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Hemostasis Management and Therapeutic Plasma Exchange: Results of a Practice Survey

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Disclosure: NDZ: Research funding: Octapharma, Terumo BCT, Bayer HealthCare, Verax Biomedical; Financial interest: Endo International PLC, Boston Scientific. MBP: Research funding: Terumo BCT. MAR: Advisory Boards: Bayer and NovoNordisk. ECCW: Consultant: Comprehensive Care Services. YW: Consultant: Verax Biomedical. The other authors have no conflict of interest to disclose.

Short title: Hemostasis Management and TPE

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jca.21653

Key words: apheresis, plasmapheresis, coagulation, bleeding, anticoagulation

Word Count: 2,778 (excluding references) Tables:5 (including1 supplement) Figures: 0

ABSTRACT

INTRODUCTION: Patients undergoing therapeutic plasma exchange (TPE) may present with risks for hemorrhage or thrombosis. Use of replacement fluids devoid of coagulation factors will decrease factor levels and platelet levels. There are no established guidelines for hemostasis management in these situations.

MATERIALS AND METHODS: A survey to evaluate current hemostasis management practice during TPE was conducted using online survey software. One response per institution was analyzed based on a hierarchical algorithm, excluding membrane filtration users, resulting in a maximum of 107 respondents. Descriptive analysis was performed with results reported as the number and frequency (%) of respondents to each question.

RESULTS: Apheresis Medicine physicians, alone (59.4%) or jointly with the requesting provider (29.2%), choose the replacement fluid. Based on a theoretical patient case receiving 5 TPEs approximately every other day, the percent of respondents who would use albumin with or without normal saline was 94.7% with no history of a bleeding or clotting disorder, 1.1% with active bleeding, and 8.8% with hypofibrinogenemia (<100mg/dL) due to recent TPE. More respondents would use albumin with or without normal saline for replacement fluid when a minor invasive procedure (49.5%) versus a major surgery (8.9%) was performed 1 day before TPE. Replacement fluid selection varied among respondents for several other clinical

conditions. The most frequent use for cryoprecipitate by respondents (14.3%) was hypofibrinogenemia.

CONCLUSION: These survey results demonstrate wide interinstitutional variation in replacement fluid selection to manage hemostasis in patients undergoing TPE. Further studies are needed to guide optimal hemostasis management with TPE.

INTRODUCTION

Apheresis is a procedure in which blood of the patient or donor is passed through a medical device which separates one or more components of blood and returns the remainder with or without extracorporeal treatment or replacement of the separated component.[1] Therapeutic apheresis has become a widely used treatment or treatment alternative for many diseases or disease conditions, among which therapeutic plasma exchange (TPE) is the procedure performed most commonly in clinical practice.[1,2] TPE is a therapeutic apheresis procedure in which the plasma is removed and replaced with a solution such as colloid solution (e.g. albumin and/or plasma) or a combination of crystalloid/colloid solution. TPE procedures performed with centrifugation based devices may remove pathologic substances (e.g. toxins, autoantibodies, paraproteins) as well as normal plasma constituents (e.g. coagulation factors and natural anticoagulants).[3-7] Circulating medications, such as anticoagulants, may also be removed.[8-11] Due to the removal of coagulation factors and anticoagulants, it is a challenge in clinical apheresis medicine to maintain patients in a safe hemostasis status, which is further compounded in patients with an underlying risk for or ongoing hemorrhage or thrombosis.

Currently there are no consensus or national guidelines regarding hemostasis management in patients undergoing TPE treatments. To understand current practice, the Coagulation Subcommittee of the American Society for Apheresis (ASFA) Applications Committee

conducted a survey regarding hemostasis management and TPE. This manuscript contains management practice data on the replacement fluid choice for patients undergoing TPE, while the laboratory testing practices are described in the associated article by Zantek et al.[12] The aim of this study is to describe and characterize the current practice of replacement fluid selection for patients undergoing TPE.

METHOD

A survey was developed by the members of the Coagulation Subcommittee of the ASFA Applications Committee to evaluate management of hemostasis in patients undergoing TPE. The development, implementation, and analysis of the survey is described in the associated article by Zantek et al.[12] The data analyzed here represents the second portion of the survey. Due to decreasing numbers of responses through the progression of the survey, only those respondents that answered question 27 of 37 questions "What method of cell separation do you typically use for TPE" are included in the data set analyzed here. From the initial 167 responses, a total of 107 were included in these analyses. The reasons that 60 responses were excluded are as follows: 16 were duplicate responses, 24 were more than one response received from an institution, 15 did not answer question 27 of 37 (method of apheresis question), and 5 indicated they use membrane filtration or centrifugation and/or membrane filtration techniques.

RESULTS

Demographic information is provided in Table 1. The respondents were mostly comprised of physicians (including physicians-in-training) and nurses and the procedures are mostly performed or overseen in the departments of Pathology and Hematology. Respondents who perform TPE on pediatric patients define a pediatric patient based on age (78.2%) or weight (22.8%). The most common age used by respondents to define a pediatric patient was 18 years (59.4%). Weight-based definitions were varied and ranged from 5 to 50 kg. The choice of replacement fluid to use for TPE procedures was made by the Apheresis Medicine physician (59.4%), jointly by the Apheresis Medicine physician and requesting provider (29.3%), the requesting provider (8.5%), and other (2.8%).

Routine Practice at a Responding Center

To understand routine practice at a center, respondents were asked how they manage a patient who presents for a series of 5 TPE approximately every other day. The most common procedural parameters were a 1.0 plasma volume (63.2%) and use of anticoagulant citrate dextrose A for extracorporeal anticoagulation (97.1%).[12] The choice of replacement fluid was albumin, albumin and normal saline, plasma, albumin and plasma, and other by 47.7%, 12.2%, 3.7%, 2.8%, and 33.6% of respondents respectively. Comments were provided by all 36 respondents who selected other for replacement fluid; no comments were entered by respondents who selected a specific replacement fluid. The comments from 27 of the 36 respondents included some form of

the word "depend". Interpreting the 36 text comments, the choice of replacement fluid would depend on the diagnosis (80.6%), laboratory values (11.1%), and both diagnosis and laboratory values (8.3%).

TPE with a Potential Bleeding Risk

When a patient presents for a series of 5 approximately every other day TPE with an associated potential bleeding risk, wide variation in the selection of replacement fluid was observed (Table 2). Similar to the case scenario used to decipher the respondent's routine practice, 27 respondents entered comments, many noting the replacement fluid choice would depend on the condition treated and other issues such as results of laboratory studies and the specific patient clinical scenario. No respondent selected the same replacement fluids for all of the situations presented. However, 2 (2.1%) respondents only selected replacement fluids containing some or all plasma and 3 (3.2%) respondents only selected replacement fluids containing some or all plasma or cryoprecipitate or would chose to delay the procedure for the scenarios they provided a response.

Invasive Procedures

The replacement fluid selection was associated with the timing of minor invasive procedures and major surgery as shown in Tables 3 and 4. There was a trend after either a minor or major procedure to switch from a replacement fluid containing coagulation factors to albumin with or

without normal saline. Some respondents entered free text comments to describe their practice, which indicated the choice of replacement fluid would depend on screening coagulation laboratory test results, such as the prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen, or liver function test results.

Kidney Biopsy

The replacement fluid choice after kidney biopsy is shown in Supplement 1. The majority of respondents (65.5%) indicated their routine practice for use of plasma in the replacement fluid after kidney biopsy depended on the number of days, hours, or procedure numbers since the biopsy, while 19.0% only use plasma when there is bleeding. When plasma is used up to specific days post biopsy, 27 respondents indicated the number of days post biopsy that plasma would be used is as follows (n, %): 1 day (5, 18.5%), 2 days (9, 33.3%), 3 days (4, 14.8%), 3-5 days (1, 3.7%), 5 days (3, 11.1%), 14 days (1, 3.7%),15 days (1, 3.7%) and other (3, 11.1%). When plasma is used up to specific hours post biopsy, 4 respondents provided a comment: 1 indicated plasma would be used up to 24-48 hours, 1 indicated up to 48 hours, and 2 indicated up to 72 hours. When plasma is used up to a specific number of procedures, 8 respondents provided a comment: 2 indicated up to 3 TPE, 1 indicated up to 7 TPE, and 5 provided a comment that did not give a specific procedure number. Additionally, a few respondents stated the amount of plasma they would use, which ranged from 30% to 100% of plasma replacement volume, and 1

respondent indicated a specific volume of 4 units of plasma would be used as part of the replacement fluid.

Antiplatelet and Anticoagulant Therapy

Antiplatelet therapy use is common among the general population and may be used by patients undergoing TPE. The replacement fluid selection in the setting of an inherited or acquired platelet disorder is described in Table 2.The survey showed 8 out of 81 (9.9%) respondents would stop ongoing aspirin therapy, an inhibitor of prostaglandin cyclooxygenase-1, during a series of TPE, while 13 out of 80 (16.3%) respondents would stop clopidogrel, an inhibitor of the $P2Y_{12}$ class of the adenosine diphosphate receptors on platelets. When the patient is on both aspirin and clopidogrel (n=79 respondents), 9 (11.4%) respondents indicated both medications would be stopped, while 3 (3.9%) would stop aspirin only, and 7 (8.9%) would stop clopidogrel only.

Anticoagulants are frequently encountered in patients undergoing TPE. See Table 2 for TPE replacement fluid choices in the settings of unfractionated heparin, low molecular weight heparin, and warfarin. Since 2010 there have been a number of new anticoagulants approved by the FDA. Respondents indicated they have performed TPE on patients receiving these therapies: 20 out of 76 (26.3%) respondents for oral direct factor Xa inhibitor (e.g. rivaroxaban, apixaban, edoxaban, betrixaban); 16 out of 73 (21.9%) respondents for oral direct thrombin

inhibitor (e.g. dabigatran); and 20 out of 72 (27.8%) respondents for intravenous direct thrombin inhibitor (e.g. argatroban, bivalirudin, lepirudin). Respondents reported encountering patients on these medications in the context of left ventricular assist device (LVAD), extracorporeal membrane oxygenation (ECMO), heparin induced thrombocytopenia (HIT), trauma, transplant rejection, Blalock-Taussig shunt, and antiphospholipid antibody syndrome (APAS). Many respondents entered comments regarding management during TPE in patients on anti-Xa or direct thrombin inhibitors. Some respondents stated a concern for thrombosis in patients on these medications outweighed concerns of bleeding so that they would not use a reversal agent or hold the procedure for 24 hours after the last dose. Replacement fluid selection varied from no change in practice to including some or all plasma. Some respondents indicated they would hold the medications while others would not.

DISCUSSION

The selection of replacement fluid is a critical management decision for patients undergoing TPE using centrifugation based apheresis instruments. Based on available evidence, the ASFA guidelines for therapeutic apheresis suggest replacement fluids, but additional situational conditions may influence this choice.[1] A survey was conducted to assess the current practice and the variation among apheresis providers.

To quote the respondents, the choice of replacement fluid "depends" on several factors including the diagnosis treated, laboratory studies, and other conditions present. Respondents were asked to describe how they would manage a case patient that is undergoing a series of 5 TPE approximately every other day. Our intent was to not bias the choice of replacement fluid by giving a specific indication for the TPE; however, this likely resulted in respondents considering very different patient scenarios. When more clarity was given regarding the patient, i.e. that the patient had no history of a bleeding or clotting disorders, 94.7% of respondents would use albumin with or without normal saline. The remaining 5 respondents would use some or all plasma or delay the procedure for all of the clinical situations for which they provided a response. In retrospect it may have been ideal to include two specific cases where the replacement fluid choice suggested by the ASFA guidelines is suggested to be albumin (e.g. myasthenia gravis) and plasma (e.g. thrombotic thrombocytopenic purpura).[1] The ASFA recommendations of the Choosing Wisely initiative of the ABIM Foundation recommends "Do not routinely use plasma as replacement fluid for therapeutic plasma exchange unless there is a clear indication to replete a plasma component".[13]

Cryoprecipitate was used by a small number of respondents. The most frequent use was for fibrinogen replacement in patients with hypofibrinogenemia due to recent TPE. Small numbers of respondents (1 to 4) would use cryoprecipitate in other situations. In patients with a coagulation factor deficiency, cryoprecipitate would also be valuable for factor VIII, von

Willebrand factor, and factor XIII replacement, though it is not clear that this was the motivation behind the selection.

Use of coagulation factor deficient replacement fluids for TPE proximate to an invasive procedure may increase the risk for bleeding due to decrease in coagulation factors. Thus some apheresis providers may use plasma or cryoprecipitate to potentially mitigate this risk. This practice varies among institutions. For example following kidney biopsy, 5 of 84 (6.0%) respondents indicate they would use plasma for up to 5 or more days after the biopsy, while 13 of 84 (15.5%) of respondents do not routinely use plasma. With other minor invasive procedures, 25.3% would use albumin with or without normal saline even if the invasive procedure is performed in the morning of the TPE. When the invasive procedure is major surgery, more respondents would include some coagulation factor replacement, but 8.9% would perform the TPE with albumin with or without normal saline 1 day after a major surgery. When considering minor versus major procedures, one limitation of our study was the different time periods queried between the two scenarios. Additionally, the data on the use of plasma after a kidney biopsy may have been clearer to interpret if we had presented the case patient at multiple days after the biopsy and inquired what replacement fluid they would use. However, this would have added several more questions to the end of an already long survey.

There is very limited data published on the anticoagulant management in patients undergoing TPE.[14-22] As illustrated in Table 2, replacement fluid containing some or all plasma or cryoprecipitate would be used by 34.5% to 67.1% of respondents with the common anticoagulants unfractionated heparin, low molecular weight heparin, and warfarin. Several respondents would use plasma as the replacement fluid (solely 6.9% or with albumin 35.6%) in a patient who is therapeutic (INR 2.5) on warfarin, a vitamin K antagonist (VKA). Plasma transfusion can be used as a reversal agent for VKAs.[23-25] The use of all plasma would be expected to result in significant reversal of the patient's anticoagulation. Although approximately a quarter of respondents have performed TPE on patients on oral (e.g. dabigatran) or intravenous (e.g. lepirudin, argatroban, bivalidrudin) direct thrombin inhibitor or an oral direct anti-Xa inhibitor (e.g. rivaroxaban, apixaban, edoxaban, betrixaban), the impact of TPE on patients on anticoagulants is not entirely clear. The procedure may remove the anticoagulant medications as well as the specific anticoagulant targets. There is limited information on medication removal with TPE, but several factors influence this including protein binding, volume of distribution, dose, timing since last dose, volume of TPE, length of the TPE procedure, successive TPE procedures, and potentially the replacement fluid.[8-11] Further investigation is needed to establish the best practice with regard to anticoagulants and antiplatelet therapy in the setting of TPE.

There are several other limitations to this study. Due to the length of the survey, there was a decrease in the number of respondents throughout the course of the survey. It is unknown if the practices of the respondents who did not complete the survey would be different from other respondents. Due to the small numbers, data from respondents using membrane filtration were excluded from analyses. The majority of respondents were from the United States of America. The number of TPE procedures performed by the respondents is not known as we inquired about total number of apheresis procedures rather than the specific number of TPE. An apheresis provider's background, training, and experiences likely contribute to the choice of replacement fluid; however, the survey did not capture adequate information to analyze these factors.

CONCLUSION

The selection of the replacement fluid for TPE depends on many variables, including the diagnosis for performing the procedure, concurrent clinical situations, and laboratory studies. There is little evidence to guide the adjustment of the replacement fluid content, which likely contributed to the wide variation in practices seen in this survey. Future research study is needed to establish best practice.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the respondents who participated in our survey, the members of the ASFA Clinical Applications Committee who provided feedback during

development and beta testing of the survey, and the ASFA head office staff for assistance with distributing the survey and administrative support throughout the project.

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Table 1 Demographic information of survey respondents and apheresis programs.

Question (Number of Respondents)*	Number (%)**
Position at institution** (n=107)†	
Physician (including physician in training-resident/fellow)	67 (62.6)
Director of apheresis service	25 (37.3)***
Member of physician teaching staff	19 (28.4)
Residency/Fellowship program director	4 (5.0)
Other	6 (9.0)
Nurse	27 (25.2)
Director of apheresis service	2 (7.4)
Member of non-physician teaching staff	1 (3.7)
Other	2 (7.4)
Director of Apheresis (did not indicate physician or nurse)	10 (9.3)
Member of non-physician teaching staff	1 (10.0)
Other	3 (2.8)
Type of institution (n=107)	
Academic medical center	74 (69.2)
Blood collection facility	13 (12.2)
Non-academic medical center	6 (5.6)
Contract provider of apheresis services	5 (4.7)
Outpatient facility that performs apheresis	1 (0.9)
Other	8 (7.5)
Number of beds for medical centers (n=87)	
>500	56 (64.4)
100-500	28 (32.2)

<100	3 (3.4)
Apheresis procedures per year (n=105)	
>700	39 (37.1)
500-700	17 (16.2)
100-500	40 (38.1)
<100	9 (8.6)
Departments which perform or oversee TPE** (n=106)[††]	
Pathology	41 (38.7)
Hematology	33 (31.1)
Nephrology	32 (30.2)
Blood Collection Facility	20 (18.9)
Neurology	15 (14.2)
Rheumatology	7 (6.6)
Medicine	6 (5.7)
Performed by outside source but overseen by pathology	7 (6.6)
Performed by outside source but overseen by neurology	3 (2.8)
Performed by outside source but overseen by hematology	2 (1.9)
Performed by outside source but overseen by nephrology	2 (1.9)
Performed by outside source but overseen by rheumatology	1 (0.9)
Performed by outside source but overseen by medicine	1 (0.9)
Other	22 (20.8)
Physician medical specialty (n=95)	
Pathology	42 (44.2)
Hematology	14 (14.7)
Nephrology	5 (5.3)
Pediatrics	3 (3.2)
Medicine	2 (2.1)

Other	10 (10.5)
I am not a physician	19 (20.0)
Perform TPE procedures on children (n=107)	
Yes, adults and children	69 (64.5)
No	32 (29.9)
Yes, children only	6 (5.6)

*For some questions respondents were requested to check all that apply and the total number of responses is greater than the number of respondents. **For questions that permitted more than 1 response, the percent is based on the number of respondents to the question. †Total number of responses=167 ††Total number of responses=173

Table 2. Replacement fluid selection for therapeutic plasma exchange (TPE) in patients with an associated clinical situation and scheduled to receive 5 TPE approximately every other day.

	Replacement Fluid					
Associated Situation	Albumin n* (%)	Albumin and Normal Saline n (%)	Albumin and Plasma n (%)	Albumin and CRYO* n (%)	Plasma n (%)	Delay Procedure n (%)
No history of a bleeding or clotting disorder (n=94)	71 (75.5)	18 (19.1)	4 (4.3)	0 (0.0)	1 (1.1)	0 (0.0)
Active bleeding (n=94)	0 (0.0)	1 (1.1)	35 (37.2)	0 (0.0)	41 (43.6)	17 (18.1)
Bleeding disorder due to coagulation factor deficiency (e.g. Hemophilia A, B or C; von Willebrand disease) (n=90)	9 (10.0)	0 (0.0)	35 (38.9)	4 (4.4)	35 (38.9)	7 (7.8)

Platelet disorder (inherited or acquired) (n=91)	39 (42.9)	11 (12.1)	24 (26.4)	2 (2.2)	12 (13.2)	3 (3.3)
Hypofibrinogenemia (<100 mg/dL) due to recent TPE (n=91)	8 (8.8)	0 (0.0)	45 (49.5)	13 (14.3)	20 (22.0)	5 (5.5)
Therapeutic on continuous IV unfractionated heparin (n=89)	31 (34.8)	9 (10.1)	28 (31.5)	2 (2.3)	13 (14.6)	6 (6.7)
Supratherapeutic on continuous IV unfractionated heparin (n=88)	19 (21.6)	7 (8.0)	24 (27.3)	2 (2.3)	22 (25.0)	14 (15.9)
Therapeutic on low molecular weight heparin (e.g. enoxaparin) (n=87)	45 (51.7)	12 (13.8)	22 (25.3)	3 (3.5)	5 (5.8)	0 (0.0)
Supratherapeutic on low molecular weight heparin (e.g. enoxaparin) (n=85)	28 (32.9)	7 (8.2)	24 (28.2)	2 (2.4)	15 (17.7)	9 (10.6)
Therapeutic (INR* 2.5) on warfarin (n=87)	39 (44.8)	9 (10.3)	31 (35.6)	1 (1.2)	6 (6.9)	1 (1.2)
Supratherapeutic (INR 4.0) on warfarin (n=85)	13 (15.3)	4 (4.7)	39 (45.9)	2 (2.4)	16 (18.8)	11 (12.9)

Liver disease with a mildly elevated INR (1.5-2.0) (n=87)	29 (33.3)	4 (4.6)	43 (49.4)	1 (1.2)	10 (11.5)	0 (0.0)

*n=number of respondents, CRYO=cryoprecipitate, INR=international normalized ratio

Table 3. Timing of minor invasive procedure and replacement fluid used for therapeutic plasma exchange (TPE).

	In the morning of TPE* n* (%) (n=91)	1 day before TPE n* (%) (n=91)	2 days before TPE n* (%) (n=91)	2 days before TPE with bleeding n* (%) (n=90)
Albumin	16 (17.6)	34 (37.4)	52 (57.1)	1 (1.1)
Albumin and NS*	7 (7.7)	11 (12.1)	17 (18.7)	3 (3.3)
Albumin and plasma	41 (45.0)	38 (41.8)	16 (17.6)	49 (54.4)
Albumin and CRYO*	1 (1.1)	0 (0)	1 (1.1)	0 (0)
Plasma	10 (11.0)	5 (5.5)	5 (5.5)	26 (28.9)
Delay procedure	16 (17.6)	3 (3.3)	0 (0)	11 (12.2)

* TPE=therapeutic plasma exchange, n=number of respondents, NS=normal saline, CRYO=cryoprecipitate

Table 4. Timing of major surgery and replacement fluid used for therapeutic plasma exchange (TPE).

	2 days after TPE* n* (%) (n=90)	1 day after TPE n* (%) (n=91)	1 day before TPE n* (%) (n=90)	3 days before TPE n* (%) (n=90)	1 week before TPE n* (%) (n=90)
Albumin	35 (38.9)	10 (11.0)	5 (5.6)	24 (26.7)	53 (58.9)
Albumin and NS*	11 (12.2)	7 (7.7)	3 (3.3)	12 (13.3)	16 (17.8)
Albumin and plasma	31 (34.4)	44 (48.4)	42 (46.7)	36 (40.0)	17 (18.9)
Albumin and CRYO*	1 (1.1)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Plasma	11 (12.2)	24 (26.4)	31 (34.4)	16 (17.8)	2 (2.2)
Delay procedure	1 (1.1)	5 (5.5)	8 (8.9)	2 (2.2)	2 (2.2)

* TPE=therapeutic plasma exchange, n=number of respondents, NS=normal saline, CRYO=cryoprecipitate

Supplement 1: Kidney biopsy and use of plasma in replacement fluid for therapeutic plasma exchange (TPE).

	Number of Responses n* (%) (n=84)
Do no use plasma routinely after biopsy	13 (15.5%)
Use plasma only if signs of bleeding	16 (19.0%)
Use plasma up to specific post-biopsy day	43 (51.2%)
Use plasma up to specific post-biopsy hours	4 (4.8%)
Use plasma up to the specific procedure number	8 (9.5%)

*n=number of respondents. Four additional respondents provided a comment only and are not included here.