Coagulation status after therapeutic plasma exchange using citrate in kidney transplant recipients

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BACKGROUND: Therapeutic plasma exchange (TPE) is increasingly used for treatment of antibody-mediated rejection (AMR) after solid organ transplants. There is concern that TPE may increase risk of bleeding, although data are limited. After TPE, clot-based coagulation tests may not accurately represent the levels of coagulation factors due to the effect of citrate. We investigated protein levels of fibrinogen using antigen detection method (FibAg) and correlated results with a clot-based fibrinogen activity test (Fib).

STUDY DESIGN AND METHODS: Nine kidney transplant recipients who received TPE for AMR were investigated. Fib, FibAg, prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT), coagulation factor X chromogenic activity (CFX), and ionized calcium (iCa) were measured at pre- and post-TPE and 1, 3, 6, 9, 24, and 48 hours after the first TPE.

RESULTS: Mean Fib/FibAg ratio before TPE was 1.08; therefore, all Fib values were normalized (n) by dividing by 1.08. Overall, the mean normalized Fib (nFib)/FibAg ratio at post-TPE was 0.89 and returned to close to 1.0 at 6 hours after the first TPE. Decreases in nFib, FibAg, and CFX and increases in PT/INR and PTT post-TPE were observed. The lowest Fib, FibAg, CFX, platelet, and iCa levels were still at levels that would be considered sufficient for hemostasis at all time points.

CONCLUSION: The mean nFib/FibAg ratio after TPE was 0.89 and normalized in 6 hours, which demonstrates a persistent effect of citrate for up to 6 hours. Therefore, similar data observed in clot-based tests of PT/INR and PTT may be falsely elevated up to 6 hours after TPE due to the citrate effect.

In recent years, therapeutic plasma exchange (TPE), combined with immunomodulation, has been increasingly used for treatment of antibody-mediated rejection (AMR), especially in kidney transplant recipients. At our institution, many patients start TPE shortly after the histologic diagnosis of AMR, and the occurrence of bleeding complications after kidney allograft biopsy in the period of 2010 to 2011 was five times higher in patients who received TPE than in patients who did not receive TPE, 1.03% in all patients versus 5.17% in patients who received TPE within 5 days of the biopsy (unpublished data, courtesy of nephrology service at our institution). One of the possible causes of this can be coagulopathy after TPE procedures. The most commonly used coagulation tests, including prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT), coagulation factor assays, and fibrinogen

ABBREVIATIONS: AMR = antibody-mediated rejection; CFX = coagulation factor X chromogenic activity; Fib = fibrinogen activity; FibAg = fibrinogen antigen; iCa = ionized calcium; INR = international normalized ratio; nFib = normalized fibrinogen; PT = prothrombin time; PTT = partial thromboplastin time; TBV = total blood volume; TPE = therapeutic plasma exchange.

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activity (Fib) are based on clotting time and are influenced by the presence of citrate, which is used for TPE procedures. Consequently, these laboratory tests may represent a patient's coagulation status, but they may not accurately represent the concentration of coagulation factors. Additionally, abnormal coagulation test results in this scenario may trigger the unnecessary use of plasma or cryoprecipitate transfusion.

The decrease of coagulation factors and Fib using clotting time–based assays (PT/INR, PTT) after TPE has been described.[1,2] However, the decrease of protein levels of fibrinogen has not been reported thus far. Therefore, we conducted a prospective investigation of fibrinogen quantity using fibrinogen antigen (FibAg) detection methodology and correlated these results with widely used clot-based Fib tests over the time in patients with AMR of kidney transplants treated with TPE within several days after the biopsy. Additionally, we investigated PT/INR, PTT, coagulation factor X chromogenic activity (CFX), ionized calcium (iCa), and platelet (PLT) count over time and correlated these data with clinical outcome.

MATERIALS AND METHODS

We obtained financial support from the University of Michigan Department of Pathology, and the study was approved by the University of Michigan Institutional Review Board. Potential subjects were identified by nephrologists or transfusion medicine physicians and consent was obtained by participating study coordinators. We recruited adult renal transplant recipients with AMR who were scheduled to receive TPE followed by IVIG per our institutional protocol for participation in the study. Exclusion criteria included children (younger than age 18 years old), patients with elevated liver function tests (reference range at our institution, AST 8-30 IU/L, ALT 7-35 IU/L), pregnant patients, mentally impaired patients, and patients who did not provide informed consent. If a patient developed any signs of bleeding such as hematoma or hematuria within 48 hours after the first TPE, the patient was discontinued from study participation and received appropriate treatment. The study was not designed to alter any standard care; therefore, the laboratory test results only for the study purposes were blinded to treating physicians and the study team.

TPE procedure

Patients received TPE between three and six times depending on the patient's donor-specific antibody level measured by Luminex-based technology (One Lambda, Thermo-Fisher Scientific, Inc.) as mean fluorescence intensity. Each procedure was performed with one plasma volume exchange, and the replacement fluid consisted of 5% albumin only or 5% albumin and plasma (up to half plasma volume) when TPE was performed within 5 days of biopsy according to our institutional protocol for AMR treatment of kidney transplant recipients. When plasma was used, the plasma dose was recorded. Citrate (ACD-A) was infused in blood draw line during the TPE procedure at the rate of 0.8 mL/min/L total blood volume (TBV) for both albumin and plasma replacement procedures. The amount of citrate was determined by an apheresis machine (Optia or Spectra, both TerumoBCT), with each patient's TBV calculated based on sex, height, and weight to meet the set infusion rate of 0.8 mL/min/L TBV. Therefore, the citrate infusion rate in all patients was constant. Calcium was added to all albumin bottles (1.2 mmol supplementation per 500 mL) for replacement and provided more in normal saline into their return line if the patients showed citrate toxicity or when plasma was used as a replacement, and the dose of total calcium supplementation was recorded.

Laboratory testing

Standard protocol orders for AMR treatment were made by the primary nephrology team. The schedule for laboratory tests follows: Fib and FibAg, PT/INR/PTT, CFX, and iCa were determined immediately before TPE (Pre-TPE), immediately after TPE (Post-TPE), and 1, 3, 6, 9, 24, and 48 hours after the first TPE; PLT count was obtained before TPE (within the same day), Post-TPE, and 24 hours after the first TPE. Additional blood draws for all parameters were obtained before third and fourth TPE procedures for the last three patients. The acceptable timing of scheduled blood draws except Pre- and Post-TPE was within 15 minutes for the 1- and 3-hour time points after the TPE and within 2 hours thereafter. All blood samples were deidentified and a study identifier was assigned to each subject. Fib, FibAg, PT/INR, PTT, CFX, iCa, and PLT results other than the tests performed as a standard care were held by the hematology and chemistry laboratory directors or supervisors to ensure blinding of the results and to avoid alteration of standard treatment due to test results. Those test results were unblinded after the last subject had completed the study. The test results performed as standard care were retrieved from the electronic medical record.

Clinical data collection

Each subject's age, sex, preprocedure use of anticoagulants, clinical, laboratory, and TPE procedural data were retrieved from the electronic medical record and recorded. After the last subject completed the study, all bleeding or thrombotic events noted by the primary nephrology team within 1 month after the last TPE procedure were retrieved from the electronic medical record. Information regarding bleeding and blood product transfusion was also obtained when applicable.

TABLE 1. Demographics, TPE procedure data, and anticoagulant use

Patient	Age (years)	Sex	% of plasma in total replacement fluid	Ca^{2+} (mmol) supplementation	Anticoagulant
A	67	Female	29.4	6.1	Warfarin, low-dose aspirin
B	19	Male	45.7	10.5	Low-molecular-weight heparin
C	63	Male	0	7.2	Heparin
D	23	Male	32.4	6.0	
E	37	Male	0	6.0	
F	52	Male	19.4	9.1	Low-dose aspirin
G	65	Male	0	9.6	
H	40	Female	0	6.9	
I	41	Female	19.4	11.2	

Statistical analysis

The correlation of Fib and FibAg was analyzed at each time point. The mean Fib/FibAg ratio before TPE (in the absence of any citrate effect) was 1.08, indicating that Fib results in 8% higher than FibAg. Therefore, all Fib results were normalized (n) by dividing by 1.08 to compensate for the difference of the test methods. All data were also divided into three groups, all patients, and patients with and without plasma replacement use depending on the days after the biopsy to see the effect of plasma use on each parameter. Extreme outliers in coagulation test results were considered to be not clinically plausible and likely due to heparin contamination of samples drawn through central catheters or soon after the regular anticoagulant dose. Therefore, data that were greater than 2 standard deviations (SDs) from the mean for each study parameter and also far different from other data in the same patient representing possible anticoagulant contamination (such as PTT $>$ 100 sec with a mean of 23 sec) were excluded from the analysis.

A linear mixed-effects regression model was used to assess changes of each parameter over the time. Specifically, we modeled the parameter as a piecewise linear function of time, with a change point fixed at the post-TPE time point. Slopes before and after the change point were then tested to determine whether they are different from the post-TPE time point. Significance was determined at a p value of less than 0.05. All analyses were conducted using computer software (SAS, Version 9.4, SAS Institute).

RESULTS

Eleven patients consented to the study. One patient was found to be pregnant after the consent was obtained and was excluded, and one patient withdrew the consent. Thus, the analysis was performed in nine subjects (A-I). Age ranged from 19 to 67 years old (median, 41 years old), six males and three females (Table 1). Table 1 also shows anticoagulant use, use of plasma as a percentage of total replacement fluid volume, and the dose of calcium supplementation during TPE. The prescribed anticoagulants were not altered during the course of TPE treatment. One patient on low-molecular-weight heparin had much lower CFX level only at the pre-TPE time point than CFX levels at other time points after TPE (more than 70% lower); therefore, these data were excluded from analysis. Two data points in PT/INR and two data points in PTT were far above 2 SDs and were excluded from the data analysis due to possible anticoagulant contamination.

TABLE 2. Mean and range value of each parameter at pre- and post-TPE time points

Variable	Pre-TPE	Post-TPE
Fib (mg/dL)	412.0 (339-465)	187.0 (110-293)
FibAg (mg/dL)	392.25 (326-513)	194.89 (135-235)
PT (sec)	11.4 (10.6-13.8)	13.53 (11.4-16.4)
INR	1.09 (1.0-1.4)	1.31 (1.1-1.6)
PTT (sec)	26.04 (21.4-33.3)	29.76 (25.5-34.4)
CFX (%)	149.11 (110-293)	68.56 (40-93)

Table 2 shows mean and range of test results in each parameter at Pre- and Post-TPE. The mean level change (%) of normalized Fib (nFib), FibAg, CFX, PT/INR, and PTT based on the pre-TPE level at each time point are shown in Figs. 1A-1F. All figures show level change in three groups: all patients, patients with plasma replacement, and without plasma replacement.

The nFib/FibAg ratio at each time point in each patient is shown in Table 3. The mean change of nFib/FibAg ratio at each time point based on pre-TPE level in the same three groups above is shown in Fig. 2. Overall, nFib/FibAg ratio decreased immediately after TPE and returned to the pre-TPE level in 6 hours. However, this ratio returned to pre-TPE level in 3 hours after TPE in the patient group with plasma replacement, and the ratio did not return to pre-TPE level in the patient group without plasma replacement although returning slope was observed toward 6-hour time point.

Significance (p value) of level decrease or increase before TPE and after post-TPE time points in all patients is shown above each graph in Figs. 1 and 2. p values of the slope before and after the Post-TPE time point in each

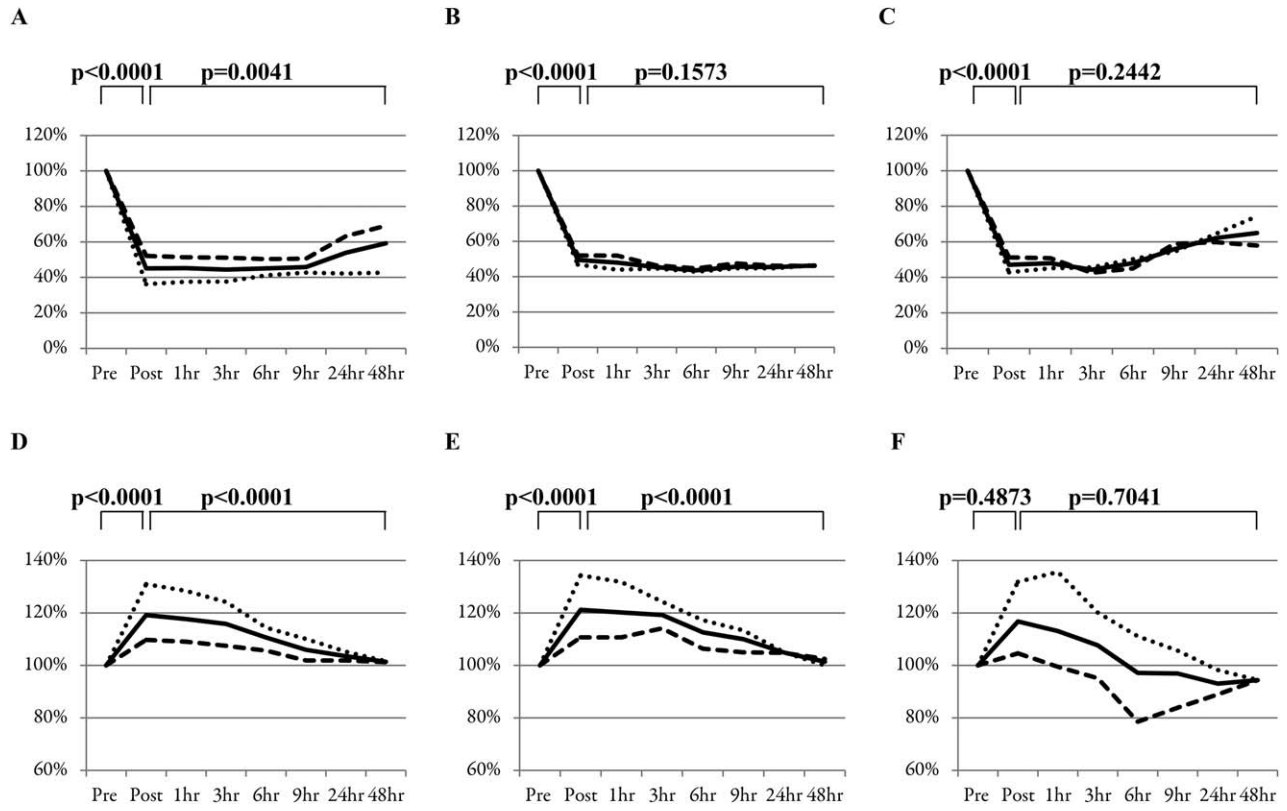

Fig. 1. The mean level change (%) based on pre-TPE level at each time point. (A) nFib; (B) FibAg; (C) CFX; (D) PT; (E) INR; (F) PTT. All data are shown in three groups, all patients (—), patients with plasma replacement use for TPE (– – –), and patients without plasma replacement use for TPE (· · ·). Significance (p value) of level change before and after the post-TPE time point in all patients (both patients with and without plasma replacement) is shown above each graph. p value on the left above each graph is level decrease or increase before Post-TPE time point and that on the right is level increase or decrease after Post-TPE time point. Significance was determined if the p value was less than 0.05.

TABLE 3. nFib/FibAg ratio at each time point in each patient

Patient	Pre	Post	1 hr	3 hr	6 hr	9 hr	24 hr	48 hr
A	1.02	0.99	0.93				1.09	1.22
B		0.83	0.89	0.70			1.04	
C	1.17	0.88	0.89	0.79	0.79	0.81	0.76	0.89
D	0.99	0.96	0.71	0.82	0.99	0.97	1.15	0.88
E	1.22	0.96	1.12	1.26	1.36		1.00	1.26
F	1.07	1.22	1.21	1.35	1.30	1.21	1.32	0.83
G	0.92	0.76	0.76	0.88	0.95	0.95	1.06	0.82
H	0.61	0.43	0.56	0.42	0.61	1.06	0.82	1.24
I	0.97	0.99	1.02	1.13	1.10		1.20	1.02
Mean	1.00	0.89	0.90	0.92	1.01	1.00	1.05	1.02

parameter in three groups (all patients and patients with and without plasma replacement) are shown in Table S1 (available as supporting information in the online version of this paper). Overall, nFib, FibAg, and CFX showed a significant decrease after TPE, but only nFib showed significance in returning slope to the pre-TPE level. Increasing slope toward Post-TPE time point and returning slope were significant in PT/INR, but not significant in PTT. Decrease of nFib/FibAg ratio toward post-TPE was not statistically significant; however, the return was significant. Between two groups, patients treated with and without plasma replacement, the differences of level change were not significant for nFib, FibAg, nFib/FibAg ratio, and CFX, but were significant for PT and PTT (Table 4).

iCa was from 0.97 to 1.45 mmol/L with one exception of 0.3 mmol/L with INR of 1.2 at Post-TPE in one patient whose iCa returned to 1.32 mmol/L at 1 hour after TPE (Fig. 3). PLT count ranged from 105×10^9 to 305×10^9/L.

Percentage of nFib, FibAg, CFX, and PLTs based on the pre-TPE level before the second (48 hr), third (96 hr), and fourth (144 hr) TPE procedures from three patients who were not on any anticoagulant is shown in Table 5. No trending decrease was observed in any of the parameter after the second TPE procedure.

Two patients had bleeding episodes after TPE treatment. One patient on warfarin had bloody bowel movements from existing nonthrombosed external hemorrhoids observed by flexible sigmoidoscopy 6 days after the first TPE procedure, 1 day after the third TPE

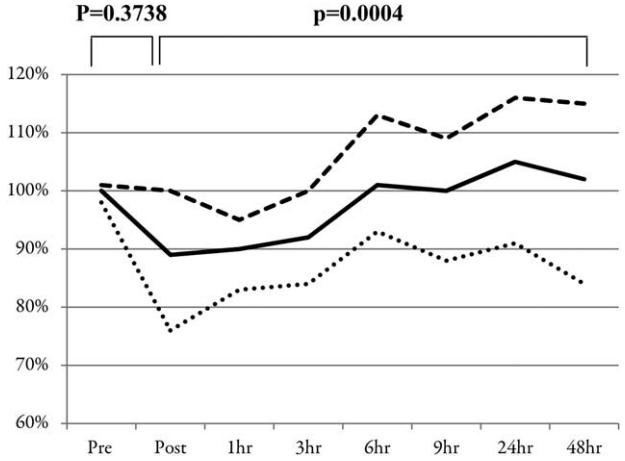

Fig. 2. The mean change of nFib/FibAg ratio (%) based on pre-TPE level at each time point. The data are also shown in the same three groups as those in Fig. 1. p value is also shown in the same manner as Fig. 1.

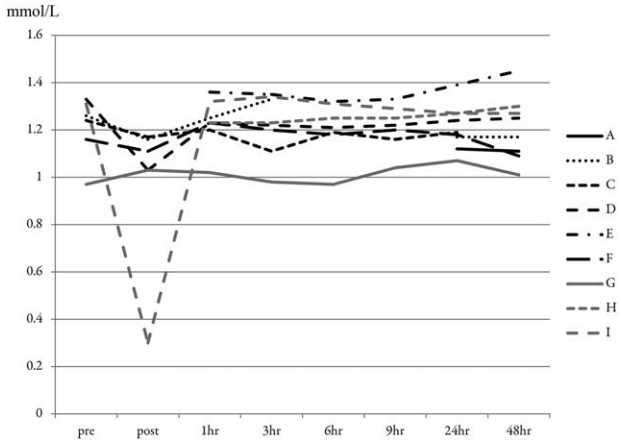

Fig. 3. iCa values at each time point in each patient. The data of each patient are shown in different line type.

TABLE 4. Significance (p value) of difference between with and without plasma replacement before and after Post-TPE time point

Change	Parameter	p value
A. Difference before Post-TPE time point		
Decreasing	nFib	0.2122
	FibAg	0.6144
	nFib/FibAg ratio	0.079
	CFX	0.0952
Increasing	PT	0.0336
	INR	0.061
	PTT	0.0187
B. Difference after Post-TPE time point		
Increasing	nFib	0.1444
	FibAg	0.3708
	nFib/FibAg ratio	0.1252
	CFX	0.1215
Decreasing	PT	0.0127
	INR	0.0219
	PTT	0.0041

procedure. This patient received a transfusion of 1 unit of plasma and iron supplementation for hemoglobin (Hb) level of 9.0 g/dL. The patient's Hb level remained stable with no further bleeding. The other patient had heavy menses 7 days after the last TPE procedure, in the setting of irregular menstrual cycles and possible leiomyoma. This patient did not receive any transfusion.

DISCUSSION

The higher likelihood of bleeding complication after invasive procedures in patients receiving TPE is a concern in patients who are undergoing AMR treatment. Percutaneous renal biopsy is a well-established procedure and the occurrence rate of bleeding complications such as hematoma and hematuria ranges from 1.0% to 33.3% (>90% clinically silent) and from 3.0% to 9.9%, respectively, in the literature.[3-6] TPE may increase the risk of bleeding by removal of coagulation factors or by the anticoagulant effect of citrate. One-plasma-volume TPE decreases plasma protein levels by approximately 65%.[7] One study showed that Fib decreased by a mean of 42% and other coagulation factors decreased between 22.7 and 55.3% immediately after the TPE; however, the absolute concentrations remained within or only slightly below the reference range.[1] At our institution, at least 10 mL/kg plasma is used as a replacement fluid for TPE to add coagulation factors in patients within 5 days of their biopsies. Thus, increased bleeding risk due to depletion of coagulation factors would not generally be expected.

Calcium is one of the cofactors in the coagulation cascade and is required by seven vitamin K–dependent coagulation factors. Citrate used during TPE binds to circulating divalent cations, including Ca^{2+} and Mg^{2+}, in the blood, leading to a decrease in 10% to 15% of iCa concentration.[8] This reduction in iCa slows the process of coagulation cascade and reduces PLT aggregation and fibrinogen binding,[9] and prevents clotting in the extracorporeal circuit during TPE. However, reduced iCa may exacerbate the effect of TPE-related decrease of coagulation factors, leading to a coagulopathic status and increased susceptibility to bleeding after the TPE until the citrate effect is diminished by normal metabolism. Strauss[10] calculated that the 15 to 24 mmol/L citrate levels achieved within cell separation circuits during a typical apheresis procedure would lower the iCa below 0.2 to 0.3 mmol/L. Since all our participants received Ca supplementation into their return lines, the post-TPE iCa value in most patients was only slightly decreased (Fig. 3). However, the dose of Ca supplementation was not constant in

each patient with variable Ca infusion rates during each procedure, the distribution and elimination of Ca may not be constant in our patients who had variable degrees of renal insufficiency, the duration of each TPE procedure was not constant, and additional citrate from plasma was administered when plasma was used for replacement. Therefore, iCa data may not be meaningful to evaluate citrate level at the post-TPE time point. In fact, nFib/FibAg ratio, nFib levels, or INR did not show correlation with iCa levels in six patients for whom iCa data were available at the post-TPE time point (Fig. S1, available as supporting information in the online version of this paper). Notably, the iCa level in one patient at the post-TPE time point was 0.3 mmol/L with an INR value of 1.2. This patient received albumin replacement at first with constant Ca supplementation in the albumin bottle and plasma replacement at the end of TPE with some additional Ca supplement in normal saline (total, 11.2 mmol Ca supplementation). This case most likely suggests that the citrate dose was enough to decrease iCa, but Ca supplementation at the end of TPE was insufficient to completely overcome this effect. Furthermore, the INR level at the post-TPE time point did not reflect low iCa level, suggesting that a temporally low iCa level may not be clinically important.

Fibrinogen is most commonly measured by the Fib test, by determining the clotting time of diluted plasma after the addition of thrombin. The clotting endpoint is compared to a standard reference curve and the fibrinogen concentration is determined. With the presence of citrate, the clotting time will be prolonged, and thus the Fib result will be lower. On the other hand, the FibAg test is performed by radial immunodiffusion and detects FibAg-antibody complex using an agarose gel containing an antibody specific for fibrinogen. Antigen-antibody complexes will form a precipitin ring and the ring size is proportional to the antigen concentration. Thus, the results of this test are not altered by the presence of citrate.

In our limited number of participants, the Fib result was on average 11% lower than the FibAg test result immediately after TPE and returned close to equivalent in 6 hours (Table 3, Fig. 2). These data suggest a citrate effect on Fib measurements, although the changes of the nFib/FibAg ratio at any time point ($p > 0.7125$, data not shown) and the decrease of the nFib/FibAg ratio ($p = 0.3738$, Fig. 2) were not significant. Similarly, any tests reliant on calcium may be affected by citrate; therefore, CFX may be falsely lower and PT/INR and PTT may be falsely higher up to 6 hours after TPE. We found that PTT also returned to the pre-TPE level at the 6-hour time point overall.

The lowest Fib, FibAg, CFX, PLT count, and iCa were 110 mg/L, 134 mg/L, 40%, 107×10^9/L, and 0.97 mmol/L (except for one patient discussed above), respectively (at the post-TPE time point), which should be sufficient to maintain hemostasis. However, all nFib, FibAg, and CFX levels did not return to pre-TPE level within 48 hours (Fig. 1), which may raise a possibility of further decreases with frequent TPE. The percentage of nFib, FibAg, CFX, and PLT count based on the pre-TPE levels before second, third, and fourth TPE procedure did not show progressive decline (Table 5) in data from three patients without anticoagulants. One patient among these three patients received plasma replacement only in the first TPE. These data were not affected by citrate because subsequent TPE procedures were performed at around 48 hours after each TPE, given that the citrate effect appears to last for 6 hours from our study. This observation suggests that coagulation factors decreased by TPE return to their pre-TPE level in 2 days after the second TPE. Therefore, plasma or cryoprecipitate transfusion is not required even with multiple procedures when TPE procedures are performed every other day or less frequently. A previous report had a similar finding.[1] Blasi and colleagues[11] showed that fibrinogen levels before the first TPE procedure and the second TPE procedure (1 or 2 days after the first TPE procedure) were similar albeit with reduced clot firmness that was without clinical implications. However, our results are based on a limited number of patients and a larger study is necessary to confirm this observation, especially since we found that fibrinogen recovery was slightly delayed relative to CFX.

TABLE 5. Mean percentage of coagulation factors based on pre-TPE level before subsequent TPE procedures on three patients without anticoagulants

Variable	Pre-TPE	Before second TPE (48 hr)	Before third TPE	Before fourth TPE
nFib	100	42.45	60.05	58.04
FibAg	100	37.73	32.79	37.09
CFX	100	56.81	50.77	49.32
PLT	100	89.62	80.52	75.19

When two groups, patients with and without plasma replacement use, were compared, nFib, FibAg, nFib/FibAg ratio, and CFX did not show significant differences (Table 4), which may also suggest plasma use for replacement may not improve coagulation status after the TPE procedure under the effect of citrate. However, PT and PTT showed a significant difference in these two groups, with the level increase toward Post-TPE time point greater in the patient group without plasma replacement. This may be due to PT and PTT being relatively sensitive to coagulation factor levels below 50%; these test results might be affected by a clinically nonsignificant decrease of coagulation factors to between 20 and 50% of reference range after TPE. Coagulation factor VIII may require more than 30% of normal for normal hemostasis, while other coagulation factors likely provide sufficient hemostasis at 10% to 20% of normal.[12] However, our study showed that the lowest CFX was 40% (32.8% of pre-TPE level) even with the citrate effect. Therefore, all coagulation factors should be more than 30% of normal unless Pre-TPE levels were also lower. Thus, PT/

INR and PTT may be increased more in patients without plasma use due to some coagulation factors of less than 50% of normal, although the amount of coagulation factors is likely sufficient for hemostasis in both groups.

Limitations of this study are the small number of participants with some missing data and the potential confounding effect of systemic anticoagulation in some patients and the possible contamination of some samples by heparin used for central line flushing. Therefore, the data from only patients who were not on anticoagulants were also analyzed. nFib/FibAg ratio and CFX over time for those patients demonstrated similar results between all patients and patients without anticoagulants (Fig. S2, available as supporting information in the online version of this paper). Therefore, overall analysis was performed using all patients' data.

Finally, two patients had bleeding episodes from sites other than kidney biopsy within several days after TPE. However, these episodes were unlikely related to either citrate or TPE effect, but rather related to the patients' underlying conditions.

In summary, we found a difference between nFib and FibAg levels up to 6 hours after TPE, although not significant, which suggests a persistent citrate effect for this period. Similarly, any tests reliant on calcium may be affected by citrate; CFX may be falsely lower, and PT/INR and PTT may be falsely higher, up to 6 hours after TPE. Both FibAg and CFX did not return to pre-TPE levels in 48 hours after the first TPE procedure; however, the levels of FibAg and CFX before the subsequent TPE did not show a tendency for progressive decline. In addition, FibAg, CFX, and PLTs showed sufficient levels to maintain coagulation status at all time points observed, even in the presence of a putative citrate effect. Therefore, blood component transfusion is not necessary for coagulation factor replacement when TPE is performed every other day or less frequently, even though the patients can be coagulopathic due to citrate effect up to 6 hours after TPE. Furthermore, nFib, FibAg, and CFX results did not show a significant difference between patients with and without plasma replacement use, which may suggest that plasma use as a replacement fluid up to 45% of total replacement volume may not have any effect on coagulation status. A larger study may be necessary to confirm these findings.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Statistical significance (p value) of level change before and after post-TPE time point

Fig. S1. nFib[†]/FibAg[‡] (normalized fibrinogen activity test result/fibrinogen antigen test result) ratio, nFib, INR and iCa[#] (ionized calcium) levels at post-TPE (therapeutic plasma exchange)

Fig. S2. The mean level change (%) based on pre-TPE* level at each time point on patients without anticoagulants. A) nFib[†]/FibAg[‡] ratio. B) CFX[§] (coagulation factor X chromogenic activity) test result. The data are shown in 3 groups, all patients (—), patients with plasma replacement use for TPE (– – –), and patients without plasma replacement use for TPE (· · ·).