

Incidence of Allergic Reactions With Fresh Frozen Plasma or Cryo-Supernatant Plasma in the Treatment of Thrombotic Thrombocytopenic Purpura

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Plasma replacement for thrombotic thrombocytopenic purpura (TTP) is accomplished with various plasma products. This study sought to determine the incidence of allergic reactions with FFP or CPP as replacement in therapeutic plasma exchange (TPE). Forty-one TTP patients were identified retrospectively who received TPE replacement with either FFP ($n = 21$) or CPP ($n = 20$). Anti-histamine was administered prophylactically following the initial occurrence of an allergic reaction (urticaria, respiratory distress, or anaphylaxis with hypotension). Fifty-one allergic reactions occurred in 65.8% of patients. Urticaria comprised 49 of 51 (96%) of reactions and respiratory distress the remaining 4%. No anaphylaxis occurred. Nineteen urticarial reactions occurred in 50% of CPP recipients compared to 71% of FFP recipients ($P = 0.28$). Anti-histamine breakthrough occurred in 36.3% of patients who experienced a previous allergic reaction with CPP and 37.5% with FFP ($P = 1.0$). The overall risk of allergy per unit of plasma was 1.37% (1.23 % CPP, 1.48% FFP), comparable to estimates in non-TTP recipients. The median number of donor exposures preceding the first allergic reaction was 35 and 32, CPP and FFP, respectively ($P = 0.63$). The mean volume of plasma transfused prior to reaction was 9,883 mL for CPP and 9,348 mL for FFP ($P = 0.85$). Neither product was advantageous in preventing allergic complications. Because of the large volume, the number of donor exposures, and prolonged duration of therapy, allergic reactions to plasma are common (65.8%) in the treatment of TTP. *J. Clin. Apheresis.* 16:134–138, 2001. © 2001 Wiley-Liss, Inc.

Key words: apheresis; plasma exchange; allergy; cryo-poor plasma; adverse reactions; solvent-detergent plasma

INTRODUCTION

The recognition of plasma as an effective therapy for thrombotic thrombocytopenic purpura (TTP) reversed an almost uniformly fatal illness to one with a mortality rate of less than 20% [1–5]. Daily plasma exchange is considered the cornerstone of treatment and is initiated promptly following diagnosis. Therapeutic plasma exchange (TPE) involves both withdrawal and infusion, thereby facilitating transfusion of large volumes of life-saving plasma while minimizing risks of volume overload. Removal of pathophysiologic factor(s), such as the recently recognized inhibitor to vonWillebrand Factor (vWF) multimerase, followed by replacement with normal plasma, promotes clearance of the unusually large multimers of vWF that have been implicated in the pathogenesis of TTP [6–8]. Minimizing the presence of these large multimers of vWF also provides the rationale for the improved efficacy of cryo-supernatant plasma (CPP) over fresh-frozen plasma (FFP) which has been demonstrated in several studies [9–12].

Adverse reactions associated with TPE are estimated at 9.7% [13]. Fortunately, severe reactions are uncommon

(0.025 to 0.2%). The most common complications include citrate toxicity, allergic reactions, and volume shifts. Among allergic complications, estimates of the incidence of urticaria range from 0.7 to 12%, bronchospasms from 0.1 to 0.4%, and anaphylactoid reactions from 0.03 to 0.7%. These percentages are derived from an extensive review of nine series that included over 15,000 TPE procedures in patients treated for diverse indications and replaced with a variety of replacement fluids including albumin and plasma [13]. Several studies have shown fewer complications when albumin is used as replacement compared to plasma products: 1.4% vs. 20% [13]; 53% vs. 32% [14]. Looking only at allergic reactions, a similar relationship emerges comparing albumin to plasma replacement: 3.35% vs. 7.81% [15] and 3% vs. 11.3% [14].

Plasma replacement for TTP is essential and currently

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Received 14 October 2000; Accepted 25 January 2001

can be accomplished with FFP, CPP, or solvent detergent treated plasma. The frequency of allergic complications for these plasma products has been considered similar [16]. However, these products are not identical. Cryosupernatant plasma is deficient in the cryoprecipitable elements: fibrinogen, vWF, and Factors VIII and XIII [17]. Solvent detergent treated plasma is a pooled plasma product and has been found to contain less Protein S, Protein C, and alpha-2 antiplasmin than FFP [18]. Since solvent detergent plasma resembles CPP with its deficient content of vWF multimers and has the advantage of lipid-enveloped viral inactivation, clinical experience with this plasma in TTP is mounting [19,20]. The differences in FFP, CPP, and solvent detergent plasma may affect the frequency of allergic complications. A few small reports suggest the frequency of allergic reactions in TTP patients treated with solvent detergent plasma appears similar and possibly lower than with FFP [21–23]. In a controlled clinical trial that compared infusions of FFP to solvent detergent plasma, the frequency of allergic reactions was 27% vs. 20% among 106 patients who had prior exposure to plasma ($P=0.50$) [18]. However, direct comparisons of allergic reactions between FFP and CPP are lacking.

With large volume plasma infusion, such as with TTP patients, anticipating a similar frequency of allergic reactions for these different plasma products may not be accurate. A higher frequency of adverse reactions to plasma exchange is typically seen with TTP patients [24]. One large study demonstrated that 31% (22/71) of TTP/HUS patients that received cryosupernatant fraction experienced urticaria [25]. Interpretation of the results from reports of allergic reactions may be unreliable when the studies do not include history of prior exposure to plasma or clarify the administration of routine pre-infusion anti-histamine. The differences (or similarities) in the frequency of allergic reactions among these plasma products in the management of TTP patients could be better defined to guide clinical practice. The goal of this study was to determine the incidence of allergic reactions when either all FFP or all CPP is used for replacement in a well-characterized group of TTP patients.

MATERIAL AND METHODS

Patient Selection

All patients that presented with a diagnosis of thrombotic thrombocytopenic purpura (TTP) at the University of North Carolina Hospitals between 1982 and 1999 were retrospectively reviewed. The diagnosis of TTP required thrombocytopenia (platelet $< 100 \times 10^9/L$), a microangiopathic hemolytic anemia (schistocytosis), with or without fever, mental status changes, and renal dysfunction. Patients with disseminated intravascular coagulation, sepsis, or malignancy were excluded from this study. Other exclusions were TTP related to bone mar-

row transplantation, chemotherapy, collagen vascular disease, such as lupus, HIV, or a history of prior exposure to plasma. From 90 patients identified by these criteria, 41 patients were selected that had received TPE replacement with either exclusively FFP ($n = [21]$) or CPP ($n = [20]$). Patients that received a combination of these plasma products ($n = 49$) were not included in this analysis. Prophylactic premedication with anti-histamines was initiated only for patients who experienced an allergic reaction during their series of TPE.

Plasma Exchange

TPE was performed on the COBE Spectra (Gambro, Lakewood, CO) apheresis separator. One plasma volume was exchanged daily. Response was defined as a platelet count of $150 \times 10^9/L$ and a normal (or approaching normal) serum lactate dehydrogenase (LDH) on 2 consecutive days. At this point, TPE was discontinued and patients were followed to assess durability of their response for a minimum of 6 months follow-up. Relapse was defined as recurrence of thrombocytopenia $< 150 \times 10^9/L$, elevation in LDH and return of schistocytes in the peripheral blood smear after cessation of TPE. Administration of prednisone (1 mg/kg p.o.) began after the first TPE at initial diagnosis and continued at this level until TTP remission, at which point steroid dosing was gradually tapered over 3–6 months.

Classification of Reactions

Allergic reactions were classified as urticaria (including hives and/or pruritis), respiratory distress (wheezing, stridor, dyspnea), or anaphylaxis (hypotension with bronchospasm or pharyngeal edema). If a patient experienced an allergic reaction, anti-histamine was administered (diphenhydramine 25 to 50 mg IV). Prophylactic anti-histamine (diphenhydramine 25 to 50 mg PO or IV) was then provided before all subsequent TPE procedures. Allergic reactions that occurred despite pre-medication with anti-histamines were classified as anti-histamine breakthrough reactions.

Calculations

The cumulative total volume (mL) of plasma transfused and the total number of donor exposures were calculated for each patient for the entire series of TPE. The total volume (mL) of plasma and the number of donor exposures that preceded the first allergic reaction were also calculated. The number of allergic reactions was determined i) per patient, ii) per donor exposure, and iii) per procedure. For patients who experienced an allergic reaction, the number of allergic reactions that occurred with the pre-TPE administration of prophylactic anti-histamine was calculated to determine the breakthrough allergy rate. Statistical comparisons between the groups receiving FFP and CPP were made using a two-sided

TABLE I. Distribution of Allergic Reaction Subtype by Replacement Plasma

	Number of reactions	Number of urticarial reactions (% patients)	Number reaction with respiratory difficulty (% patients)	Anaphylaxis	Risk of allergic reaction per unit (%)
CPP	20	19 (50)	1 (5)	0	1.23
FFP	31	30 (71)	1 (5)	0	1.48
Total	51	49 (66)	2 (10)	0	1.37

Fisher's Exact Probability Test and the Student's t-test. Statistical significance was taken at $P < 0.05$.

RESULTS

A total of 51 allergic reactions occurred in 27 of the 41 (65.8%) TTP patients. Urticarial reactions comprised the largest proportion, 49 of 51 (96%). Respiratory symptoms occurred in two patients, which accounts for the remaining 4% of allergic reactions. No severe hypotensive anaphylactic reactions occurred. Nineteen urticarial reactions occurred in 10 of 20 (50%) patients that received only CPP compared with 30 reactions in 15 of 21 (71%) patients that received FFP group ($P = 0.28$). One patient (5%) in each group had respiratory manifestations of allergy (Table I). In this study, 51 of 306 procedures (16.7%) involved an allergic reaction.

Breakthrough urticarial reactions occurred in the setting of anti-histamine premedication in 4 of 11 (36.3%) patients who experienced a previous allergic reaction in the CPP group and 6 of 16 (37.5%) in the FFP group ($P = 1.0$) (Fig. 1). Among patients that experienced allergy, the number of reactions ranged from 1 to 5 with a mean of 1.8 reactions per patient receiving CPP and 1.9 for FFP. Respiratory symptoms did not recur.

The overall risk of allergic reaction per unit of plasma transfused in this study was 1.37%. By replacement type, the risk was 1.23% per unit of CPP and 1.48% per unit of FFP. For the CPP group, there were 1,626 donor exposures and 501.2 L of plasma infused in aggregate. For the FFP group, there were 2,092 donor exposures and 535.2 L of plasma infused in aggregate. The average volume of plasma per unit was 308 mL for CPP and 256 mL for FFP. For those patients that experienced an allergic complication, the median number of donor exposures preceding the first allergic reaction was 35 (mean = 30.2 ± 27.3) for CPP and 32 (mean = 35.1 ± 22.3) for FFP ($P = 0.63$). The mean cumulative volume of plasma these patients had received prior to initial allergic reaction was 9,883 mL for CPP and 9,348 mL for FFP ($P = 0.85$) (Fig. 2).

At the time of remission of TTP when daily TPE was discontinued, the median number of donor exposures 76.5 (mean = 81.3 ± 35.4) for the CPP recipients compared to 82 (mean = 99.6 ± 59.8) for FFP recipients ($P = 0.24$) corresponds to a median of 23 L of CPP (mean = 24.2 ± 10.6) and 22.4 L of FFP (mean = 25.5 ± 12).

To attain clinical response required a mean of 7 ± 3.2 daily TPE procedures for the CPP group and a mean of 7.9 ± 4.2 TPE procedures for the FFP group ($P = 0.44$). The dose per kilogram to achieve clinical response in this study was 45 mL/kg of CPP and 40 mL/kg of FFP. The frequency of relapse was 40% and 43% for CPP and FFP, respectively ($P = 1.00$).

DISCUSSION

This study demonstrates that 65.8% of TTP patients, treated with apheresis experienced at least one allergic reaction. Ninety-six percent of these reactions were limited to urticaria with the remaining 4% associated with respiratory symptoms of dyspnea, stridor, or wheezing. Urticaria occurred in 71% of patients that received all FFP compared to 50% that received all CPP ($P = 0.28$). The development of the first allergic complication occurred following 32 or 35 donor exposures (FFP vs. CPP; $P = 0.63$). This is equivalent to transfusion of 9.3 or 9.8 L of donor plasma (FFP vs. CPP; $P = 0.85$) before the first allergic manifestation. Among patients that experienced one allergic reaction (who were subsequently given anti-histamine prophylaxis), there was no difference in occurrence of breakthrough allergic reactions, 37.5% for FFP and 36.3% for CPP ($P = 1.0$). Therefore, roughly one third of patients who experience allergic complications will require medical management beyond prophylactic anti-histamine for allergic complications.

The reason for the relatively high proportion of TTP patients who experience allergic reactions during TPE is most likely related to the large volume of plasma required for their management. In this study, the overall risk of an allergic reaction was 1.37% per unit of plasma transfused, with a similar risk for CPP and FFP (1.23% and 1.48%, respectively). These results are consistent with published estimates of the incidence of allergic complications per unit of plasma, which range from 1–3% [26]. However to achieve independence from plasma, the TTP patients in this study were exposed to a median of 76.5 units of CPP (mean = 81.3 ± 35.4) or 82 units FFP (mean = 99.6 ± 59.8). This data suggests that the cumulative exposure to plasma and the duration of exposure contribute to the occurrence of allergic reactions. The higher mean number of FFP vs. CPP was related to greater use of whole blood-derived plasma in

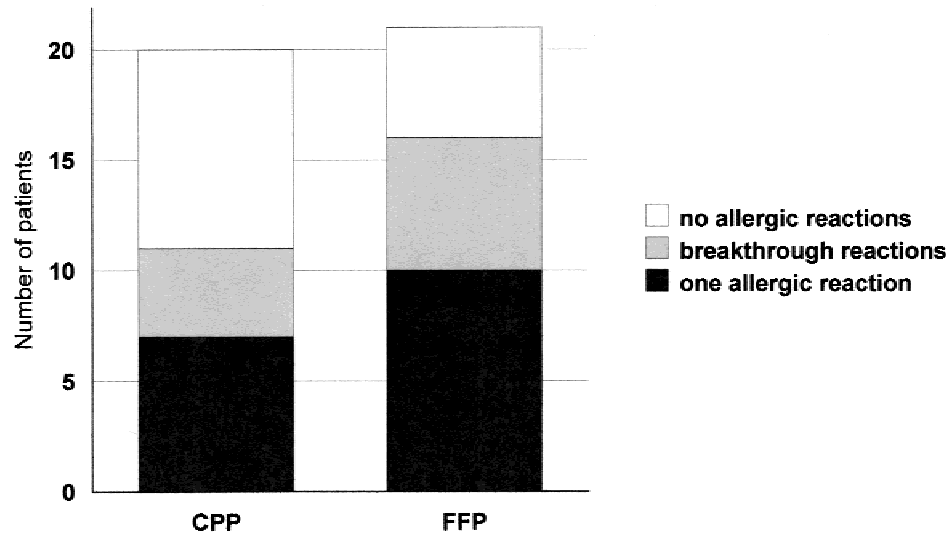


Fig. 1. Profile of allergic reactions by replacement plasma type. The shaded areas correspond to the total number of patients who experienced an allergic reaction. The black-shaded areas correspond to the number of patients who experienced one allergic reactions; the gray-shaded areas the number of patients who experienced breakthrough allergic reactions. Breakthrough reactions are those that recurred despite subsequent pre-medication with anti-histamine.

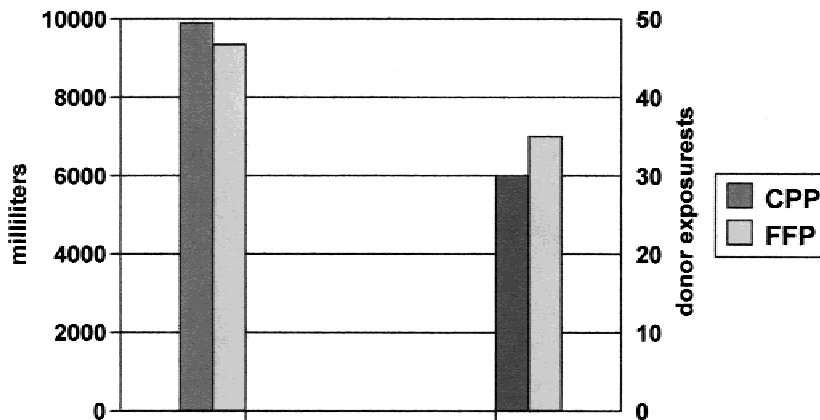


Fig. 2. Mean total volume of plasma transfused and mean number of donor exposures patients had received at the time of their initial allergic reaction. Dark gray represents CPP and light gray represents FFP.

the treatment of the FFP patients as opposed to apheresis derived units of plasma in the CPP group. This resulted in a higher aggregate number of units transfused in the FFP group (2,092 vs. 1,626), which likely underlies the higher proportion of patients in this group who experienced an allergic reaction (71% FFP vs. 50% CPP; $P=0.28$).

In summary, approximately two thirds of patients with TTP can be expected to experience an allergic complication during TPE therapy whether being treated with FFP or CPP. The onset of allergy typically occurs following exposure to 30 donors or 9–10 L of plasma. The overall incidence of allergic reaction per unit of plasma transfused is similar in the TTP patient as to estimates of allergy in non-TTP recipients. The higher proportion patients' experiencing allergic reactions is the result of the relatively large volume, the number of donor exposures,

and prolonged duration of therapy for TTP patients. While anti-histamine prophylaxis is prudent with the onset of allergy, it may be insufficient in up to one third of patients in preventing recurrent allergic complications. Regardless of the choice of plasma replacement, medical and nursing management of these adverse reactions should be anticipated.

ACKNOWLEDGMENTS

The authors thank the Apheresis Nursing Staff at UNC Hospitals, Chapel Hill, NC.

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