Virus-inactivated plasma - Plasmasafe: a one-year experience

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Background. Fresh-frozen plasma (FFP) is a widely used blood transfusion product. The transfusion safety of this product is ensured by legally obligatory tests, but can be further improved by using some technical procedures, such as methylene blue (MB) and solvent-detergent (SD) viral inactivation methods. Mainly organisational criteria led us to introduce the SD viral inactivation technique as a service activity. In this report we describe our first year of experience, following the introduction of the SD technique, and thus the use of SD-virally inactivated plasma (PlasmaSafe).

Materials and methods. In order to evaluate the appropriate use and the therapeutic efficacy of PlasmaSafe in our Blood Transfusion Unit, the following programme was planned: quality control [prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen] of the FFP units (N=312); evaluation of the clinical effectiveness on 490 patients (879 transfusion events); pre- and post-treatment monitoring of indicators of coagulation (PT, aPTT, fibrinogen, proteins S and C, factor VIII) on 15 patients; treatment of three patients with thrombotic thrombocytopenic purpura (TTP) undergoing plasma-exchange; haemovigilance of adverse reactions provoked by SD-plasma.

Results. The indicators of coagulation in the FFP units varied greatly: the PT ranged from 50-120%, the aPTT from 24-41 seconds and the fibrinogen concentration from 1.42-6.84 g/L. Seventy-six percent of the patients responded to the plasma administration; moreover, two of 15 patients in whom protein S was assayed, showed no increase of this haemostatic protein. The TTP patients responded to plasma exchange treatment following four sessions of apheresis. During the observation period 8,422 PlasmaSafe units were transfused and no adverse reactions were recorded.

Conclusion. PlasmaSafe, a pharmaceutical-like product with a standardised content of coagulation factors, was found to be effective at correcting coagulation defects and for treating TTP. No thrombotic complications or transfusion-related adverse reactions were recorded.

Key-words: Solvent-detergent technique, PlasmaSafe, clinical effectiveness, haemovigilance.

Introduction

Transfusion safety constitutes one of the major strategic goals of a transfusion system, as also acknowledged by the IV Venetian Regional Blood and Plasma Programme (*IV Piano Sangue e Plasma della Regione Veneto*) [1], which identifies safety as the cornerstone of its transfusion service.

In the Region of Venice, all plasma products assigned for clinical use are treated by viral inactivation methods at all main Blood Transfusion Units, in order to reduce the risk of blood-transmissible infections.

Currently, the most widely used inactivation methods are treatment with solvent-detergent (SD) and photoinactivation following the addition of methylene blue (MB). Both of these methods have *pros and cons*, so that, among the various European countries, some have opted to use one or other of the techniques, while in other countries both the procedures coexist [2-6].

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SD virus-inactivated plasma (SD-plasma) is fresh-frozen plasma (FFP) derived from pooled plasma (up to 2,500 blood donors), treated using the solvent Tris (n-butyl)phosphate and the detergent Triton X-100. This treatment effectively inactivates lipid-enveloped viruses, namely HIV-1/2, HCV, HBV, and HTLV-I/II, but has no effect on non-enveloped viruses, including HAV and Parvovirus B19, or on prions. SD treatment can induce a reduction of procoagulant factors, although their levels remain within the normal range. Moreover, it has been discovered in the USA that, unlike FFP, SD-plasma does not cause a post-transfusion increase of protein S (PS), and produces a reduction of the plasminogen inhibitor: however, the SD-inactivation procedure applied in the USA is different from the one used in Europe, as the process involves an ultrafiltration step, which decreases the plasma concentrations of alpha-1-antitrypsin, alpha-2-antiplasmin and PS [7-10].

So far, no thromboembolic episodes have been associated with the infusion of European-produced SD-plasma, even if, in a review in 2003, Yarranton *et al.* described the occurrence of seven thromboembolic events in a total of 68 patients treated for TTP with plasma-exchange using Octaplas; all seven patients had known risk factors for thromboembolism[11]. The clinical indications for the use of SD-plasma are the same as those for FFP.

Methylene blue virus-inactivated plasma (MB-plasma): treatment of FFP with MB and photoinactivation is an efficient technique for reducing the transfusion risk due to enveloped viruses, but not that due to non-enveloped viruses. Once the inactivation process has been completed, up to 90% of the MB can be removed using suitable filters. MB treatment can be applied to single FFP units, unlike the SD method, which is carried out on pooled FFP. Despite the low MB content, without definitive proof to exclude toxicological risks, the use of the MB-plasma without subsequent filtration is contraindicated in the following cases: pregnant women; premature neonates, newborn babies and intrauterine transfusions; patients with severe renal insufficiency; patients with methaemoglobinaemia and congenital glucose-6-phosphate dehydrogenase deficiency. The content of coagulation factors in MB-plasma is reduced, by as much as 35% (FV, FIX and fibrinogen): the amount of the product to administer must be calculated, taking this into account [12-14]. The clinical indications and toxicity are the same as those for FFP.

The SD technique is an industrial process and can be acquired as a "service": Blood Transfusion Units give the industry the raw material, the FFP, and the industry returns the inactivated product, charging the Units for cost of the processing. In Italy this treatment is carried out by Kedrion S.p.A (Castelvecchio Pascoli - Barga, Lucca, Italy), using an industrial process involving two filtration phases (1µ and 0.22 µ). On the other hand, the MB technique can be implemented, 'in-house', in single Blood Transfusion Units, that acquire all the necessary instrumentation, reagents and materials.

The Padua Blood Transfusion Unit preferred the SD technique, a "service activity", for three reasons:

1 organisational, particularly because of the lack of physical space and the progressive reduction of staff, with constantly increasing activity;
2 therapeutic, since virus-inactivated plasma is basically a pharmaceutical product; a standardised, known content of coagulation factors enables correct monitoring of the product's effectiveness;
3 quality certification of the product and of the inactivation process: while "in-house" inactivation does not permit any verification or control of the effectiveness of the process, SD-inactivation performed by an industrial organisation implies guarantees and certification of all phases of the productive process.

In the initial period of the project, the new transfusion product, named PlasmaSafe, was presented, first to the Committee for the Good Use of Blood Products and then to the transfusion referents of all the medical and surgical departments, in order to re-establish the correct indications for the use of FFP, to introduce the PlasmaSafe and to describe the possible side effects reported in literature.

The aim of this study is to describe the Padua experience with the use of this new blood product. We evaluated the content of clotting factors, the product's therapeutic efficiency and the occurrence of adverse effects; moreover, cost and utilisation monitoring was performed, taking the regional analytical accounting system as the reference.

Materials and methods

The following programme was planned:

1 evaluation of coagulation parameters of the FFP units produced from whole blood fractionation and by apheresis;
2 evaluation of the clinical effectiveness of treatment with SD-plasma;
3 monitoring of pre-and post-transfusion coagulation parameters of SD-plasma in patients undergoing cardiac surgery, with particular attention to the protein S (PS);
4 monitoring of pre-and post- transfusion coagulation parameters of SD-plasma in patients undergoing orthotopic liver transplantation, with particular attention to PS;
5 treatment of patients with TTP;
6 haemovigilance of adverse reactions to SD-plasma.

1 - Evaluation of coagulation parameters of the FFP units

Of the 312 FFP units tested, 154 were from plasma fractionation and 158 from apheresis. Plasma fractionation was carried out by centrifugation of whole blood withdrawn in quadruple SAG-M blood bags (Terumo Corporation, Japan); apheresis plasma was obtained by using MCS Plus 9000 cellular separators (Haemonetics Corporation, Braintree, MA, USA), and ACD-A anticoagulant in a 1:10 ratio. Plasma sampling for laboratory testing was performed immediately before the freezing procedure and within 6 hours of collection. The following laboratory tests were determined: prothrombin time (PT, %), activated partial thromboplastin time (aPTT, seconds) and fibrinogen concentration (g/L). The PT was measured with a Diagen Tromboplastina S kit (Dasit, Milan, Italy). The aPTT was measured with an APTT-P Biopool kit (Trinity Biotech, Dublin, Eire). Fibrinogen was assayed with the Bovine Thrombin 100 NIH kit (Biopool); analyses were performed using the Sysmex CA 7000 (DADE Behring, Milan, Italy) and the manufacturer's specified reagents.

The laboratory results obtained for PT were calculated for 5% point increments for values ranging from 0 to 60 %, and then all values > 60%.

2 - Evaluation of clinical efficiency

All patients undergoing therapy with PlasmaSafe to prevent and/or treat haemorrhagic episodes were considered. The clinical and laboratory data, in particular those concerning a possible cessation of bleeding, observed during the therapy were reported in a data form, which was compiled in the clinical department, for each patient. The dose of PlasmaSafe was 10 mL/kg/transfusion episode.

3 - Monitoring of pre- and post-transfusion coagulation parameters of SD-plasma administration in patients undergoing heart surgery, with particular attention to PS

Seven patients undergoing heart surgery were evaluated, of whom one case received a heart transplant. Controls were performed before SD-plasma administration and then 24 hours after the last transfusion episode; for repeated transfusion events, the pre-transfusion sample was taken as being the post-control of the immediately preceding transfusion. In these patients, routine coagulation parameters were measured (PT, aPTT, fibrinogen) and total PS, free PS, PS activity, protein C antigen (PC Ag) and factor VIII (FVIII) were assayed.

PS is a vitamin K-dependent plasma glycoprotein, a co-factor for PC and a natural anticoagulant inhibitor. About 40% circulates in the free form; the remaining 60% circulates linked to a complement regulatory protein. The two forms are in equilibrium, and only the free form is functionally active.

The determination of PS (total and free) was performed using a "in-house" ELISA method and NUNC plates (NUNC MaxiSorp, Roskild, Denmark) coated with anti-PS antibodies (polyclonal rabbit anti-human, DAKO, Glostrup, Denmark), and, the as secondary antibody, an antiserum labelled with anti-PS HPR (polyclonal rabbit anti-human, DAKO). Free PS is obtained by precipitation of the C4b-BP-plasma PS complex with PEG-6000. Results are expressed as a percentage in comparison to a curve calculated from pooled donors' plasma.

PS activity was determined with an ACL 9000 instrument manufactured by IL (Instrumentation Laboratory, Corporate Headquarters, Barcelona, Spain), using the manufacturer's specified reagents.

PC Ag determination was performed with a "in-house" ELISA method using NUNC plates coated with anti-PC antibodies (polyclonal rabbit anti-human, DAKO), and, as secondary antibody, an antiserum labelled with anti-PC HPR (polyclonal rabbit anti-human, DAKO). Results are expressed as a percentage in comparison to a curve calculated from pooled donors' plasma.

FVIII was determined with an ACL 9000, instrument manufactured by IL, using chromogenic reactants from Roche Diagnostics (Roche Holding Ltd., Basel, Switzerland), in excess of thrombin. Results are expressed as apercentage in comparison to a curve calculated from pooled donors' plasma.

4 - Monitoring of pre-and post- transfusion coagulation parameters of SD-plasma administration in patients undergoing orthotopic liver transplantation, with particular attention to PS

Eight patients who underwent orthotopic liver transplantation were evaluated before the transfusion and 24 hours after the transfusion of SD-plasma or, in any case, before the subsequent transfusion. In these patients all the previously described tests were performed.

5 - Treatment of patients with TTP

Three patients with TTP were treated with SD-plasma as the replacement fluid for the plasma exchange, using as a replacement fluid 4% albumin solution (1/3 plasma volume) plus SD-plasma (2/3 plasma volume). For each patient, 7, 7 and 6 procedures were carried out in, respectively 8, 7 and

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8 days, using the COBE Spectra cellular separator (Gambro, Lakewood, CO, USA). The patients were administered 12,600; 21,000 and 15,000 mL of SD-plasma, corresponding to an average of 244.3 mL/kg.

6 - Haemovigilance of SD-plasma induced adverse reactions

Our Transfusion Centre has an active haemovigilance system, that receives notification of adverse events caused by the transfusion of blood and/or blood products.

Results

1 - Evaluation of coagulation parameters of the FFP units

When considering the general data on PT, aPTT and fibrinogen (Table I), it is clear that the mean values of the 312 plasma tested units were satisfactory for therapeutic use. In our experience, the average of these parameters differs between FFP and apheresis-derived plasma; the mean values of PT and aPTT of the latter are lower than those of FFP (Table II).

In contrast, SD-plasma, derived from FFP delivered to industry and returned after treatment, is homogeneous and has a standardised coagulation factor content, as declared for a single batch production.

2 - Evaluation of clinical effectiveness

From May 2005 to April 2006, 879 consecutive transfusion events in 490 patients transfused with SD-plasma were considered, by evaluating the response to plasma administration in terms of variation between pre- and post-PT values. From an analysis of the data analysis (Figure 1) it was found that:

1- in 267 (30%) transfusion episodes the PT value remained in the pre-treatment range (Figure 1);
2- in 208 (24%) transfusion episodes the PT value moved to an lower range (data not shown);
3- in 404 (46%) transfusion episodes the PT value moved to a higher range(data not shown).

Therefore, from a laboratory or clinical viewpoint, 76% (46% + 30%) of transfusion episodes responded to the plasma infusion, with improved coagulation balance or a stabilisation of the clinical status, by controlling haemorrhage. It must also be noted that more than 60% of the transfusion events were provoked by clinical data of active bleeding: nevertheless, 198 bleeding episodes (22.5%) were not confirmed by laboratory testing, since subsequent coagulation results were within the normal range, and thus made the diagnosis of a bleeding complication unlikely. Of the 490 patients transfused, 374 (76%) needed a single SD-plasma transfusion, given the clinical improvement, while 116 patients required two or more transfusions.

Diseases that frequently required plasma transfusion support were:
abdominal aortic aneurysm/aorto-coronary bypass =23%
liver cirrhosis/orthotopic liver transplantation = 22%
cancer = 13%.

3 - Monitoring of pre- and post-transfusion coagulation parameters of SD-plasma administration to patients undergoing heart surgery, with particular attention to PS

Seven patients who underwent heart surgery were transfused with an average of 4.6 SD-plasma units (range 3-11), each in a single transfusion episode. As indicated in table III, a large increase of free PS was detected, while the increase in PS activity was small. Only in one patient (data not shown), who was transfused with 4 SD-plasma units, were the coagulation parameters not corrected by the transfusion, but remained below the lower normal limit.

Table I - Coagulation parameters of all units

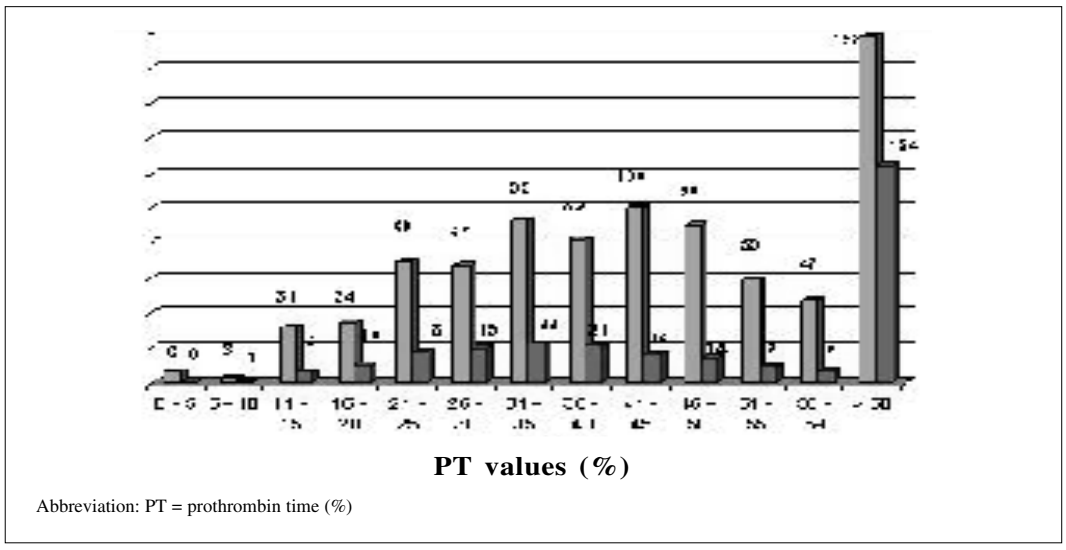
FFP Units (N=312)	PT (%)	aPTT (sec)	Fibrinogen (g/L)
Mean	80.5	30.5	2.91
Range	50-120	24-41	1.42-6.84

Abbreviations: FFP = Fresh-frozen plasma; PT= prothrombin time; aPTT = activated partial thromboplastin time

Table II - Coagulation parameters of FFP produced from whole blood fractionation (FFP 1) and by apheresis (FFP 2)

FFP 1 (N=154)	PT (%)	aPTT (sec)	Fibrinogen (g/L)	FFP 2 (N=158)	PT (%)	aPTT (sec)	Fibrinogen (g/L)
Mean	83.4	31.4	2.72	**Mean**	77.6	29.7	3.10
Range	52-120	26-39	1.42-5.32	**Range**	50-103	24-41	1.6-6.84

Abbreviations: FFP = Fresh-frozen plasma; PT= prothrombin time; aPTT = activated partial thromboplastin time



Abbreviation: PT = prothrombin time (%)

Figure 1 - Distribution of all patients related to basal PT value (light grey columns) compared to distribution of 267 patients who doesn't change PT value after plasma infusion (dark grey columns), both related to basal PT values.

4 - Monitoring pre- and post-transfusion coagulation parameters of SD-plasma administration to patients undergoing orthotopic liver transplantation

To the eight patients who underwent orthotopic liver transplantation, an average of 13.8 SD-plasma units (range: 4-25 units) was transfused, in a total of 15 transfusion episodes. As shown in table IV, the highest average increase was observed for PS-activity (75 %), while the smallest was for PC Ag (11.8%). Only in one patient was the pre-transfusion PS value not corrected by SD-plasma administration (data not shown); this patient, however, required minor transfusion support (4 units).

5 - Treatment of patients with TTP

All three patients with TTP, who were treated with plasma exchange using SD-plasma as the replacement fluid, responded to therapy, in the absence of any adverse effect, although they received overall plasma volumes of > 200 mL/kg in a very short period (7-8 days). The platelet counts in these patients were higher than 100,000/μL after 5, 4 and 4 plasma exchange sessions. It should be noted that one patient was transferred to our Centre from another, where she had been treated with FFP, which caused severe adverse reactions, without producing any clinical response.

6- Haemovigilance of adverse reactions induced by SD-plasma

In the period from May 1, 2005 to April 30, 2006, a total of 8,422 SD-plasma units and 1,734 FFP units were transfused.

Two cases of adverse reactions to FFP administration were notified, while no reaction following SD-plasma administration was recorded.

Table III - Coagulation parameters of patients undergoing heart surgery (N=7)

	PT (%)	aPTT (sec)	Free PS (%)	Total PS (%)	PS activity (%)	PC Ag (%)	F VIII (%)
Pre- values	51.7	32.1	53	68	59	64	49.4
Post- values	74.3	27.4	66	83	66	77	71
Increase %	43.7	14.6	24.5	22	11.8	20.3	43.7

The results are expressed as the mean.
Abbreviations: PT = prothrombin time; aPTT = activated partial thromboplastin time; PS = Protein S; PC = Protein C

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Table IV - Coagulative parameters on patients undergoing OLTx (N=8))

	PT (%)	aPTT (sec)	Free PS (%)	Total PS (%)	PS activity (%)	PC Ag (%)	F VIII (%)
Pre- values	38.2	52.2	30	38	22	34	42.4
Post- values	43.1	37.2	41	49	38.5	38	54.7
Increase %	12.8	28.7	36.6	28.9	75	11.8	29.1

The results are expressed as the mean.
Abbreviations: OLTx = orthotopic liver transplant; PT = prothrombin time; aPTT = activated partial thromboplastin time; PS = Protein S; PC = Protein C

Table V - Comparison between FFP, MB-plasma and SD-plasma (Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. British Committee for Standard in Haematology, Blood Transfusion Task Force. Br J Haematol 2004; **126**:11-28, partially modified)

	FFP	MB-plasma	SD-plasma
Raw material	Apheresis-derived or fractionation plasma	Apheresis-derived or fractionation plasma	Pooled apheresis-derived or fractionation plasma
Serologic tests (according to the Italian legislation)	Anti-HIV1/2, HBsAg, anti-HCV, VDRL, ALT	Anti-HIV1/2, HBsAg, anti-HCV, VDRL, ALT	Anti-HIV1/2, HBsAg, anti-HCV, VDRL, ALT
Molecular biology tests	HIV, HBV, HCV (according to the Venetian region standards)	HIV, HBV, HCV (according to the Venetian region standards)	HIV, HBV, HCV (according to the Venetian region standards) + HAV and parvovirus B19
Volume	500-600 mL or 250 mL ± 50 mL	200 - 300 mL	200 mL (standard)
Residual toxic additives	No	Possible: filtering recommended	Non toxic levels
Coagulation factors content	Variable among units, not declared	Variable among units, not declared	Constant per batch, PS reduction declared
Allergic reactions	Possible	Possible	Decreased
TRALI	Possible	Possible	Rare

Abbreviations: FFP = fresh-frozen plasma; MB-plasma = methylene-blu plasma; SD-plasma = solvent-detergent plasma; TRALI = Transfusion related acute lung injury

7 - Monitoring of plasma consumption and cost analysis

In the period May 1, 2005 to April 30, 2006, we transfused 8,422 SD-plasma units (corresponding to 1,684.4 litres, and equivalent to 75% of the total transfused plasma), 1,227 FFP units separated from whole blood (corresponding to 306.7 litres), and 507 units from apheresis (corresponding to 253.5 litres), i.e., a total 2,244.6 litres. In the previous period from May 1, 2004 to April 30, 2005 a total of 2,308.3 litres of FFP had been transfused. There was, therefore, a slight reduction (-3.0 %). Although this reduction may seem of little relevance, it does assume a significance, if it is considered that the consumption of packed red cell units in the same period increased by 5.6%. Furthermore, the average regional consumption of plasma for clinical uses in 2005 increased 5.5%, compared to the value for 2004.

The industrial cost of the inactivation procedure is 36 • for each 200 mL unit; this cost could be reduced if, as a result of other Transfusion Services joining the project, the plasma lots delivered to the manufacturer were larger. The average cost of the "home made" MB plasma inactivation procedure, based on the data of the 2004 regional analytical accounting report, is 43.58 • for a 200-300 mL unit.

Discussion and conclusions

Beginning from the mid-1980s, SD treatment of plasma was introduced in the USA and in Europe with the aim of

increasing the safety of transfusion therapy. Such treatment has been shown to be efficient in viral inactivation of plasma, while simultaneously maintaining normal protein levels. In particular, it is able to inactivate lipid-enveloped viruses, including the West Nile virus (WNV)[15]. More recently, the transfusion risk due to variant Creutzfeldt-Jacob disease has driven the use of inactivation techniques, that, although non-specific, can reduce the risk of transmission [3,16].

With regard to the envelope-free viruses, such as Parvovirus B19 and hepatitis A, each plasma unit sent for industrial inactivation is accompanied by a well-identified sample, on which to perform NAT testing for hepatitis A virus and Parvovirus B19 at the Kedrion laboratories [17].

Transfusion safety is an extremely important issue in Italy, both at the level of single Blood Banks, as well as at regional and national levels. Therefore, like other areas of Europe, Italy has introduced virus inactivation methods for the treatment of plasma. In some Italian regions, such as Piedmont, Marche and Molise, specific indications for the use of SD-plasma were given, also taking into account the cost to the institution for the activity, whereas in other regions the commercially available product was considered. On the other hand, many Blood Transfusion Services opted for the MB photo-inactivation method, which is a practical procedure for single Blood Banks. Both these methods offer advantages and disadvantages that, also in comparison with FFP, are summarised in the table V.

Regarding SD-plasma, which was the preference of our Blood Bank, the main critical points are:

1 reduction of PS levels, in comparison with those in FFP and MB-plasma;
2 need to prepare a plasma pool, thus increasing the number of allogeneic exposures to the patient.

Reduction of PS levels

It is commonly agreed that the FFP treatment used to reduce viral risk causes little loss of coagulation factors, but a more noticeable loss of PS. Literature reports of venous thrombosis and pulmonary embolism in patients transfused with high volumes of SD-plasma, during plasma exchange treatment for TTP, as well as during orthotopic liver transplantation[7-10], have resulted in the U.S. Food and Drug Administration, forbidding the use of this product in patients with severe liver disease. As a matter of fact, as rightly reported by several Authors, it is necessary to distinguish between the U.S. and the European products [8,10,15]. The main difference lies in the raw material used in the process, namely the type of plasma. In fact, European plasma is derived from pools of 500 to 1,600 donations (corresponding to 380 L), while the North American one is derived from a larger pool (2,500 donations, corresponding to 1,500 L), requiring more time for processing and resulting in greater stress to clotting factors; moreover, the North American SD-plasma goes through an ultrafiltration step to concentrate the coagulation factors, but this reduces the levels of serpines (α1-antitrypsin and α2-antiplasmin).[18-20]

As far as concerns differences in the raw material used, PlasmaSafe is derived from the processing of Italian plasma, frozen within 6 hours of collection (prevalently from apheresis), in accordance with national legislation; in contrast, North American SD-plasma is derived from FFP, frozen within 15 hours of collection. It is well known that in FFP, rapidly frozen, and in apheresis derived-plasma, levels of clotting factors, including PS, are higher[15].

In both groups of patients we studied (one group underwent cardiovascular surgery, and the other orthotopic liver transplantation), all but one patient had an increase in coagulation parameters. There were also increases in free PS, total PS and PS activity. The lack of increase in coagulation parameters in the one patient concerned only the three PS parameters, as the levels of the other coagulation factors, were corrected by the plasma administration (data not shown).

Finally, the specificity of PS activity tests, as well as its clinical significance, still need to be defined since there are still some technical difficulties related to the determination of PS. Moreover, three different types of genetic defects of PS have been identified, in some cases with normal values of total and/or free PS, characterised by a decrease of only functional activity [21].

Need to prepare a pool

The use of plasma pools can apparently constitute a disadvantage as, in the case of contamination by infectious agents, this will involve many more patients.

Actually, the dilution of the viral load (if present) and the content of specific antibodies (very probable owing to the pool's composition) make an infectious risk only hypothetical.

Furthermore, the principal objection that, when using pooled plasma in comparison with single units, the advantage of a reduced number of allogenic exposures is lost, must be overcome as has already been achieved for the production of albumin, immunoglobulins and other plasma products, with some indisputable advantages.

Most Authors have indicated that the transfusion safety

Table VI - Transfusion consumption from 2002 to 2005 in the Hospital of Padua

	2002	2003	2004	2005
FFP (kg)	1,875	1,960	2,316	2,135
FFP (n. of units)	8,522	8,909 (+4.5 %)	10,527 (+18.2 %)	10,079 (-4.4 %)
RBC (n. of units)	26,636	28,910	30,062	31,954
Autologous RBC (n. of units)	1,670	1,840	2,004	2,122
RBC (total n. of units)	28,305	30,594 (+8.1 %)	32,066 (+4.8 %)	34,076 (+6.3 %)
FFP/RBC ratio	1:3.3	1:3.4	1:3.0	1:3.4

Abbreviations: FFP = fresh-frozen plasma; RBC = red blood cells

characteristics of SD-plasma, also apart from any infectious risk, are as follows:

1 the proven better standardization of the protein content[15] and, particularly, of the clotting factors, which were shown to be effective also in the correction of rare coagulation defects[22,23];
2 the definitive demonstration that the reduction of high molecular weight vWF multimers maintains nearly unchanged ADAMTS-13 activity; for this reason, the product is particularly suitable for TTP, as the replacement fluid in plasma exchange [10,24-26];
3 the observed decreased immunological risk, due to the removal of cells and cell fragments from the treated plasma; in this context, episodes of transfusion-related acute lung injury (TRALI), which is still undervalued because of diagnostic difficulties, but constitutes one of the main causes of transfusion-related mortality [15,27,28], have never been described following SD-plasma administration; our haemvigilance of the use of SD-plasma, although limited to 1 year, confirms these data.

The effectiveness of the product was confirmed, considering that, in 76% of transfusion events that underwent monitoring pre- and post-transfusion of SD-plasma, the coagulation parameters either remained within the pre-transfusion range or were corrected, and that 374 (76%) of 490 transfused and tested patients needed only a single plasma transfusion, at a dose of 10 mL/kg, probably because of a clinical improvement.

The availability of a product with a standardised content of coagulation factors, with pharmaceutical value, has encouraged a more correct use of plasma, which indeed led to a reduction in the consumption of this blood component with respect to its consumption in previous years, and in countertendency to the increase in the use of packed red blood cell units (Table VI).

All three patients with TTP, who were treated during the same period by plasma exchange, responded to the treatment, without showing any immunological reactions. The patient who had been transferred from another hospital, where she had begun apheretic treatment with FFP that caused severe allergic reactions, was treated with SD-plasma without any adverse effects and with complete disease remission. Indeed, there were no notifications of any adverse reactions in the study period, during which more than 8,000 SD-plasma units were administered to the whole patient population.

In conclusion, our 1-year experience of the use of SD-plasma revealed positive clinical aspects, in particular its effectiveness and the lack infectious as well as immunological complications.

There were no reported complications, even those previously described in the literature, due to the administration of this transfusion product, in spite of its use in various clinical setting, thus confirming experiences in Norway [2] and Ireland [3].

The organisational implications for the Transfusion Centre are acceptable, since the delivery of plasma to industry for the production of plasma derivatives is a tried and tested procedure.

Obviously, the inactivation process constitutes an important economic burden, but one that is absolutely comparable to those verified by the regional entities for other systems used in the main Blood Transfusion Units in the Region.

As for every blood product, SD-plasma must be assigned only to those patients having an appropriate indication for its use, in accordance with well-accepted guidelines [17]. In these patients, the expected benefit from the transfusion must be greater than the risk, albeit remote, of any adverse effect.

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