Thrombotic Thrombocytopenic Purpura and Dose of Plasma Exchange

By Edwin G. Taft

Four patients with thrombotic thrombocytopenic purpura (TTP) were treated by plasma-exchange transfusion, three of whom recovered completely. Because previous reports in the literature describing exchange transfusion as treatment for TTP have demonstrated variable success rates, particular attention was given to “dose” and frequency of plasma exchange. Evans blue dye studies established a measure of “dose” under conditions of varying efficiency. Serum LDH activity was found to be diminished by plasma exchange, and the rate of return of serum LDH activity reflected residual disease activity. The magnitude of LDH activity reduction correlated with the adequacy of dose of plasma exchange and was an indicator for the need of repeated daily exchanges. Failure to obtain a spontaneous increment in platelet count also suggested the need for additional exchanges and/or larger dose of exchange. There is a need for a standard expression of dose of plasma exchange. Utilizing these markers (LDH, platelet count), it may be possible to improve the survival in TTP if adequate dose and frequency of plasma exchange are used.

PLASMA-EXCHANGE TRANSFUSION is of variable benefit in the management of over 30 different conditions. A survey of the reports in which the methodology is adequately described reveals that the volume of exchange transfusion varies considerably, some centers using 2-liter exchanges and others using 5–6 liters or more. A heterogeneous response to plasma exchange in thrombotic thrombocytopenic purpura (TTP) is reported, recent reports being divided as to its efficacy. As plasma-exchange transfusion therapy must be considered comparable to phase I and phase II drug studies, there must be closer attention given to the “dose” and frequency of plasma exchange and to appropriate markers of response to treatment. Data from four patients suggest that TTP may serve as a disease prototype with several markers to assess appropriate dose and frequency of treatment.

CASE REPORTS

Patient 1

This 52-yr-old woman was admitted with a 3-day history of crampy abdominal pain and bloody diarrhea. Admission leukocyte count was 17,400/µl, hemoglobin 18.8 g/dl, hematocrit 57%, BUN 17 mg/dl, and LDH 250 U. Inflammatory bowel disease was suspected, a barium enema was interpreted as showing mucosal changes compatible with the clinical diagnosis, and sulfasalazine was begun. Over the next 48 hr, she became confused, progressively oliguric, and mildly jaundiced. Thrombocytopenia was noted on the blood smear at this time, BUN had risen to 54 mg/dl, hematocrit had fallen to 33.6%, and bilirubin had risen to 2.5 mg/dl from 0.9 mg/dl. Sulfasalazine was discontinued, and she was transferred to Albany Medical Center Hospital for management of renal failure. Initial laboratory values following transfer are shown in Table 1. Microangiopathic red cell changes were present on peripheral blood smear. She became totally anuric, and simultaneous hemodialysis and plasma...
Table 1. Four Patients With Thrombotic Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Hemoglobin (g/dl)</th>
<th>Preexchange Hematocrit (%)</th>
<th>Platelet/μl</th>
<th>BUN (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>LDH (U)</th>
<th>Duration of Symptoms Before First Exchange (Days)</th>
<th>Outcome</th>
<th>Dose of Total Exchange (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/F</td>
<td>5.7/17.1</td>
<td>34,000</td>
<td>123</td>
<td>6.9</td>
<td>3,740</td>
<td>10</td>
<td>Recovered</td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>2</td>
<td>14/M</td>
<td>6.1/18.0</td>
<td>3,600</td>
<td>56</td>
<td>1.6</td>
<td>2,830</td>
<td>23</td>
<td>Recovered</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>3</td>
<td>21/F</td>
<td>8.2/23.8</td>
<td>8,500</td>
<td>27</td>
<td>1.8</td>
<td>1,647</td>
<td>13</td>
<td>Died</td>
<td></td>
<td>322</td>
</tr>
<tr>
<td>4</td>
<td>43/F</td>
<td>8.0/22.6</td>
<td>4,000</td>
<td>81</td>
<td>1.9</td>
<td>2,330</td>
<td>3</td>
<td>Recovered</td>
<td></td>
<td>770</td>
</tr>
</tbody>
</table>

Clinical features, initial (prior to first exchange transfusion) laboratory values, total exchange volume in mL/kg, and outcome of four patients with thrombotic thrombocytopenic purpura (TTP) are shown. The upper limit of normal for serum LDH is 200 U.

exchange were begun on the second hospital day (day 1 in Fig. 2). On the third day she was oriented, but again became confused on the fourth day, and despite hemodialysis, remained so on days 5 and 6. She became oriented after the second plasma exchange and remained so after a third exchange. Twelve hemodialyses over 28 days were required, and total anuria persisted for 15 days. During the course of her hospitalization, she was also treated with prednisone, acetylsalicylic acid (600 mg/day), dipyridamole (400 mg/day), and sulfipyrazone (800 mg/day). She has regained normal renal function and remains well during 17 mo follow-up.

**Patient 2**

Over 12 hr prior to admission, this 14-yr-old boy developed abdominal pain, vomiting, a petechial rash, and hematuria. Initial leukocyte count was 8100/μl, hemoglobin 14.1 g/dl, and hematocrit 38%. Serum LDH was 863 U (upper limits of normal, 130 U), BUN was 41 mg/dl, and creatinine was 2.1 mg/dl. Two days later, the hematocrit had decreased to 19.8%, and the platelet count was 38,000/μl. Corticosteroids were given. On the morning of the sixth hospital day, he was thought to have had a seizure and was transferred to Albany Medical Center Hospital. On admission, he appeared alert, but there was a mixed aphasia, a right homonymous hemianopia, and decreased deep tendon reflexes on the right. Platelet count had decreased to 4000/μl, creatinine was 1.8 mg/dl, and serum LDH was 1800 U (normal up to 200 U). Severe erythrocyte fragmentation was present on peripheral blood smear. Corticosteroids (hydrocortisone and later methylprednisolone) were continued, and heparin was begun. For the first 8 days after transfer, dipyridamole (up to 400 mg/day) was given. On the eighth day, with progressively worsening neurologic status, daily transfusions of plasma were given, and serum LDH rose from 2170 U to 2830 U. By the 15th day, he no longer withdrew from painful stimuli. On the 16th day (day 1 in Fig. 2), the first plasma exchange was done, and on the following day, he recognized his parents for the first time in 9 days. Following the fifth plasma exchange, there was still clinical evidence of metabolic encephalopathy, which subsequently cleared. He remains well with normal blood counts 16 mo later on no medication.

**Patient 3**

This 21-yr-old woman was admitted to another hospital with a 1-wk history of occipital headaches (for which she took acetylsalicylic acid), ecchymoses, and petechial rash of the lower extremities. Physical examination, including neurologic, was otherwise unremarkable. Admission leukocyte count was 11,600/μl, hemoglobin 8.4 g/dl, hematocrit 24.7%, and platelet count 28,000/μl. Schistocytes were noted on the peripheral smear. Initial serum LDH was 975 U (normal up to 225 U), bilirubin 1.9 mg/dl, BUN 14 mg/dl, and creatinine 1.4 mg/dl. Prednisone was begun. On the fourth hospital day, she was transferred to Albany Medical Center Hospital and underwent the first plasma-exchange transfusion (day 1 in Fig. 3). Prednisone and/or methylprednisolone was continued throughout the hospitalization; no antiplatelet drugs were given. Following the second plasma exchange, a transient spontaneous increment in platelet count was observed. No abnormal neurologic signs were observed until the fifth day after the first plasma exchange (day 6 in Fig. 3), when she complained of nausea, headache, and vomited twice. Six hours later, she became restless and rapidly unresponsive. Neurologic examination demonstrated diminished left-sided movement and the presence of a Babinski response on the left.
Examination of cerebrospinal fluid was unrevealing. Two subsequent plasma-exchange transfusions failed to improve neurologic status or platelet count. Terminally, BUN rose to 43 mg/dl and creatinine to 4.2 mg/dl. Twelve hours after the fifth plasma exchange, she developed cardiac arrhythmias, resulting in cardiac arrest, and expired. Permission for autopsy was not granted.

Patient 4

Three days prior to admission, this 43-yr-old woman developed cough, nausea, and vomiting. She developed progressive fatigue, low-grade fever, headaches, and petechial rash of the extremities, epistaxis, and gingival bleeding; the morning of admission she manifested confusion. Because of jaundice, she was referred to another hospital, where leukocyte count was 8000/µl, hemoglobin 8.2 g/dl, hematocrit 23.6%, and platelet count 21,000/µl. BUN was 83 mg/dl, creatinine 2.1 mg/dl, and LDH 3620 U (normal up to 230 U). There was marked anisocytosis and poikilocytosis with many schistocytes present on peripheral blood smear. A diagnosis of thrombotic thrombocytopenic purpura was strongly suspected, and the patient was referred for plasma-exchange transfusions, which were begun that evening (day 1 in Fig. 3). Unresponsive to verbal stimuli, she awoke and was alert and oriented the next morning following the first exchange (4 liters), in which replacement was plasma protein fraction (PPF) and Ringer’s solution. A second exchange of 4 liters (day 2) failed to maintain the neurologic improvement, and the volume of the third exchange was increased to 6 liters; plasma was added to the last part of the exchange to prevent bleeding from coagulation-factor depletion in the presence of thrombocytopenia, and she became alert and oriented again. Neurologic signs remained absent for the rest of her course. Acetylsalicylic acid (600 mg/day) and sulfinpyrazone (800 mg/day) were added on days 3 and 5, respectively; she received corticosteroids (methylprednisolone, 75–300 mg/day) on day 3 through day 10, when they were tapered. Following the tenth exchange, platelet counts have been maintained in the normal range over a 6-mo follow-up.

MATERIALS AND METHODS

Plasma-exchange transfusion was accomplished using a continuous-flow centrifuge (Aminco Celltri-fuge), with vascular access by peripheral vein, femoral venous catheters (Seldinger/Shaldon), or arterial-venous shunt (Scribner). Human investigations were performed after approval of protocols by the local Committee for Research Involving Human Subjects, and informed consent was obtained. In the first two patients, fresh frozen plasma was used for replacement, and in the second two patients, various combinations of albumin (as plasma protein fraction), Ringer’s solution, isotonic sodium chloride solution, and fresh frozen plasma were used.

When Evans blue dye studies were done, a known amount of dye was injected, plasma volume calculated by dye-dilution, and the recovered dye measured colorimetrically in the plasma removed from the patients. The volume of plasma exchange was calculated as the net volume of patient plasma removed, rather than as the volume of plasma/albumin/electrolyte solution replaced. Serum LDH was determined by the method of Morgenstern et al.

RESULTS

Figure 1 shows the comparison in the same patient of Evans blue dye recovery in two procedures: one in which there was considerable bypassing of patient’s plasma, and the other done bypassing less plasma. An efficient plasma exchange requires in excess of 1 plasma volume (35–40 ml/kg) to recover greater than 50% of the injected dye.

Figures 2 and 3 show the courses of four patients with TTP treated by plasma exchange. Following treatment of the first two patients, we noted the marked decrement of serum LDH following plasma exchange and a correlation between the rate of increment in serum LDH following exchange and apparent disease activity. When the rate of increment in serum LDH slowed, increments in platelet count were observed. The failure to reduce serum LDH to less than 770 U on any occasion in patient 3 is, in retrospect, an indicator of insufficient “dose” of plasma.
Fig. 1. Comparison of two plasma-exchange procedures in the same patient: the first (O--O) in which considerable amounts of plasma were bypassed to accommodate simultaneous hemodialysis (i.e., RBC returned with hematocrit approximately 25%); before addition of replacement plasma during the second procedure (●--●), considerably less plasma was bypassed (i.e., hematocrit of RBC returned to patient 60%–70% before addition of replacement plasma). For a 50% exchange (Eu), the first procedure required 52 ml/kg (4003 ml), while the second exchange required only 36 ml/kg (3010 ml). In terms of volume, for the first exchange to equal the second in efficiency, an exchange of approximately 80 ml/kg (6600 ml versus 4000 ml actual) would have been required.

Fig. 2. Sequential platelet counts and serum LDH values are shown over the first 16 days (day 1 is the day of first plasma exchange) for patients 1 and 2. Replacement for all plasma exchanges in these two patients was fresh frozen plasma. Large arrows indicate plasma-exchange transfusion; the small arrow (↓) indicates a platelet transfusion. Numbers in parentheses indicate the volume of exchange in ml/kg.
Fig. 3. Sequential platelet counts and serum LDH values are shown over the first 16 days (day 1 is the day of first plasma exchange) for patients 3 and 4. Large arrows show the plasma exchanges, small arrows (1) indicate platelet transfusions. Numbers in parentheses indicate the volume of each exchange in ml/kg. When written as a fraction, the numerator indicates the volume of exchange (in ml/kg) replaced as fresh frozen plasma, and the denominator the total volume of the exchange (in ml/kg).

exchange per procedure, and the rapidity of LDH increment terminally is a reflection of progressive disease activity.

DISCUSSION

Plasma-exchange transfusions may vary considerably in their efficiency, depending on the centrifuge system used and the hematocrit of the patient being treated. Severe anemia requires a larger extracorporeal volume for intermittent-flow centrifuges in order to maintain the maximum efficiency of plasma exchange. Suboptimal exchange efficiency, insufficient volume of exchange, and inadequate frequency of exchange may be responsible for the highly variable results reported for the treatment of TTP by plasma exchange.5,6,8,9,12,13

A comparison of other experiences with whole blood/plasma exchange in TTP (Table 2) suggests that some patients will respond to fairly low-dose exchange, while those apparently not responding to treatment may have had insufficient volume and frequency of exchange, particularly for patients described as having had “transient” responses. In the patients described in reference 4 (Bukowski et al., 1976), the average dose of plasma exchanged in the patients who died is approximately 82 ml/kg, and 104 ml/kg for those who recovered. Because there is no standard expression for dose of plasma exchange, evaluation and comparison of other reports has been impaired. Evaluation of other treatment modalities is further complicated by many reports in which patients experienced large-volume hemor-
Table 2. Exchange Transfusions for Thrombotic Thrombocytopenic Purpura (TTP)

| Reference | Patient No. (Age, Sex) | Hb/Hct | Platelets/ul | No. of Exchanges | Interval Days | Total Volume of Exchanges (ml) | Total Volume of Exchange (ml/kg) | Outcome | Splenectomy | Corticosteroids | Antiplatlet Drugs | Other
|-----------|------------------------|--------|--------------|------------------|--------------|-------------------------------|--------------------------------|---------|-------------|----------------|----------------|----------------|
| Wise (1966) | 2 (10 mo, F) | 7.3/- | 5,000 | 2 | 2 | 3,200 ml | 328 | Died | Yes | No | No | WB transfusions
| Rubinstein (1969) | 1 (11, F) | 4.7/14.0 | 48,000 | 2 | 6 | 2,250 (104)* | 75 | Recovered | No | Yes | No | Antibiotics
| Dekker (1974) | 2 (17, M) | -21.0 | 7,000 | 1 | 1 | 4,527 (19u) | 61 | Recovered | Yes | Yes | No |
| Bukowski (1976) | 7 (48, F) | 9.3/- | 20,000 | 1 | 1 | 2,700 (12u)* | 39 | Recovered | Yes | Yes | No |
| (1976) | 8 (48, F) | 9.0/- | 42,000 | 4 | ? | 10,800 (48u) | 154 | Recovered | No | Yes | No |
| 9 (80, F) | 9.4/- | 20,000 | 4 | ? | 10,800 (48u) | 154 | Recovered | No | Yes | No |
| 10 (10, F) | 9.3/- | 10,000 | 2 | 11 | 3,250 (17u) | 122 | Recovered | No | No | No |
| 11 (28, F) | 5.6/- | 20,000 | 1 | 1 | 5,400 (24u) | 77 | Died | No | Yes | No | Heparin
| 12 (15, F) | 8.3/- | 30,000 | 2 | 5 | 5,400 (24u) | 90 | Recovered | No | Yes | No |
| 13 (25, F) | 11.5/- | 10,000 | 2 | 7 | 5,400 (24u) | 77 | Recovered | No | Yes | Yes |
| 14 (49, F) | 6.5/- | 10,000 | 2 | 7 | 5,400 (24u) | 77 | Died | Yes | Yes | No |
| 15 (32, F) | 6.8/- | 30,000 | 3 | 7 | 8,100 (36u) | 116 | Died | Yes | Yes | No | Heparin
| 16 (52, M) | 8.9/- | 10,000 | 2 | 5 | 5,400 (24u) | 77 | Died | No | Yes | No | Heparin
| 17 (28, M) | 10.1/- | 13,000 | 3 | 8 | 8,100 (36u) | 116 | Recovered | No | Yes | No |
| 18 (51, M) | 8.1/- | 20,000 | 2 | 5 | 5,400 (24u) | 77 | Died | No | Yes | No |
| 19 (51, M) | 8.2/- | 22,000 | 3 | 8 | 8,100 (36u) | 116 | Died | Yes | Yes | No |
| Bukowski (1977) | 1 (32, M) | 10.4/- | 4,000 | 10 | 36 | 22,500** | 321 | Recovered | No | Yes | No |
| (1977) | 2 (21, F) | 6.5/- | 20,000 | 12 | 82 | 27,900** | 399 | Recovered | No | No | No |
| Byrnes (1977) | 1 (18, F) | 6.4/20.0 | 6,000 | 10 | 88 | 23,400 | 334 | Recovered | Yes | Yes | Yes | Plasma transfusions
| Passier (1977) | 1 (19, F) | 9.9/28.0 | 3,000 | 1 | 1 | 3,150 (14u) | 45 | Died | Yes | Yes | Yes | Dextran, hemodialysis
| (late relapse) | 2 (43, F) | —/22.0 | 20,000 | 1 | 1 | 2,025 (9u) | 29 | Recovered | No | Yes | No |
| 3 (40, M) | 7.0/24.0 | 8,000 | 3 | 19 | 8,775 (39u) | 125 | Recovered | No | Yes | Yes |
| Abramson (1978) | 1 (54, F) | —/29.0 | 21,000 | 2 | 4 | 5,400 (24u) | 77 | Recovered | Yes | Yes | Yes | Vincretine
| Ross (1978) | 1 (39, F) | 6.8/21.2 | 10,000 | 3 | 8 | 6,750 (30u) | 96 | Recovered | No | Yes | Yes | Plasma transfusions
| Present series | 1 (52, F) | 5.7/11.1 | 34,000 | 3 | 9 | 10,902 | 133 | Recovered | No | Yes | Yes |
| 2 (114, M) | 6.1/18.0 | 3,600 | 5 | 11 | 17,280 | 286 | Recovered | No | Yes | Yes | Heparin
| 3 (21, F) | 8.2/33.8 | 8,500 | 5 | 7 | 21,222 | 322 | Died | No | Yes | Yes |
| 4 (43, F) | 8.0/22.6 | 4,000 | 10 | 15 | 48,991 | 770 | Recovered | No | Yes | Yes |

*When the number of units are stated, a " unit" is assumed to contain 225 ml of plasma.
†Weight of the patient is estimated to be 30 kg.
‡Weight of the patient is estimated to be 60 kg.
§Whole-blood exchange, stated to be "8-12" U., are assumed to be 12 U in this series.
**Plasma exchanges of "2-3" liters are estimated at 2,500 ml for these two patients.

This patient estimated to be 27 kg.
This patient estimated to be 60 kg.

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rhage and blood replacement, in effect an exchange transfusion, for which no estimate of volume can be made.²

Recently, it has been suggested that replacement of a normal plasma factor is necessary,⁵¹⁴ although a dilutional effect of plasma transfusion has not been excluded. The use of large quantities of fresh frozen plasma, with potential for hepatitis transmission, may not be in the best interests of these patients and further exploration of “plasma-free” replacement is essential. Data presented here neither confirm nor exclude the proposed beneficial effect of plasma transfusion.

Reiss et al. illustrate two points in a letter describing their experience with one patient.¹³ The patient’s condition worsened during the procedure, and they noted brown plasma in the collection bag. It has been our experience that there may be a marked discrepancy in the patient’s apparent and actual clinical condition (a patient may look well and suddenly deteriorate). Patient 2 experienced a seizure during the second exchange, with no long-term sequelae, and we feel that fluctuations in the clinical condition do not necessarily require cessation of the exchange. Brown plasma was seen in both patients 3 and 4 (maximum bilirubin 5.7 mg/dl and 4.5 mg/dl, respectively), and to us this indicates active disease and demands daily plasma exchanges of adequate volume. The darkness of plasma during active disease is disproportionate to the level of bilirubin measured and is not due to free hemoglobin, but probably results from marked hemolysis.

LDH is a high-molecular weight substance (>200,000), and serum activity is virtually unaltered by hemodialysis, but readily removed by plasma exchange. In patients 3 and 4, in whom LDH was fractionated, 75% of LDH was divided almost equally among bands 1–3 (LDH2 slightly greater than LDH1, slightly greater than LDH3), with lesser amounts of LDH4 and LDH5. While hemolysis is probably a major source of serum LDH activity, organ damage may also contribute. The fall and rise of serum LDH activity provides a readily available marker for the dose and frequency of plasma exchange. Failure to reduce LDH below 300 U (our normal range, 50–200) suggests that a larger volume (“dose”) of plasma exchange should be used. A rapid reaccumulation (to >500 U overnight) suggests that the frequency of the procedure should be daily. Failure to achieve a spontaneous increment in the platelet count within 24 hr also suggests that daily exchange is required.

It appears that TTP provides an abundance of parameters with which to monitor dose and frequency of plasma exchange. It is imperative to develop a common term (such as ml/kg) for expression of dose of plasma exchange, so different series of patients with conditions responding to plasma exchange can be compared critically. TTP still must be considered unpredictable and lethal, and data from additional patients will be required to establish the relative contributions of plasma transfusion, plasma exchange, and medications in the treatment of this disease. It remains to be demonstrated whether large-volume, daily plasma exchange during the period of maximum disease activity can shorten the course of the disease or prevent relapses.

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PLASMA EXCHANGE FOR TTP

REFERENCES


ADDENDUM

A fifth patient with severe TTP has been treated since submission of this paper. This 15-yr-old girl presented with a platelet count of 4000/μl, hemoglobin 7.2 g/dl, hematocrit 20.2%, with fragmented erythrocytes on peripheral blood smear. BUN was 54 mg/dl, creatinine 1.8 mg/dl, and serum LDH 1924 units. She became disoriented and agitated over 3 hr the evening of admission. A total of 10 consecutive daily plasma exchange transfusions ranging from 138 (7.4 l) to 87 ml/kg (total = 1103 ml/kg) were required to achieve clinical and hematologic remission. No antiplatelet drugs were given, and corticosteroids were begun only after the tenth exchange, primarily for increased intracranial pressure.
Thrombotic thrombocytopenic purpura and dose of plasma exchange

EG Taft