Coagulation factor levels in solvent/detergent-treated plasma

Recently, an extensive committee report on the current status of solvent/detergent (S/D)-treated frozen plasma was published by Klein et al.[1] in **TRANSFUSION**. Although S/D-treated plasma is now widely used, little is published about the amount and the stability of the individual coagulation factors in S/D-treated plasma.[2,3] According to the manufacturers, S/D treatment does not significantly alter the concentration of coagulation factors, and a concentration of the individual coagulation factors of at least >0.50 U per mL (50% of normal) is guaranteed. Although this level is above the hemostatic value of most coagulation factors, it may be insufficient for correction of severe deficiencies of coagulation factors.

We studied the levels of several coagulation factors in seven batches of S/D-treated plasma (ESDEP, CLB, Amsterdam, the Netherlands). This S/D-treated plasma is prepared from pooled fresh-frozen plasma (FFP) from healthy unpaid Dutch blood donors. The technology used to prepare S/D-treated plasma was developed by Octopharma AG (Glarus, Switzerland).[4] S/D-treated plasma was thawed in a waterbath at 37°C for 20 minutes according to the manufacturer's instructions. Plasma samples were tested in duplicate immediately after thawing and after storage at room temperature for 2, 4, and 8 hours. Antithrombin, plasminogen, and antiplasmin were measured wtih chromogenic assays. Other coagulation factors, including protein S and protein C activity; factors II, V, VII, VIII, IX, X, XI, and XII; and fibrinogen, were determined according to standard clotting assay procedures. Protein C, protein S, and von Willebrand factor (vWF) antigen levels, as well as binding of vWF to collagen were determined by enzyme-linked immunosorbent assays. For our laboratory assays, reference pooled plasma was obtained from 40 healthy volunteers. Coagulation factors were not determined in FFP before S/D treatment.

The results of the concentrations and activities of coagulation factors in S/D-treated plasma are shown in Table 1. Most coagulation factors are present at a level that is found in normal pooled plasma. However, antiplasmin and protein S activities are decreased to less than 50 percent of those in normal pooled plasma. All coagulation factors were stable at room temperature for at least 8 hours, except protein S activity, which decreased from a median of 0.45 U per mL (range, 0.42-0.53) to one of 0.34 U per mL (0.29-0.36).

The low levels of antiplasmin and protein S activity in S/D-treated plasma may be of clinical importance. Besides being low in patients with a congenital antiplasmin deficiency, the levels of antiplasmin can be greatly decreased in patients with severe liver disease, after thrombolytic therapy, during liver transplantation, in patients with amyloidosis, and in patients with acute promyelocytic leukemia.[5,6] In these patients, the infusion of S/D-treated plasma may be insufficient to correct the antiplasmin deficiency. It is known that levels of 50 percent, as are found in patients who are heterozygous for antiplasmin deficiency, may be associated with a mild hemorrhagic tendency.[5] Therefore, in case of severe antiplasmin deficiency, FFP instead of S/D-treated plasma may be required to achieve an antiplasmin level >50 percent of normal.

The importance of the low levels of protein S is less clear. Hereditary protein S deficiency is associated with a thrombotic tendency. In patients with purpura fulminans caused by bacterial or viral infections, reduced levels of protein C and protein S have been reported.[7] Because these patients are nearly always treated with plasma substitution, the concentration of proteins S and C in the infused plasma may be of importance. Theoretically, the infusion of plasma that is deficient in protein S may be less effective in this patient group than the infusion of FFP.

All other coagulation factors that we measured, including vWF, were present at normal levels when compared to the levels in normal pooled plasma. Earlier studies indi-

TABLE 1. Coagulation factor levels in S/D-treated plasma

Factor*	Median	Range	Normal range
Antithrombin	0.84	0.81 - 0.89	0.80 - 1.20
Fibrinogen	2.6	2.6 - 2.7	1.5 - 3.6
Antiplasmin	0.47	0.45 - 0.49	0.80 - 1.20
Factor			
II	0.85	0.72 - 0.88	0.60 - 1.40
V	0.87	0.81 - 0.90	0.50 - 1.50
VII	1.00	0.95 - 1.04	0.60 - 1.40
VIII	0.92	0.78 - 1.01	0.60 - 1.40
IX	0.83	0.80 - 0.99	0.60 - 1.40
X	0.84	0.79 - 0.85	0.60 - 1.40
XI	0.95	0.88 - 1.00	0.60 - 1.40
XII	0.93	0.85 - 1.03	0.60 - 1.40
VWF			
Antigen	1.65	1.60 - 1.95	0.60 - 1.40
Collagen-binding activity	1.05	0.86 - 1.26	0.60 - 1.40
Plasminogen	0.93	0.87 - 1.01	0.85 - 1.20
Protein S			
Total	0.85	0.79 - 0.93	0.70 - 1.40
Activity	0.45	0.42 - 0.53	0.70 - 1.40
Free	0.83	0.72 - 0.95	0.76 - 1.40
Protein C			
Antigen	1.05	0.95 - 1.18	0.70 - 1.40
Activity	0.69	0.66 - 0.71	0.70 - 1.40

* All values U per mL, except for fibrinogen, for which values are g per L.

cated, however, that the levels of high-molecular-weight vWF multimers are lower in S/D-treated plasma than in FFP. The clinical importance of this decrease is not yet known.[8,9]

In conclusion, we state that virus-inactivated plasma obtained by S/D treatment contains normal levels of nearly all coagulation factors and that, in our system, those factors are stable even after the plasma has rested for 8 hours at room temperature. However, it is important to be aware that S/D-treated plasma has low levels of antiplasmin and protein S. Therefore, in cases in which severe coagulation disturbances are corrected by S/D-treated plasma infusion, it would be advisable to measure these individual coagulation factors. Clinical studies are necessary to establish the clinical importance of these low coagulation factor levels in S/D-treated plasma.

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