83, 84]. Since 1993, in Norway, more than 250,000 units of S/D plasma have been successfully transfused to all categories of patients, including neonates and liver transplant patients, with no cases of transmission of viral diseases, thrombotic complications or TRALI [27, 28]. Similar findings emerged in a Belgian retrospective analysis of 5,064 S/D plasma units transfused in 894 recipients [85]. In the UK more than 350,000 units of S/D plasma have been transfused after the introduction of the Serious Hazards of Transfusion (SHOT) haemovigilance system without reports of serious problems [86]. Supporting data was also provided by the Austrian haemovigilance registry, which, in 2004, reported 19 allergic reactions after FFP and only 1 after S/D plasma [87], and by the Italian haemovigilance registry, which reported a significantly lower rate of adverse reactions to S/D plasma compared with non-pharmaceutical FFP [adverse reactions/units \times 1000: 0.06 with PlasmaSafe (Kedrion SpA, Castelvechchio Pascoli, Lucca, Italy) vs 0.48 with FFP, $p < 0.01$] following the transfusion of over 250,000 units from 2009 to 2011 [88].

Economic issues

The availability of systems for inactivating pathogens in FFP for clinical use raises the question of whether and, if so, to what extent, these treatments, notoriously used to reduce the risk of post-transfusion infections, should be introduced. The current level of transfusion safety makes the cost-benefit ratio of introducing the use of pathogen-inactivated FFP unfavourable, even in the most economically developed countries, if the benefit is measured only in relation to the residual risk of infection.

The first cost-effectiveness analysis of S/D-treated plasma was published in 1994 by Aubuchon and Birkmeyer and concluded that “from a public health perspective, the relatively high costs and small benefits of reducing

enveloped virus infection risks with S/D plasma (and the additional risks of non-enveloped virus transmission)” did not appear “to justify widespread implementation of this technology” [89]. Another two studies assessed the cost-effectiveness of S/D plasma [90, 91]. All three studies yielded a wide range of cost/quality-adjusted life year (QALY) estimates (\$ 289,300 [89], \$ 2,156,000 [90], and \$9,743,000 [91]) and concluded that the increased level of safety of S/D plasma did not justify its considerable additional cost.

However, as these studies did not consider several relatively common non-infective transfusion-related complications, they greatly underestimated the cost-effectiveness of this blood component.

When Riedler and co-workers considered various infective and non-infective transfusion-related complications, such as TRALI, S/D plasma proved to be a cost-effective treatment for all patients aged 48 and under (the cost per life-year saved remained below £ 50,000) and in older patients with good clinical prognosis [92].

van Eerd et al. [93] confirmed the cost-effectiveness of S/D plasma also in critically ill patients through an analysis based on a model structure originally developed by the Canadian Agency of Drugs and Technologies in Health (CADTH). However, differently from the CADTH study [94], which highlighted incremental cost per each QALY gained of \$79,100 and incremental cost per life-year saved of \$95,700, they also included severe allergic reactions in their cost-utility analysis model. Treatment with inactivated plasma resulted in 0.03 QALYs and 0.03 life-years saved compared to FFP and pathogen-reduced plasma was considered to be cost-effective at a threshold of £ 30,000 (\$ 47,548) per QALY.

The latest published cost-effectiveness and budget impact study includes the risk of (severe) allergic reactions, bacterial infections, prion disease and two unknown viruses in the analysis [95]. S/D plasma resulted in 0.021 QALYs gained in comparison with FFP and the probability of being cost-effective at a CA\$ 30,000 per QALY threshold was greater than 98 %. Therefore, it can be considered cost saving and is also able to provide additional benefits in terms of safety in comparison to FFP, which is the current standard of care.

In conclusion, as cost-effectiveness analyses relate the costs of a programme/technique to its key outcome or benefits, we deem that when the projected benefits of S/D plasma usage also include the elimination/reduction of complications such as TRALI and (severe) allergic reactions as well as the prevention of complications caused by emerging/unknown infectious agents the computed cost-effectiveness ratio can really be able to support a (robust) recommendation aiming at including this therapeutic tool in the current standard of care.

Conclusions

S/D plasma is a pharmaceutical product with a standardised content of clotting factors, devoid of antibodies implicated in TRALI pathogenesis, and with a very high level of decontamination from transfusion-transmissible infectious agents that has been in production for thirty years now. Many clinical studies have confirmed its efficacy in congenital and acquired bleeding disorders and several cost-effectiveness analyses show that its use is justified as it can decrease health care expense for plasma transfusions and improve the already high level of transfusion safety.

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