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Therapeutic plasma exchange is feasible and tolerable in severely injured patients with trauma-induced coagulopathy

Sarah A Moore,[1] Marian A Rollins-Raval,[2] Jennifer M Gillette,[2] Joseph E Kiss,[3] Darrell J Triulzi,[4] Mark H Yazer ,[4] Jasmeet S Paul ,[1] Christine M Leeper ,[5] Matthew D Neal ,[6] Jay S Raval [2]

[1]Surgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[2]Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA
[3]Medicine, University of Pittsburgh Medical Center Health System, Pittsburgh, Pennsylvania, USA
[4]Pathology, University of Pittsburgh Medical Center Health System, Pittsburgh, Pennsylvania, USA
[5]Surgery, UPMC, Pittsburgh, Pennsylvania, USA
[6]Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Correspondence to
Dr Jay S Raval; JRaval@salud.unm.edu

MDN and JSR are joint senior authors.

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ABSTRACT

Objectives Trauma-induced coagulopathy (TIC) occurs in a subset of severely injured trauma patients. Despite having achieved surgical hemostasis, these individuals can have persistent bleeding, clotting, or both in conjunction with deranged coagulation parameters and typically require transfusion support with plasma, platelets, and/or cryoprecipitate. Due to the multifactorial nature of TIC, targeted interventions usually do not have significant clinical benefits. Therapeutic plasma exchange (TPE) is a non-specific modality of removing and replacing a patient's plasma in a euvolemic manner that can temporarily normalize coagulation parameters and remove deleterious substances, and may be beneficial in such patients with TIC.

Methods In a prospective case series, TPE was performed in severely injured trauma patients diagnosed with TIC and transfusion requirement. These individuals all underwent a series of at least 3 TPE procedures performed once daily with plasma as the exclusive replacement fluid. Demographic, injury, laboratory, TPE, and outcome data were collected and analyzed.

Results In total, 7 patients received 23 TPE procedures. All patients had marked improvements in routine coagulation parameters, platelet counts, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activities, inflammatory markers including interleukin-6 concentrations, and organ system injuries after completion of their TPE treatments. All-cause mortality rates at 1 day, 7 days, and 30 days were 0%, 0%, and 43%, respectively, and all patients for whom TPE was initiated within 24 hours after injury survived to the 30-day timepoint. Surgical, critical care, and apheresis nursing personnel who were surveyed were universally positive about the utilization of TPE in this patient population. These procedures were tolerated well with the most common adverse event being laboratory-diagnosed hypocalcemia.

Conclusion TPE is feasible and tolerable in severely injured trauma patients with TIC. However, many questions remain regarding the application of TPE for these critically ill patients including identification of the optimal injured population, ideal time of treatment initiation, appropriate treatment intensity, and concurrent use of adjunctive treatments.

Level of evidence Level V.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Trauma-induced coagulopathy (TIC) is characterized by persistent bleeding, clotting, or both in conjunction with deranged coagulation parameters that typically requires transfusion support with blood products despite having achieved surgical hemostasis.

⇒ As outcomes are poor in TIC despite various interventions due to the multifactorial nature of elements that contribute to this condition, a non-specific technology like therapeutic plasma exchange (TPE) may be beneficial due to its ability to simultaneously influence a wide range of plasma-associated parameters.

WHAT THIS STUDY ADDS

⇒ Early implementation of a 3-procedure TPE treatment series performed once daily in patients with severe traumatic injury who developed TIC was: feasible; tolerable; corrected derangements in coagulopathy, thrombocytopenia, inflammatory markers, and kidney function; associated with decreased all-cause mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While centers evaluating treatment options for such TIC patients can consider TPE based on the encouraging findings from this initial investigation, controlled studies that further characterize specific safety and efficacy end points need to be performed.

INTRODUCTION

Severe traumatic injury is typically defined as those with an injury severity score (ISS) >25 and often profoundly impacts multiple organ systems.[1] In a subset of these individuals, trauma-induced coagulopathy (TIC) can occur. This condition is characterized by persistent bleeding, clotting, or both in conjunction with deranged coagulation parameters that typically requires transfusion support with plasma, platelets, and/or cryoprecipitate despite having achieved surgical hemostasis.[2] While various interventions have been attempted for treating TIC, outcomes are poor. This is, in part, due to the multifactorial nature of elements that contribute

to TIC, including hemorrhagic shock, tissue injury, dysfunction of endothelium and platelets, inappropriate thrombin generation, fibrinogen depletion, and dysregulated fibrinolysis.[2] Due to the complicated, multistep pathophysiology of this condition consisting of numerous elements of variable contributions and interdependence, it is unlikely that treating any single element will result in a clinically meaningful change.

Therapeutic plasma exchange (TPE) is an extracorporeal technology that efficiently and euvolemically removes and replaces a patient's plasma with a replacement fluid.[3] When donor plasma from the blood bank is used as the replacement fluid, coagulation and anticoagulation factors can be replenished and a variety of abnormal compounds can be removed. Indeed, procoagulation elements such as fibrin degradation products and d-dimers, hormones, pro-inflammatory cytokines, endotoxin, acute phase reactants, complement proteins, extracellular microvesicles, plasma-free hemoglobin, lipids, damage-associated molecular pattern molecules, toxic metabolites, and histone-associated DNA (as part of neutrophil extracellular traps (NETs)) are all pathological substances identified in TIC that are located in the plasma fraction and can be removed.[4–11] This technology has an exquisite safety profile in a variety of settings, including critical illness, pregnancy, medical, surgical, and pediatrics.[12 13] Importantly, TPE is a non-specific technology, which means that all elements within the plasma are removed. A host of complex conditions that have overlap with features of TIC have been successfully treated with TPE.[11] Due to the potential advantages for a non-specific technology like TPE to normalize plasma in those with TIC, a clinical practice change was initiated to assess feasibility and tolerability in this patient population.

MATERIALS AND METHODS

In this 2-year prospective case series, the Trauma Surgery or Surgical Critical Care teams could refer any patient with severe trauma and diagnosed TIC to the Therapeutic Apheresis Program. Indications for TPE included confirmed traumatic injury; directly transported from site of injury to the University of New Mexico Hospital and admitted on hospital day 0; age ≥18 years (estimated or confirmed); surgical/mechanical control of hemorrhage; mechanical ventilation requirement; transfusion need of plasma, platelets, and/or cryoprecipitate; and persistence of thrombocytopenia (platelet count $<100\times10^9$/L despite platelet transfusion) and/or laboratory evidence of coagulopathy (international normalized ratio (INR) >2.0, fibrinogen <100 mg/dL, and/or viscoelastic testing demonstrating hyperfibrinolysis or fibrinolytic shutdown despite plasma/cryoprecipitate transfusion). TPE was not performed in patients for whom blood products could not be transfused; pregnant patients; pediatric patients (aged <18 years); and those whose injuries were deemed non-survivable at time of consultation.

For all patients, the first TPE was initiated within 12 hours of consultation. Prior to performing the first TPE and after completing the final TPE, laboratory specimens were collected for a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) activity and interleukin (IL)-6 concentration as markers of injury and critical illness severity. The referring team placed a non-tunneled double lumen dialysis catheter (if not already present) at the time of consultation. TPE procedures were performed once daily for 3 consecutive days using the Spectra Optia Apheresis System (Terumo BCT, Lakewood, Colorado, USA). The intensity of TPE was 1.0 plasma volumes, citrate was the anticoagulation used, supplemental calcium was provided via a continuous intravenous infusion of calcium gluconate, and plasma was the exclusive replacement fluid. Ionized calcium levels were collected every 30 minutes. The Surgical Critical Care team was informed ahead of the first TPE that vasopressors, inotropes, and/or antiseizure medications may require increased infusion rates during TPE due to iatrogenic drug removal.[14 15] After completion of 3 TPE, up to an additional 3 procedures (for a maximum total of 6 TPE) could be performed if requested.

Prespecified outcomes included the following: feasibility and tolerability of TPE in this patient population; all-cause mortality within 1 day, 7 days, and 30 days counting from the time of admission on the first day of hospitalization; platelet recovery; coagulation recovery; decreases in proinflammatory markers; plasma, platelet, and cryoprecipitate utilization during the days TPE was performed; impressions about use of TPE in these patients from Trauma Surgery and Surgical Critical Care physicians, as well as apheresis nurses. Demographic, clinical, and laboratory data were collected for all patients. The presence of 2 or more of following criteria were used to define systemic inflammatory response syndrome (SIRS): body temperature >38°C or <36°C; heart rate >90 beats per minute; tachypnea >20 respirations per minute or PCO_2<32 mm Hg; and white blood cell count $>12.0\times10^9$/L, $<4.0\times10^9$/L, or >10% band neutrophils.[16] Changes in laboratory values were calculated using the results available immediately prior to and after the TPE series. Viscoelastic testing was performed using the ROTEM delta (Werfen, Bedford, Massachusetts, USA). Data were analyzed and presented as median values (IQR), percentages of a whole, or percent change from pre-TPE to post-TPE timepoints unless otherwise specified. Student's t-test was used to compare continuous variables, and statistical significance was defined as $p<0.05$.

RESULTS

Seven trauma patients with TIC were referred to the Therapeutic Apheresis Program. Demographic and injury severity data at the time of apheresis consultation are shown in table 1. All patients were male and had blunt traumatic injuries. The median ISS was 48, indicating a severely injured trauma patient cohort. All patients had thrombocytopenia, coagulopathy, and SIRS, and over half of individuals were on continuous renal replacement therapy (CRRT). All patients had massive transfusion protocols activated for their injuries on hospital arrival with at least 3 rounds of blood products issued, as well as dysfunction of at least 3 organ systems. The median time from admission to apheresis consultation was 1 day (range 1–3 days).

Table 2 contains laboratory data at the time of initial apheresis consultation prior to initiation of TPE. Median ADAMTS13 activity and IL-6 concentration immediately prior to TPE were 35% (normal >60%) and 140 pg/mL (normal ≤2 pg/mL), respectively, and 6 patients had maximum lysis at 60 minutes of 0% (normal <15%). Patients had a median of 3 TPE procedures performed (range 3–4), and a total of 23 TPE procedures were performed in these 7 individuals (see table 3 for TPE procedures performed, changes in laboratory data after completion of TPE treatment series, and outcomes). Application of TPE coincided with significant increases in platelet counts ($p=0.0006$) and fibrinogen concentration ($p=0.0145$ for those who had hypofibrinogenemia at initial consultation), as well as significant decreases in INR ($p=0.0040$) and creatinine ($p=0.0008$). Additional observed changes included marked decreases in creatine kinase (maximum % change −89%), lactate (maximum % change −85%), erythrocyte sedimentation rate (maximum

Table 1 Patient demographic and injury severity data at time of initial apheresis consultation

Patient	Age (decade)	Sex	Injury	ISS	Thrombocytopenia	Coagulopathy	SIRS	CRRT	Injury-consult time duration (days)
1	Third	Male	Blunt (MVC)*	59	Yes	Yes	Yes	Yes	3
2	Fifth	Male	Blunt (MVC)*	57	Yes	Yes	Yes	Yes	3
3	Seventh	Male	Blunt (MVC)	43	Yes	Yes	Yes	Yes	2
4	Fifth	Male	Blunt (crush)	41	Yes	Yes	Yes	Yes	1
5	Fourth	Male	Blunt (MVC)*	48	Yes	Yes	Yes	No	1
6	Second	Male	Blunt (MVC)*	43	Yes	Yes	Yes	No	1
7	Second	Male	Blunt (MVC)	50	Yes	Yes	Yes	Yes	1
Total	Fourth	100% Male	100% Blunt	48 (10.5)	100% Yes	100% Yes	100% Yes	71% Yes	1 (1.5)

*Traumatic brain injury present.
CRRT, continuous renal replacement therapy; ISS, injury severity score; MVC, motor vehicle collision; SIRS, systemic inflammatory response syndrome.

% change −64%), C reactive protein (maximum % change −67%), ferritin (maximum % change −84%), IL-6 concentration (maximum % change −78%), and fever (maximum absolute change −3.2°C), and marked increases in pH (maximum absolute change +0.24) and ADAMTS13 activity (maximum % change +132%). Furthermore, cessation of CRRT occurred faster than anticipated by the clinical teams (median 4 days of circuit use in survivors).[17]

Excluding the plasma as replacement fluid used in the TPE procedures, blood product utilization was low in these severely injured trauma patients during the 3-day to 4-day timespan in which TPE was performed. Median simple transfusions of plasma, platelets, and cryoprecipitate during the entire TPE treatment period totaled 3 units, 4 units, and 2 pools, respectively. All-cause mortality rates at 1 day, 7 days, and 30 days were 0% (0/7), 0% (0/7) and 43% (3/7).

All patients completed all TPE procedures in this prospective case series (23/23, 100%). The most common adverse event was laboratory-diagnosed hypocalcemia (7/23, 30.4%) measured on a point-of-care ionized calcium analyzer. Vasopressor infusion rates had to be acutely increased in 2 procedures in 2 different patients (2/23, 8.7%). Despite the large volumes of plasma used (3000–5000 mL per TPE), transfusion reactions were rare with only 1 mild allergic transfusion reaction reported (1/23, 4.3%). All adverse events were classified as Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 incidents. Notably, there were no vascular access issues, codes, cardiac and/or respiratory arrests, or deaths while patients received TPE.

Trauma Surgery and Surgical Critical Care physicians were surveyed regarding their impressions about performance of TPE in this patient population (box 1). Overall, physicians were very comfortable with TPE being used in their severely injured trauma patients with TIC. Similarly, apheresis nurses were also surveyed and were very comfortable with the performance of TPE in these patients (box 2). While apheresis nurses universally expressed concerns over hypocalcemia and iatrogenic drug removal (particularly vasopressors), these are concerns that would exist with any patient being treated with TPE in the intensive care unit.

DISCUSSION

This prospective case series is the first reported experience specifically to treat severely injured trauma patients using TPE for the purpose of halting and reversing TIC. It has been previously demonstrated that dysregulation of the ADAMTS13-von Willebrand factor (VWF) axis occurs with traumatic injury.[18–21] Decreased ADAMTS13 activity and increased VWF occur at time of injury and, despite numerous medical and surgical interventions, persists 24 hours later. This depression of ADAMTS13 activity and associated impaired cleaving capacity of VWF correlates with various laboratory and clinical markers of coagulopathy as well as ISS.[19] Restoration of the ADAMTS13-VWF axis using either simple transfusion of plasma or administration of recombinant ADAMTS13 has been reported to result in improvements in pulmonary endothelial permeability and organ injury; however, only recombinant ADAMTS13 was found to improve the trauma-associated ADAMTS13 deficits.[20] The current report has demonstrated that a short course of 3–4 TPE can also normalize numerous parameters in severely injured trauma patients, including ADAMTS13 activity.

Patients in the current report had ISS scores that were associated with 35%–75% mortality rates[22]; they also had ADAMTS13 deficiency and elevated IL-6 concentrations that have been

Table 2 Laboratory data at time of initial apheresis consultation

Patient	ADAMTS13 activity (ref >60%)	IL-6 (ref ≤2 pg/mL)	Platelets (ref 150–400×10^9/L)	INR (ref 0.8–1.3)	Fibrinogen (ref 170–450 mg/dL)	$ML_{60\ min}$ (ref <15%)	Creatinine (ref 0.7–1.35 mg/dL)
1	36%	10044	37	2.8	65	0%	3.3
2	28%	66	74	3.4	74	0%	5.3
3	40%	124	49	3.1	531	0%	3.0
4	31%	432	57	1.6	98	32%	3.3
5	20%	98	29	2.0	143	0%	1.5
6	35%	140	43	1.7	96	0%	2.6
7	41%	279	71	2.7	109	0%	4.1
Total	35% (8.5%)	140 (244.5)	49 (24)	2.7 (1.1)	98 (41)	0% (0%)	3.3 (0.9)

IL, interleukin; INR, international normalized ratio; $ML_{60\ min}$, maximum lysis at 60 minutes; ref, reference range.

Table 3 TPE procedures performed, changes in laboratory data after completion of TPE treatment series, and outcomes

Patient	# TPE	ADAMTS13 activity (ref >60%)	IL-6 (ref ≤2 pg/mL)	Platelets (ref 150–400×10⁹/L)	INR (ref 0.8–1.3)	Fibrinogen (ref 170–450 mg/dL)	$ML_{60\ min}$ (ref <15%)	Creatinine (ref 0.7–1.35 mg/dL)	Outcome
1	4	61%	4524	63	1.4	298	4%	2.1	Death (HD 7, CMO)
2	3	65%	28	115	1.2	115	6%	2.7	Death (HD 7, CMO)
3	3	71%	52	131	1.3	395	7%	1.8	Death (HD 11, sepsis)
4	3	68%	100	108	1.2	215	11%	1.7	Alive at 30 days
5	3	78%	29	83	1.1	190	13%	0.8	Alive at 30 days
6	3	74%	31	92	1.4	177	12%	1.4	Alive at 30 days
7	4	80%	73	99	1.2	220	11%	2.9	Alive at 30 days
Total	3 (0.5)	71% (9.5%)	52 (56.5)	99 (24)	1.2 (0.15)	215 (75.5)	11% (5%)	1.8 (0.85)	43% 30-day mortality

CMO, comfort measures only; HD, hospital day; IL, interleukin; INR, international normalized ratio; $ML_{60\ min}$, maximum lysis at 60 minutes; ref, reference range; TPE, therapeutic plasma exchange.

found to be potential predictive and prognostic markers of mortality in critically ill patients.[23–26] Most of these patients also had maximum lysis at 60 minutes of 0%; while this is technically within the normal range of <15%, having no detectable lysis at all at this timepoint suggests fibrinolytic shutdown in these severely injured patients, indicating that these patients had a thrombotic element in addition to the overt hemorrhagic picture of their TIC.[2] In this particular trauma population with TIC, simple transfusion of plasma in this setting was unlikely to have a significant effect. Indeed, it is doubtful that any single intervention would have had a clearly positive result because TIC is a classic complex system, which is 'a system that is intrinsically difficult to model due to the dependencies, competitions, relationships, or other types of interactions between its parts and/or between a given system and its environment'.[27] These systems often contain pathways with complicated, multistep pathophysiology, and have multiple sources of causing the disease phenotype with unknown weightings and interdependencies. In TIC, the complexity of interactions between injury, inflammation, primary and secondary hemostasis, and acute blood losses are exacerbated by the fact that the clinical effects in severe traumatic injury are life-threatening, treatment protocols are heterogeneous, hemostatic phenotypes can range from thrombotic to hemorrhagic (or both), and that these patients all have diverse medical histories, medications, and genetics that can modify TIC in often unknown ways.[2]

Although complex conditions like TIC are unlikely to be successfully treated by modification of any single pathological element, here lies the benefits of TPE: this technology does not simply provide missing coagulation factors or enzymes, but also removes pathological substances that are present in circulation. Furthermore, this removal and replacement occurs on a strikingly large scale. With a single 1.0 plasma volume TPE, 63% of a patient's plasma can be removed and replaced.[3] This efficiency is compounded when daily TPE is employed as was done in the current report. Such TPE protocols have been

Box 1 Surgery and critical care physician impressions of performing TPE in severely injured trauma patients with TIC at the end of the prospective case series

1. Do you feel that the performance of TPE is safe in your trauma patient with TIC?
   Yes (14/14, 100%)
2. Do you have any concerns about providing vascular access for TPE?
   No (14/14, 100%)
3. Do you view the 1–2 hours immediately after TPE as the time period with best possible coagulation status in your patient?
   Yes (14/14, 100%)
4. Would you preferentially schedule interventional procedures or maneuvers with increased bleeding risks immediately after a TPE procedure was completed?
   Yes (14/14, 100%)
5. Outside of major interventional procedures or unforeseen complications, has bleeding improved?
   Yes (11/14, 78.6%); 3 responded bleeding was unchanged.
6. Do you have any concerns about the volumes of plasma used during the TPE treatment series?
   No (13/14, 92.9%); a single individual cited risk of TRALI as a concern

TIC, trauma-induced coagulopathy; TPE, therapeutic plasma exchange; TRALI, transfusion-related acute lung injury.

Box 2 Apheresis nursing impressions of performing TPE in severely injured trauma patients with TIC at the end of the prospective case series

1. Do you feel that the performance of TPE is safe in trauma patients with TIC?
   Yes (5/5, 100%)
2. Do you have any concerns about the vascular access provided for TPE?
   No (5/5, 100%)
3. Are intensive care team members supportive of efforts to help you make TPE as safe as possible?
   Yes (5/5, 100%)
4. Do you have any concerns about the citrate anticoagulation or iatrogenic drug removal associated with TPE?
   Yes (5/5, 100%)—all were concerned for decreased ionized calcium and removal of vasopressors with TPE.
5. Do you have any concerns about the volumes of plasma used during the TPE treatment series?
   No (5/5, 100%)
6. Is performance of TPE within 12 hours of consultation feasible? How about 4 hours?
   Yes (5/5, 100%); No (5/5, 100%)

TIC, trauma-induced coagulopathy; TPE, therapeutic plasma exchange.

successfully performed in other complex conditions such as thrombocytopenia-associated multiorgan failure (TAMOF) with sepsis, acute liver failure, catastrophic antiphospholipid antibody syndrome, and thrombotic microangiopathies (TMA) of various etiologies (including thrombotic thrombocytopenic purpura and complement-associated TMA/atypical hemolytic uremic syndrome).[11] Importantly, although ADAMTS13 activities and IL-6 concentrations did improve with TPE treatment, these are not necessarily therapeutic targets that need to be normalized as the clinical advantages of doing so in this patient population has not been demonstrated in high-quality studies.

The findings of kidney function improvement and, in those who received it, shortened duration of CRRT were unexpected but very interesting. The kidney is often involved to variable extents in diseases or conditions that adversely impact multiple organ systems. In severe traumatic injury, it has been previously demonstrated that those with acute kidney injury have significantly greater levels of high molecular weight VWF multimers.[28] Murine models of polytrauma and hemorrhage demonstrated microangiopathy and microthrombi due to intraluminal deposition of VWF and fibrinogen that obstructed renal vasculature and was associated with dilatation and denudation of renal tubular lumens and tubule cells. The ability of TPE to rapidly provide ADAMTS13 to halt renal microthrombi formation while simultaneously normalizing other factors and removing various pathogenic molecules known to be present in severe trauma and TIC so that such lesions can be resorbed more rapidly is a possible explanation for the observed improvement in kidney function. TPE can already be applied to conditions that cause microthrombi and TMA in the kidney.[29] Efficient removal of nephrotoxic substances such as creatine kinase and myoglobin is another mechanism by which acute kidney injury may have improved more rapidly.[30 31]

TPE was tolerated well by all patients in the current report. This should not be surprising given the types of conditions, often present in critically ill patients, to which this technology has been applied previously.[32] The adverse events of laboratory-diagnosed hypocalcemia, iatrogenic drug removal necessitating increased infusion rates, and a mild allergic transfusion reaction due to plasma are expected events that can be readily treated by and, for subsequent procedures, likely prevented through modifications in the apheresis instrument settings to increase the whole blood-anticoagulation ratio, increasing supplemental calcium infusion rates, empiric increases in medications that are delivered intravenously during the procedure, and premedication with anti-allergy agents such as antihistamines.[33] Notably, all adverse events were CTCAE grade 1 or 2 incidents, meaning that at worst they were moderate events that were correctable with non-invasive interventions and had no lasting injurious effects. While 3 of the patients ultimately died by day 30 (43% mortality), this is on the lower end of the 35%–75% predicted mortality based on the ISS of our patients. Additionally, survivors at day 30 in the current report had their consultations to the Therapeutic Apheresis Program placed in the first 24 hours of hospitalization. Early initiation of TPE may have benefitted these individuals. TPE has been previously applied to trauma patients who developed TMA and other conditions, demonstrating its feasibility and tolerability in other post-traumatic states.[34–38] Moreover, both providers and apheresis nurses were uniformly positive about the application of TPE in this patient population (boxes 1 and 2). Although transfusion-related acute lung injury (TRALI) was cited by a single physician as a potential risk factor for using high volumes of plasma with TPE, the US blood supply is TRALI risk-reduced and it is no longer the leading cause of transfusion-associated fatalities.[39 40]

Limitations of this analysis include the inherent shortcomings due to its study design and non-standardized patient referral strategy. There was also variability in terms of referral lag; patients referred to the Therapeutic Apheresis Program soon after initiating this clinical practice change were done so on hospital day 2 or 3; however, as familiarity and comfort increased, referrals routinely occurred within the first 24 hours of injury. It is unknown if earlier initiation of TPE in TIC confers any benefits but given that these patients have high mortality rates and the possibility of therapeutic benefit of halting or reversing TIC earlier was appealing, our services agreed to streamline this process by making referrals as soon as TIC was diagnosed and initiating TPE within 12–24 hours of consultation, that is, an urgent need for apheresis intervention.[41] Intensity of the TPE regimen was also variable, in that up to an additional 3 TPE procedures could be requested by the Trauma Surgery or Surgical Critical Care teams. As no explicit therapeutic target was prespecified, it is unknown if a more intensive TPE regimen conferred any benefits. Given the overlapping features of TIC and TAMOF with sepsis that can involve NET-osis, cytokine storm, and impaired hemostasis including a dysregulated ADAMTS13-VWF axis and coagulopathy,[42] future investigations should include combined targets of clinical and laboratory parameters.

Despite the successes of the current experience, many questions still remain and new ones have emerged. Are we treating these severely injured trauma patients too late with TPE? Are we missing potential trauma patients that may benefit from TPE? Would a trauma population with lower ISS, penetrating trauma, female sex, or age <18 years benefit from TPE? Are there meaningful clinical findings and biomarkers that we can serially follow to customize the TPE regimen intensity for each patient? Are there other ways of differentiating traumatically injured patients to identify subpopulations that would benefit from TPE? What are the mechanisms of TPE in improving kidney dysfunction in TIC? What adjunctive therapies would improve observed positive impacts of TPE in these trauma patients? Can we modify the apheresis procedure to remove both plasma and a fraction of the cellular elements of the buffy coat to remove pathological substances more extensively? These problems must be investigated.

In conclusion, TPE is feasible and tolerable in severely injured trauma patients with TIC. A successful workflow was implemented to provide this therapy to these critically ill patients that required care from multiple teams. Clinically significant adverse events were uncommon during TPE, and all of those that did occur were readily treatable and preventable for subsequent procedures. Future investigations that will more definitely determine safety as well as target specific clinical and laboratory parameters as efficacy goals of TPE in trauma patients with TIC who are referred for this treatment in a prescriptive manner need to be performed.

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ORCID iDs
Mark H Yazer http://orcid.org/0000-0001-6740-2758
Jasmeet S Paul http://orcid.org/0000-0002-4030-6624
Christine M Leeper http://orcid.org/0000-0001-9902-0340
Matthew D Neal http://orcid.org/0000-0001-8931-6236
Jay S Raval http://orcid.org/0000-0001-9835-957X

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