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Risk factors for allergic reaction at initial therapeutic plasma exchange in a single-center study: beware of high rates of severe allergic reaction

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Abstract

Background: Therapeutic plasma exchange (TPE) is an important treatment modality for various diseases, but its use can be restricted by allergic reactions (AR). The aim of our study was to elucidate the frequency of and risk factors for AR at initial TPE using fresh frozen plasma (FFP).

Methods: Presences of AR were extracted from the medical records of consecutive patients receiving TPE from 2002 to 2012. The following data at initial TPE were retrieved: age, gender, history of allergy, steroid use, timing of steroid use, mean steroid dose, immunosuppressant use, indication for TPE, and laboratory data.

Results: Eighty-eight patients (median age 57 years) underwent TPE, and 28% had an episode of AR. Younger age (odds ratio (OR), 1.04 (95% CI, 1.01–1.08)) and indications other than hepatic insufficiency (OR, 17.8 (95% CI, 1.95–429.4)) were associated with higher incidence of AR.

Conclusions: Close observation for AR may be warranted at initial TPE for these conditions.

Keywords: Age, Hypersensitivity, Liver failure, Plasma exchange, Risk factors

Background

Therapeutic plasma exchange (TPE) is an important treatment option for various diseases, including thrombotic microangiopathy, antineutrophil cytoplasmic antibody-associated vasculitis, rheumatic diseases (such as systemic lupus erythematosus and scleroderma), and hepatic failure. Therapeutic plasma exchange is essential in ABO-incompatible kidney transplantation, which has gradually become a common therapy in living-related kidney transplantation in Japan [1]. In most instances, the therapeutic goal of TPE is the removal of harmful proteins or antibodies. The use of albumin may be favored as a replacement fluid when possible because of its low cost and low frequency of adverse events. However, replacement using fresh frozen plasma (FFP) is the most physiologic approach as it replenishes all normal plasma constituents.

Though TPE is not without adverse events. Bramlage et al. [2] reported that up to 25.6% of TPE procedures were associated with adverse events including catheter-related problems, infections, and allergic reactions (AR). One review [3] noted that AR due to TPE occurred in 3–12% of cases and were more frequent after TPE using FFP than using serum albumin. However, the predictors of AR after TPE using FFP are not well known. The aim of this study was to determine the frequency of AR after initial TPE using FFP and to document possible risk factors involved in the incidence of AR in TPE.

Methods

Study population and definition of allergic reaction

Medical records of consecutive patients who received TPE using FFP at St. Marianna University School of Medicine hospital from March 2002 to February 2012

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were retrospectively reviewed. The following data at the time of initial TPE were retrieved: age, gender, history of allergy, steroid use, timing of steroid use, mean steroid dose (as equivalent of prednisolone), immunosuppressant use, indication for TPE, and laboratory data (white blood cell count, hemoglobin, platelet count, creatinine, albumin, and C-reactive protein).

Episodes of AR were extracted from the medical records of clinically diagnosed AR by the attending physician such as rashes, pruritus, transient decrease of blood pressure, tachycardia, and respiratory symptoms (i.e., sudden onset of dyspnea, wheezing). Nonspecific symptoms such as nausea and vomiting were interpreted as AR when other symptoms coexisted or treated as AR. The severity of AR was classified as mild, moderate, or severe by the corresponding medical action taken to treat AR in reference to previous literature [2]. Briefly, mild AR included reactions of transient nature with little or no clinical significance that did not cause any procedural delays. Moderate AR included complications that required medical intervention but were not life-threatening. Severe AR included life-threatening events that required termination of the procedure.

The study protocol was reviewed by the Ethics Committee of St. Marianna University School of Medicine (the committee's reference number: No. 2452, 12 June 2013). Because of the anonymous and retrospective nature of the study, the Ethics Committee waived the need for informed consent. The study was conducted in accordance with the ethical standards of the Helsinki Declaration as revised in Fortaleza, 2013.

Therapeutic plasma exchange procedure

Therapeutic plasma exchange was carried out using an OctoNova1 system (Diamed, Cologne, Germany) with an OP05W (L) 1-filter (Asahi, Tokyo, Japan). The replacement fluid was FFP. The blood flow rate ranged from 50 to 200 ml/min, and the plasma removal and replacement rates ranged from 25 to 35 ml/min. The exchanged plasma volume was 35 to 40 ml/kg body weight per TPE session. Nafamostat mesilate (30 mg/h) was administered by infusion as an anticoagulant.

Statistical analysis

Univariate logistic regression analysis was conducted to identify risk factors for AR at initial TPE. Variables with $P < 0.2$ were identified by stepwise backward elimination and further investigated as independent risk factors using multivariable logistic regression. Data are presented as median and interquartile range (25th to 75th percentile) or percentage. All analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC, USA). All tests are presented with two-sided P values, and $P < 0.05$ was considered significant.

Results

Patient characteristics

Demographics and clinical characteristics are described in Table 1. During the study period, a total of 88 patients (52 men) received TPE. The median age was 57 years (interquartile range, 36–70 years). The distribution of patient age seemed to be common in 20s and from 50s to 70s (Fig. 1). Indications for TPE were ABO-incompatible kidney transplantation ($n = 13$, 15%), hepatic failure ($n = 18$, 20%), and other diseases ($n = 57$, 65%). Other diseases for indication included rheumatic disease, thrombotic microangiopathy, myasthenia gravis crisis, hyperviscosity syndrome, ANCA-associated vasculitis/nephritis, anti-glomerular basement membrane nephritis, interstitial pneumonia, crescentic glomerulonephritis due to purpura nephritis, systemic lupus erythematosus, alveolar hemorrhage, and cryoglobulinemia. Twenty-six patients (30%) had past history of allergy. Seventy-two patients

Table 1 Patient characteristics and results of univariate logistic regression analysis of association between AR

	Whole cohort ($n = 88$)	P value
Age (years)	57 (36–70)	0.01**
Gender, men	52 (59%)	0.71
Body weight (kg)	54 (48–63)	0.12*
Use of steroid before TPE	72 (77%)	
Start of steroid use	No steroid on day of TPE	Reference
The day of TPE	5 (6%)	0.15*
1–7 days before TPE	24 (27%)	0.29
>7 days before TPE	39 (44%)	0.40
Prednisolone-equivalent dose on day of TPE (mg/day)	20 (0.63–60)	0.63
Use of immunosuppressant before TPE	26 (28%)	0.04**
History of allergy	26 (30%)	0.47
History of blood transfusion	27 (31%)	0.07*
Indication for TPE		
ABO-incompatible kidney transplantation	13 (15%)	Reference
Hepatic failure	18 (20%)	0.01**
Others	57 (65%)	0.11*
Amount of FFP (units/kg)	0.69 (0.60–0.75)	0.14*
White blood cell count (/μl)	8850 (5100–13,100)	0.04**
Hemoglobin (g/dl)	8.8 (7.0–10.7)	0.80
Platelet count (10^3/μl)	108 (54.5–217.8)	0.59
Serum creatinine (mg/dl)	2.77 (0.69–6.25)	0.02**
Serum albumin (g/dl)	3.0 (2.6–3.5)	0.33
Serum C-reactive protein (mg/dl)	1.12 (0.16–4.52)	0.39

Data presented as median (interquartile range) or n (%)
FFP fresh frozen plasma, *TPE* therapeutic plasma exchange
*$P < 0.2$, ** < 0.05 the correlation in univariate logistic regression analysis. Categories that were associated in $P < 0.2$ were adapted to multivariate analysis

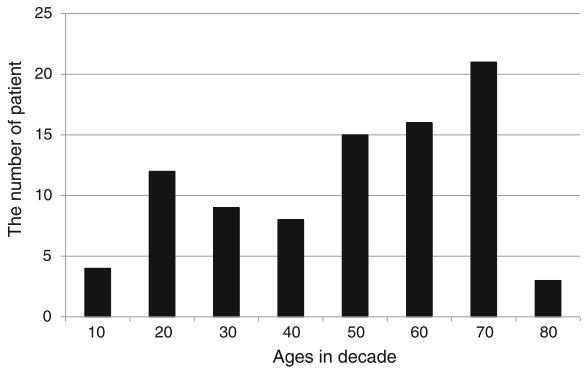

Fig. 1 Graph showing the distribution of patient age. Ages are represented in decades

(77%) used steroids prior to initial TPE at a median prednisolone-equivalent dose of 20 mg (interquartile range, 0.63–60 mg), and 26 patients (28%) used immunosuppressants.

Incidence and predicting factors of allergic reaction

Twenty-five out of 88 patients (28%) experienced AR. The severity of AR was evaluated as mild in 8 patients (32% of whole AR patients), moderate in 11 (44%), and severe in 6 (24%; Table 2).

The factors related with AR by univariate logistic regression analysis ($P < 0.2$) were age, body weight, start of steroid use (from the day of TPE), use of immunosuppressant, history of blood transfusion, indication for TPE (hepatic failure, others), amount of FFP used, white blood cell count, and serum creatinine. Multivariable logistic regression analysis revealed that the risk of AR in hepatic failure was significantly low and that younger age was independently associated with a higher occurrence of AR (Table 3).

Following TPE procedures after AR in initial TPE

The incidence and context of second TPE within those with AR is described in Table 4. Within the 25 presenting with AR, 11 were withdrawn from the following TPE.

Table 2 Occurrence and severity of allergic reaction to initial therapeutic plasma exchange

	Number	% of total cohort ($n = 88$)	% of patients with allergic reaction ($n = 25$)
Allergic reaction	25	28	
Severity of allergic reaction			
Mild	8	9.1	32
Moderate	11	12.5	44
Severe	6	6.8	24

Table 3 Results of multivariable logistic regression analysis for allergic reaction to initial TPE

		Odds ratio	95% CI	*P* value
Age		0.96	0.93–0.99	0.01
Indication for TPE	ABO-incompatible kidney transplantation	Reference		
	Hepatic failure	0.06	0.002–0.51	0.03
	Others	0.73	0.17–3.10	0.66

CI confidence interval, *TPE* therapeutic plasma exchange

Discussion

In this single-center study, 28% of 88 patients experienced AR after initial TPE using FFP as a replacement fluid. We focused on AR at initial TPE because this is likely to have the greatest impact on the decision to continue or discontinue TPE and select subsequent treatment. As far as we know, there are no studies on AR that have focused on initial TPE using FFP. Apheresis using albumin has been reported to present rash or pruritus in 0.2 to 0.3% of cases [4]. The incidence of AR observed in this study was unexpectedly high compared to others that reported rates of 3~12% [3] which included TPE with albumin-saline exchange. The high incidence of AR compared to other studies may be caused because our study was limited to events on the initial session and those with AR on initial PE tend to withdraw the following sessions which will raise the rates of AR per session. In such perspective, the rate of AR cannot simply be compared with other studies including all PE sessions. The AR seen in this study may reflect reactions not only to FFP but also to other components of TPE, such as anticoagulation drugs [5] and materials used in the extracorporeal circuit [6]. Our analysis cannot differentiate the cause of AR. It is noteworthy, however, that FFP transfusion causes AR in less than 3% of patients [7], suggesting that FFP may not be the primary cause. Although severe AR were less common than mild or moderate AR, 24% of all AR were graded as severe, which cannot be disregarded.

Younger age and disorders other than hepatic insufficiency as indications for TPE were suggestive of higher risk for AR. The reason for the association between younger age and AR is not clear; however, it may reflect the fact that the response against foreign antigens decrease along

Table 4 Incidence and context of second TPE within those with AR at initial TPE

	FFP	Albumin	Withdrawn	Total
Mild	5	0	3	8
Moderate	8	0	3	11
Severe	1	0	5	6
Total	14	0	11	25

with aging, termed immunosenescence [8, 9]. In fact, a single-center study showed that acute allergic reactions after blood transfusion in children were more frequent than in adults [10]. Warm et al. reported that the association between allergic sensitization and rhinitis was strongest among the youngest age group and the prevalence of allergic sensitization among patients with asthma decreased by increasing age of asthma onset [11]. As shown in the figure, although the median age of our cohort was 57 years old, many elderly were also involved which perhaps may be one of the reasons why we experienced quite a few incidents of AR.

Patients with acute and chronic liver dysfunction show a similar degree of cellular immune depression as patients with severe sepsis, with features of systemic inflammation and progression to functional immunoparesis [12, 13]. Since immediate-type allergy is induced by network of not only the humoral immunity but also the cellular immunity [14], these features of immunoparesis might explain the low frequency of AR in patients who received TPE due to hepatic insufficiency.

This result suggest that close observation would be required when conducting TPE using FFP especially in the younger patients and those with conditions other than hepatic insufficiency. Prevention of AR is another important point that needs to be considered. Our result did not show association of steroid use before TPE and allergic reactions. The use of steroid for the prevention of AR is somewhat controversial. A systematic review concluded that data supporting the use of steroids as premedication in patients with a history of AR are lacking [15]. On the other hand, guidelines for pharmacological prophylaxis for contrast media-related AR recommend the use of steroids for more than 12 h before a procedure [16]. This guideline was based on the improved prophylactic effect obtained by steroids administered at least 6 h in advance [17], as well as the observation that the reduction of histamine in sedimented leukocytes reaches a maximum at 8 h after steroid administration [16]. Although our result did not show significant prophylactic effect with steroid use, further investigations are needed to verify whether premedication with steroids might be beneficial when administered more than 1 day prior to TPE. Whether immunosuppressants are effective on prevention of AR may need more data including type of drug, serum concentration, and period of therapy. Concerning the use of antihistamine drug, we could not investigate the actual conditions in detail. The lesson learned from our study was that AR in initial TPE using FFP is quite frequent. As incidence of AR is reported to be lower with albumin exchange [3, 4], those indicated should be recommended for albumin exchange. Furthermore, those with non-hepatic indication and young are at higher risk of AR when initiating FFP replacement, even when on steroids or immunosuppressants, rendering further attention for AR in this population.

Compared to previous reports [2, 4] and reviews [3], we included patients with a wider variety of indications, including hepatic failure, desensitization before ABO-incompatible kidney transplantation, various rheumatic diseases (or autoimmune diseases including systemic lupus erythematosus, vasculitis), and thrombotic thrombocytopenic purpura. We categorized these diseases into three groups for comparison analysis according to major mechanism and/or purpose. The purpose of TPE in hepatic failure is the removal of toxic metabolites and the replacement of mainly coagulant factors; desensitization before ABO-incompatible kidney transplantation is the removal of antibodies not harmful to autoantigen and the replacement of mainly coagulant factors; and others, primarily rheumatic diseases, are the removal of antibodies harmful to autoantigen and replenishing plasma proteins.

The limitations of this study are its small sample size and retrospective, single-center design. The wide variety of disorders diverse in pathophysiology and each small in number were allocated into three groups for analysis. The indication for FFP use was hepatic dysfunction and TMA which is acknowledged in many facilities as relative indications. However, indication for other diseases were left to the judgment of the attending physician which may potentiate selection bias. The definition of AR was challenging which should be stated as another limitation in this study. Precise differentiation between other pathophysiological disorders are difficult especially when analyzed retrospectively, and therefore, many adverse events may be over-diagnosed as allergic reactions. In addition, our analysis cannot differentiate the cause of AR, i.e., cannot identify whether AR was due to FFP or to other allergens present in TPE (such as anticoagulants) or the extracorporeal circuit. Further research should also investigate the role of the complex pathophysiology of the indicative diseases, which were more varied in this population compared to previous studies.

Conclusions

We found that AR at initial TPE using FFP occurred frequently (28% of all cases). Moreover, greater than 24% of AR were classified as severe, requiring termination of TPE and treatment. Younger patients and those with indications other than hepatic failure were at relatively higher risk for AR and warrant close observation during initial TPE.

Abbreviations

AR: Allergic reactions; FFP: Fresh frozen plasma; OR: Odds ratio; TPE: Therapeutic plasma exchange

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Availability of data and materials
Data are available on request to the authors.

Authors' contributions
MH, HK, MO, KT, TS, SS, RK, and YS contributed to the conception and design of the research. MH, HK, MO, KT, TS, SS, and RK analyzed the data. MH, HK, MO, KT, TS, SS, RK, KK, and YS interpreted the results of the experiments. MH and HK prepared the figure and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable

Ethics approval and consent to participate
The study protocol was reviewed by the Ethics Committee of St. Marianna University School of Medicine (the committee's reference number: No. 2452, 12 June 2013). Because of the anonymous and retrospective nature of the study, the Ethics Committee waived the need for informed consent. The study was conducted in accordance with the ethical standards of the Helsinki Declaration as revised in Fortaleza, 2013.

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