Treating Thrombotic Thrombocytopenic Purpura With Plasma Exchange

ABSTRACT Plasma exchange with fresh-frozen plasma has been used for several years as therapy for thrombotic thrombocytopenic purpura (TTP), among other disorders. A review of the literature describing TTP indicated successful treatment with cryoprecipitate-poor plasma in plasma exchange alone or with fresh-frozen plasma. Inquiry with our hospital’s plasma supplier provided information about cryoprecipitate-poor plasma and a newly approved plasma product, solvent/detergent-treated plasma, that substantially reduces the risk for transmission of HIV or hepatitis C virus. Use of more than one plasma product can result in more effective and economic treatment than with one product alone and can provide flexibility for both the blood bank and the supplier when demand exceeds supply.

From Norton Southwest Hospital, Louisville, Ky.

Reprint requests to Mr Womack, Norton Southwest Hospital Laboratory, 9820 Third Street Rd, Louisville, KY 40272.
**Fresh-Frozen Plasma, Cryoprecipitate-Poor Plasma, and Solvent/Detergent-Treated Plasma**

FFP is defined as anticoagulated plasma that has been separated from RBCs, frozen within 8 hours of collection, and kept at or below a temperature of -18°C. At this temperature FFP has a shelf life of 12 months.5 FFP contains all of the clotting factors, including vWF, in normal concentrations. The current price per unit is $53.00.*†

Cryoprecipitate-poor plasma (CPP) is the supernatant remaining after cryoprecipitated anti-hemophilic factor (Cryo) has been removed from frozen plasma. Cryo is prepared by thawing FFP at 1°C to 6°C, and the resulting CPP contains fewer procoagulants than found in whole plasma, including vWF. It has a shelf life of 5 years when stored at or below -30°C. 6 The current cost per unit is $40.00.*†

Solvent/detergent-treated plasma (S/DP), a relatively new product, is pooled and treated ABO-specific fresh plasma from as many as 2,500 donors. The treatment used in production of S/DP is effective in removing enveloped viruses such as hepatitis C virus, hepatitis B virus, HIV-1 and HIV-2, cytomegalovirus, and herpes simplex virus-1.7 The pooled plasma is incubated for 4 hours at 31°C with 1% vol/vol tri(n-butyl) phosphate solvent (TNBP) and 1% vol/vol Triton X-100 detergent (Union Carbide Chemicals and Plastics, Danbury, Conn). The solvent and detergent fractions are removed, and the treated plasma is sterile filtered into 200-mL plasma bags. It has a shelf life of 12 months when stored at or below -18°C.* The current national list price per unit is $150.00.

A recent study quantitated several coagulation factor differences between FFP and CPP. There was a significant decrease in fibrinogen, factor VIII, and von Willebrand factor antigen (vWF:Ag) across all ABO groups for CPP, but no substantial decrease in factor V levels (Table 1). vWF:Ag is an immunologically determined concentration of vWF, as opposed to traditional measurement by clotting time. For all groups, prothrombin time did not change, but activated partial thromboplastin time increased.8

S/DP is equivalent to FFP in terms of coagulation, fibrinogen, and immunoglobulins.9 It has nearly the same levels of coagulation factors as FFP, decreased levels of factors IX and XI,10 and virtually no large vWF multimers.8 It provides a safer alternative to FFP when large volumes of plasma are required, because of viral inactivation during the treatment process. The treatment utilized in production of S/DP does not inactivate nonenveloped viruses, especially hepatitis A and human parvovirus B19,10 which can be present in large pools. S/DP has been as effective as FFP for treating coagulation disorders,11 including one case of TTP that was refractory to FFP treatment.6

**Plasma Exchange With Fresh-Frozen Plasma, Cryoprecipitate-Poor Plasma, and Solvent/Detergent-Treated Plasma**

Plasma exchange with FFP has proved effective for treating patients with TTP for at least two decades, and the long-term effects are fairly well known.12-14 In one study focusing on long-term outcomes, follow-up of four patients who under-

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*Holly Popeck, River Valley Region American Red Cross Blood Services (Louisville, KY), personal communication, February 1999.

†Availability and price will vary by region and distributor.

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### Table 1. Comparison of Procoagulants and Coagulation Times

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<tr>
<th>Test</th>
<th>Fresh-Frozen Plasma</th>
<th>Cryoprecipitate-Poor Plasma</th>
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<tbody>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>278 ± 3</td>
<td>181 ± 29</td>
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<tr>
<td>Factor V activity (%)</td>
<td>87 ± 4</td>
<td>81 ± 9</td>
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<tr>
<td>Factor VIII activity (%)</td>
<td>80 ± 6</td>
<td>23 ± 6</td>
</tr>
<tr>
<td>von Willebrand factor antigen (%)</td>
<td>83 ± 15</td>
<td>22 ± 13</td>
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<tr>
<td>Prothrombin time (s)</td>
<td>12.6 ± 0.2</td>
<td>13.0 ± 0.6</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (s)</td>
<td>26.9 ± 0.3</td>
<td>35.1 ± 1.8</td>
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plasma exchange (37 to 108 procedures) demonstrated good recovery and remission over a period of years. Several studies have been conducted that used both FFP and CPP in plasma exchange to evaluate their use in treating TTP, most involving patients with TTP who were unresponsive or refractory to FFP therapy. In one study of 18 patients with TTP refractory to FFP plasma exchange, 11 (61%) showed improvement (platelet count >150 X 10^3/µL), and 15 (83%) survived to 1 month after seven CPP plasma exchange treatments. This study compared results with a previous finding that 61% of patients refractory to FFP responded to CPP plasma exchange, with an 83% survival rate at 1 month. This response was also seen in a study with seven patients who showed improvement (defined as an increase in platelet count) after treatment was changed from FFP to CPP plasma exchange. Another study compared two groups of similar patients, one treated with FFP plasma exchange between 1985 and 1989 and the other treated with CPP plasma exchange between 1989 and 1993. Its findings showed a 72% survival rate for the group treated with CPP plasma exchange, compared with 47% for the group treated with FFP plasma exchange.

Two Italian studies using CPP plasma exchange showed rapid disappearance of neurologic symptoms, but platelet counts and lactate dehydrogenase levels did not return to normal any faster than had been seen with FFP plasma exchange. Plasma hemoglobin and lactate dehydrogenase values, and platelet count have not shown any prognostic value for TTP; thus the significance of these studies is unclear. CPP plasma exchange is usually performed without complications, with the exception of possibly low plasma concentrations of fibrinogen, factor VIII and factor V, and vWF from multiple treatments, and citrate toxicity from the use of acid citrate dextrose anticoagulant (ACD) in CPP and FFP.

**Discussion**

Plasma exchange treats the symptoms of TTP and facilitates remission. Advantages and disadvantages of each plasma product used in plasma exchange are shown in Table 2.

Awareness of each product's advantages, disadvantages, and availability, together with the needs of the patient, allows the blood bank to use all three products effectively during treatment. In unresponsive patients, treatment can be switched from FFP to CPP, reducing the patient's expense and risk for refractory TTP. S/DP could be used effectively for long-term massive plasma exchange or when FFP or CPP is not available. Blood banks could justify larger stocking levels of FFP for infusion and emergency plasma exchange while waiting for CPP and S/DP shipments to arrive. Similarly, the longer shelf life of CPP permits storage for emergencies and infusion with less cost from returning outdated units.

<table>
<thead>
<tr>
<th>Table 2. Comparison of Plasma Products</th>
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<tr>
<td><strong>Advantages</strong></td>
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<tr>
<td>Fresh-Frozen Plasma</td>
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<td>Cryoprecipitate-Poor Plasma</td>
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<tr>
<td>Solvent/Detergent-Treated Plasma</td>
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<tr>
<td>Availability</td>
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vWF indicates von Willebrand factor.
Conclusion
The documented effectiveness of FFP, CPP, and S/DP in plasma exchange can provide flexibility when demand exceeds supply. The effectiveness of plasma exchange lies more in multiple treatments than in the product used, which allows short-term substitution without compromising patient care. In an era of managed care, the low cost of CPP along with its effectiveness in treating patients with TTP can cut the overall cost to the facility and to the patient. Efficient use of supplier stock can also hold down the ultimate cost to the blood bank by limiting import costs generated by the supplier. Patients with TTP may require costly, extensive treatment, but by understanding how the disease can be treated, blood banks can facilitate efficient use of products derived from a limited supply of donated whole blood.

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References