Articles

Thrombotic Thrombocytopenic Purpura Treated With Plasma Exchange or Exchange Transfusions

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Of 40 patients with thrombotic thrombocytopenic purpura, 17 were treated with plasma exchange, 15 with exchange transfusions, and 6 with both types of therapy. One patient died before being treated and another patient was seen but not treated. Plasma exchange was performed daily for a mean of seven exchanges per patient. The replacement fluid during plasma exchange was fresh frozen plasma in all cases. The complete response rates for each type of treatment were as follows: 88% for plasma exchange (15 patients), 47% for exchange transfusions (7 patients), and 67% for exchange transfusions and plasma exchange (4 patients). Clinical and laboratory factors were examined for any statistically significant association with therapy response. Treatment with plasma exchange was statistically the initial factor most strongly associated with prognosis. Paresis, paresthesias, seizures, mental status change, and coma showed no association with response to treatment. Some of the laboratory factors that did not show significant association with treatment response were the initial creatinine, hemoglobin, platelet count, lactate dehydrogenase, and total bilirubin. This study supports the hypothesis that plasma exchange has significantly improved the prognosis of patients with thrombotic thrombocytopenic purpura. These patients should be treated aggressively regardless of the severity of their symptoms.

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Thrombotic thrombocytopenic purpura (TTP) is a rare syndrome of unknown etiology that is characterized by the clinical picture of a microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms, renal disease, and fever. The disease was first described by Moschcowitz in 1925.[1] In 1964, Amorosi and Ultmann reviewed 271 cases of TTP and reported a 90% mortality rate in these patients regardless of their treatment.[2] Ridolfi and Bell reviewed another 275 cases of TTP reported from 1964 to 1980.[3] In these patients, treatment with corticosteroids, blood or plasma exchange, plasma infusion, antiplatelet agents, or splenectomy resulted in a 46% survival rate.

The pathogenesis of TTP is poorly understood. On histologic study, TTP is characterized by the presence of intravascular hyaline thrombi composed mainly of platelets with some fibrin in the arterioles and capillaries.[4] Many treatment regimens have been employed with varying success, including splenectomy, corticosteroids, antiplatelet agents, heparin, whole blood exchange transfusions, hemodialysis, plasma infusions, vincristine, and plasma exchange.[5-18] Due to the rarity of this disorder, clinical studies of the treatment of TTP usually include only a few patients. The literature is particularly devoid of clinical reports studying plasma exchange and exchange transfusions in the treatment of TTP in large numbers of patients. Although certain initial clinical findings indicate a poor prognosis in the natural history of patients with TTP, it is important to study these same clinical findings to determine if they are still prognostically important in the face of the modern therapy for this disease.[19,20]

At the Cleveland Clinic Foundation interest in TTP and its treatment with exchange transfusions first developed more than two decades ago when patients were first treated successfully by this method.[12] In the 1970s we reported the successful treatment of a series of patients with TTP with plasma exchange.[17] The purpose of this report is to review our updated clinical experience with the treatment of TTP with plasma exchange or exchange transfusions and to study any factors that may be important in predicting the treatment outcome.

Patients and Methods

We reviewed the medical records of all patients admitted to the Cleveland Clinic Foundation with the diagnosis of TTP between 1960 and 1986. The diagnosis was considered consistent with the classic picture of TTP if defined by five clinical findings: microangiopathic hemolytic anemia, thrombocytopenia, renal abnormalities, fever, and neurologic changes. Microangiopathic hemolytic anemia and thrombocytopenia had to be present with at least one of the other three clinical findings. Four patients were excluded because their records showed insufficient criteria for the definition of TTP. In all, 23 (58%) were women. Of the 40 patients, 30 were white, 9 were African American, and 1 was Native American.

Of the 40 patients, 17 were treated with plasma exchange alone. The initial frequency of plasma exchange was once a day except for one patient who received plasma exchange every other day. The procedure was done using the Aminco continuous-flow blood cell separator through catheters placed in the antecubital veins. During each treatment, 5,000 units of heparin was administered. In all the patients, 2 to 3 liters of plasma was exchanged for fresh frozen ABO- and

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ABBREVIATIONS USED IN TEXT

SD = standard deviation
TTP = thrombotic thrombocytopenic purpura

Rh-compatible plasma. The mean number of total exchanges per patient was 6.8 ± 3.7 standard deviations (SD) (range, 3 to 21). The procedure required two to three hours to exchange the desired amount of plasma. The mean number of total liters exchanged per patient was 18.2 ± 16.1 SD (range, 4.3 to 64.9).

Of the 40 patients, 15 were treated with exchange transfusions alone by the following method: The skin overlying the femoral vein was prepared with benzalkonium chloride and thimerosal. The skin was then infiltrated with 1% lidocaine, and a small incision was made. An 18-gauge Seldinger needle was inserted into the vein, the stylet removed, and the guide wire directed into the inferior vena cava. A Sheldon cannula was then advanced over the wire and into the vein with subsequent removal of the wire. A second Sheldon catheter was then placed in the same vein by a similar technique. Donor blood was then collected in acid-citrate-dextrose solution and used within three hours.

A unit of fresh whole blood was infused through one catheter. When the infusion was completed, a unit of blood was removed through the other cannula. The blood was then alternately infused and removed in this manner until the desired number of units had been exchanged. A transfusion pressure pump and vacuum bottle were used to facilitate the procedure. After every fourth unit transfused, 10 ml of a solution of 10% calcium gluconate was administered intravenously. Patients' vital signs and electrocardiograms were monitored during the exchange. The total time usually required for completion of the exchange transfusion was two to three hours. The number of units exchanged varied from 8 to 12 units.

Six patients were treated with exchange transfusions and then, when they failed to respond, plasma exchange. One patient died before being treated, and one patient was seen but not treated. None of the patients received aspirin as treatment of their TTP, but 7 patients received dipyridamole and 24 patients received corticosteroids at some time during their treatment course. Only one patient had a splenectomy with no therapeutic response before being successfully treated with exchange transfusions.

A complete response to therapy was defined as the resolution of the following indices after treatment with plasma exchange or exchange transfusions for at least three months: an increase of the platelets to more than 150×10^9 per liter (150,000 per μl), a normal peripheral blood smear, and normal results on neurologic examination. To be eligible for

TABLE 1.—*Physical and Historical Findings of 40 Patients With Thrombotic Thrombocytopenic Purpura*

Physical and Historical Findings	*Patients, No. (%)*
Mental status change	25 (63)
Malaise	24 (60)
Fever	22 (55)
Ecchymoses	22 (55)
Headache	20 (50)
Petechiae	19 (48)
Neurologic focal deficits	15 (38)
Jaundice	13 (33)
Coma	13 (33)
Abdominal pain	13 (33)
Nausea	12 (30)
Paresis	11 (28)
Paresthesias	10 (25)
Seizures	10 (25)
Dysarthria	9 (23)
Vision changes	6 (15)
Aphasia	5 (13)
Splenomegaly	1 (3)

TABLE 2.—*Association of Clinical Variables With Treatment Response**

Variable	*Complete Responders, %*	*Non-responders, %*	*P Value†*
Petechiae			
Yes	38	73	.08
No	62	27	
Nausea			
Yes	40	18	.27
No	60	82	
Neurologic focal deficits	31	55	.27
Abdominal pain			
Yes	38	18	.28
No	62	82	
Seizures			
Yes	23	36	.44
No	77	64	
Coma			
Yes	27	45	.44
No	73	55	
Jaundice			
Yes	31	50	.44
No	69	50	
Paresis			
Yes	36	20	.45
No	64	80	
Headache			
Yes	62	45	.47
No	38	55	
Ecchymoses			
Yes	54	73	.47
No	46	27	
Race (white)			
Yes	73	82	.57
No	27	18	
Fever			
Yes	54	55	.63
No	46	45	
Dysarthria			
Yes	29	18	.69
No	71	82	
Paresthesias			
Yes	25	36	.69
No	75	64	
Mental status change			
Yes	62	73	.71
No	38	27	
Malaise			
Yes	62	70	.72
No	38	30	
Gender			
Male	38	45	.73
Female	62	55	
Splenomegaly			
Yes	4	0	.99
No	96	100	
Vision changes			
Yes	17	9	.99
No	83	91	
Aphasia			
Yes	17	9	.99
No	83	91	

*26 patients had a complete response, and 12 had no response to treatment. Information on some of the variables was absent for some patients.
†As determined by Fisher's exact test.

evaluation of response, patients had to be observed for at least three months after therapy. A Fisher's exact test was used for categoric variables. Because many of the continuous factors of interest have extreme values or have abnormal distributions, a nonparametric test (Wilcoxon rank sum test) was used to test for location differences between the complete responders and the nonresponders.

Results

Many of the demographic and clinical factors listed in Table 1 were studied for any statistically significant association with treatment response. None of the factors analyzed from the patients' characteristics, history, or physical findings were associated with a response or lack of response to therapy (Table 2). Table 3 lists the initial laboratory data available at the time of a patient's presentation. Of these factors, only an elevated initial leukocyte count was significantly associated with a good treatment response (Table 4).

Of 17 patients treated with only plasma exchange whose treatment response was evaluated, 15 (88%) had a complete response; of 15 patients treated with only exchange transfusions, 7 (47%) had a complete response; and of 6 patients treated with both exchange transfusions and plasma exchange, 4 (67%) had a complete response.

When the treatment modalities were compared, the presence of plasma exchange in the therapy regimen was a statistically significant factor predicting a complete response ($P = .03$) (Table 5). Treatment with plasma exchange alone or in combination with exchange transfusions produced a higher response rate than did exchange transfusions alone ($P = .04$). At some time during their clinical course, 24 patients were given corticosteroids, but no significant difference was noted in treatment response rates between patients who received corticosteroids and those who did not ($P = .68$). Only seven patients were given dipyridamole at some time during their clinical course, and the addition of these antiplatelet agents did not appear to make a difference in the treatment response.

TABLE 3.—*Initial Pretreatment Laboratory Data of Patients With Thrombotic Thrombocytopenic Purpura*

Test	Patients, No.*	Median	Reference Interval
Blood tests			
Leukocytes × 10^9/liter	39	9.8	5 to 11
Hemoglobin, grams/liter	39	88	125 to 160
Lactate dehydrogenase, U/liter	34	1,358	100 to 185
Total bilirubin, mg/dl†	38	2.7	0.3 to 1.0
Creatinine, mg/dl†	34	1.5	1.4
Blood urea nitrogen, mg/dl†	37	29	10 to 20
Fibrinogen, grams/liter	26	2.9	2.0 to 4.0
Prothrombin time, seconds	35	13	10 to 13
APTT, seconds	26	25.5	21 to 31
Platelets × 10^9/liter	39	20.5	150 to 400
Urine protein (dipstick)			
Negative	8		
Trace +	14		
1 to 2 +	9		
3 to 4 +	3		
Urine sediment			
Normal	8		
Abnormal	28		

APTT = activated partial thromboplastin time

*Not all values are available for each patient.

†Values are given in conventional units. To convert to Système International (SI) units, the conversion factor for total bilirubin is 17.10 (to μmol per liter), for creatinine is 88.40 (to μmol per liter), and for blood urea nitrogen is 0.357 (to mmol per liter of urea).

With the mean follow-up time of the responders being 5.2 years as of June 1, 1987, three patients have had relapses of TTP after successful treatment at the Cleveland Clinic Foundation. Two of the patients originally had been treated with plasma exchange and exchange transfusions and the other patient with plasma exchange and splenectomy. The relapses occurred at two years after treatment in one patient and at one and nine years after treatment in another patient. The third patient has had six relapses 1½ years to 8 years after initial treatment. All patients' relapses were treated successfully.

Discussion

For four decades after the initial description of thrombotic thrombocytopenic purpura by Moschcowitz in 1925, this unusual syndrome led to death in almost all cases.[2] Although some patients with TTP had a more prolonged clinical course (chronic TTP), the vast majority of cases showed an acute course sometimes leading to death in hours or days. Some of the early therapeutic efforts included splenectomy and the use of corticosteroids and heparin.[5,6,11] The use of antiplatelet agents such as aspirin, dipyridamole, or dextran has met with varying success.[7-10]

The first breakthrough in the treatment of TTP was the use of whole blood exchange transfusions. This method of treatment was first attempted by Rubinstein and colleagues,[21] and the patient recovered. Bukowski and co-workers reported the cases of 13 patients who were treated with exchange transfusions, 7 of whom had remissions.[12] This re-

TABLE 4.—*Median Initial Laboratory Values Associated With Therapeutic Outcome*

Variable	Complete Responders (n=26) Median	Non-responders (n=12) Median	P Value*
Leukocytes × 10^9/liter	11.9	6.8	.05
Hemoglobin, grams/liter	96	72	.15
Blood urea nitrogen, mg/dl†	31	26	.40
Prothrombin time, seconds	13	14	.44
Age, yr	37	49	.49
Lactate dehydrogenase, U/liter	1,358	1,750	.59
Total bilirubin, mg/dl†	2.8	2.9	.69
Fibrinogen, grams/liter	2.9	3.0	.75
Creatinine, mg/dl†	1.3	1.5	.91
Platelets × 10^9/liter	20	20.5	.80

*As determined by the Wilcoxon rank sum test.

†Values are given in conventional units. See Table 3 for conversion factors to Système International units.

TABLE 5.—*Association of Treatment Method With Therapeutic Response*

Treatment	Complete Responders, No. (%)	Non-responders, No. (%)	P Value*
Plasma exchange			
Yes	19 (73)	4 (33)	.03
No	7 (27)	8 (67)	
Exchange transfusion			
Yes	11 (42)	10 (83)	.03
No	15 (58)	2 (17)	
Plasma exchange alone	15 (58)	2 (17)	.04
Exchange transfusion alone	7 (27)	8 (67)	
Both	4 (15)	2 (17)	

*As determined by Fisher's exact test.

port was followed by that of Pisciotta and associates, which confirmed that about 50% of patients with TTP could survive when treated with exchange transfusions.[22]

As plasma exchange technology was developed, it was successfully applied in the management of patients with TTP.[17] Although this technique has been studied alone and in combination with a variety of other therapies—such as corticosteroids, hemodialysis, splenectomy, antiplatelet agents, and vincristine—most of these clinical series have had a small number of patients, usually fewer than ten.[9,16-20] One problem with small clinical series that have used the multiagent approach in treating TTP is that the interpretation of results is difficult. The multiagent approach has been successful in many clinical series, but it offers no clear answers regarding which treatment methods are most important.

This report of patients with TTP treated at the Cleveland Clinic Foundation represents the largest number of patients treated with plasma exchange or exchange transfusions at a single institution. It therefore presents a group of patients treated in a relatively uniform manner, and it allows the efficacy of plasma exchange and exchange transfusion to be studied. Thus, the prognostic factors that may predict treatment outcome can be more precisely analyzed.

Thrombotic thrombocytopenic purpura can no longer be regarded as fatal in most patients; plasma exchange successfully treated 88% of the patients in our study. Of the patients treated with exchange transfusions alone, 47% had complete responses. This figure is consistent with other studies[17,20,22] in which approximately half of the patients had complete responses when treated in this manner. A direct comparison of the two methods must be made with caution, however, because the majority of patients treated before 1975 were treated with exchange transfusions.

The mechanism underlying the therapeutic success of different treatment methods remains speculative, in part because many clinical series have a multiagent approach to treating TTP. It may be that the effects of plasma exchange and whole blood exchange transfusions are related to the removal of a soluble toxic material.[4,23] Alternatively, the addition of a deficient "plasma factor" or a dilutional effect by the transfusion of whole blood or plasma in plasma exchange may be the crucial factor in the successful treatment of TTP.[24,25]

In this study, the strongest therapeutic factor associated with prognosis was treatment with plasma exchange. An elevated initial leukocyte count was the only laboratory factor that showed a significant association with response. Most important, no clinical findings predicted a poor response to treatment. Neither age nor gender was predictive. Patients with severe symptoms, such as the presence of seizures, paresthesias, paresis, aphasia, mental status changes, or coma, did as well as patients with milder symptoms. This is contrary to other clinical studies, in which it was found that patients with certain clinical factors did less well than other patients with TTP.[19,20] The results from our study emphasize that the treatment of a patient with severe neurologic symptoms can be as successful as the treatment of less symptomatic patients if aggressive treatment with plasma exchange or exchange transfusions is instituted.

Treatment with plasma exchange has substantially improved the prognosis of patients with TTP. There are no clearly prognostic clinical findings, and even patients with severe initial clinical findings may respond well to aggressive treatment. The mechanism of the benefit of plasma exchange remains speculative, as does the question of whether additional therapeutic modalities will improve an 88% rate of response to plasma exchange.

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