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Removal Dynamics of Immunoglobulin and Fibrinogen by Conventional Plasma Exchange, Selective Plasma Exchange, and a Combination of the Two

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Abstract: While plasma exchange (PE) can eliminate plasma proteins, including all immunoglobulin (Ig) and coagulation factors, selective plasma exchange (SePE) can retain fibrinogen (Fbg). Here, we investigated the removal dynamics of Ig and Fbg in 53 patients with immunological disorders by PE, SePE, and a combination of the two. When the mean processed plasma volume (PPV) was 0.9 plasma volume (PV), the mean percent reductions of Ig and Fbg by PE were both approximately 62%–65%. When the mean PPV was 1.1 PV, the mean percent reductions by SePE were 53.1% for IgG, 30.1% for IgA, 3.6% for IgM, and 19.0% for Fbg, respectively. In the three plasmapheresis sessions performed on alternate days, we classified treatments into three categories: PE group (PE–PE–PE, $N=2$), SePE group (SePE–SePE–SePE, $N=14$), and PE/SePE group (PE–SePE–SePE, $N=4$). The mean percent reductions of IgG, IgA, IgM, and Fbg were 82.0%, 80.4%, 87.3%, and 80.9%, respectively, for the PE group; 76.4%, 57.7%, 43.3%, and 35.9%, respectively, for the PE/SePE group; and 75.4%, 50.6%, 3.2%, and 29.3%, respectively, for the SePE group. Plasmapheresis modalities can be combined according to clinical conditions, for instance, to achieve both the unspecific removal of pathogens by PE and retention of coagulation factors, such as Fbg, by SePE. **Key Words:** Combination therapy, Fibrinogen, Immunoglobulin, Plasma exchange, Selective plasma exchange.

Plasmapheresis is often performed as an optional treatment for autoimmune diseases, most commonly targeting immunoglobulin G (IgG), including autoantibodies (1). In most instances, the therapeutic goal of plasmapheresis is depletion of harmful antibodies (2). The modality of plasmapheresis includes simple plasma exchange using a conventional plasma membrane separator (PE), simple plasma exchange using a selective plasma separator (SePE), double filtration plasmapheresis (DFPP), and plasma immunoadsorption (IA). All plasmapheresis modalities have both advantages and disadvantages. For instance, PE, SePE, and DFPP can eliminate IgG regardless of the IgG subclass (3,4), but in IA, tryptophan desorption of IgG2 and IgG4 occurs when the processed plasma volume (PPV) is >1 L (5). Only IA can remove pathogenic substances by selective adsorption, while requiring no plasma replacement, although replacement of fluids, such as with albumin (Alb) solution, is necessary during PE, SePE, and DFPP (6). SePE can retain coagulation factors, such as fibrinogen (Fbg) (7,8), while PE, DFPP, and IA with tryptophan remarkably reduce Fbg concentrations (8–10).

Evacure EC-4A10 (EC-4A) (Kawasumi Laboratories, Inc., Tokyo, Japan) is a selective membrane plasma separator with a relatively smaller pore size (0.03 μm) of 1/10, compared with conventional plasma separators, such as Plasmaflo OP-05 W (OP-05) (Asahi Kasei Medical Co., Ltd., Tokyo, Japan). We previously reported that the sieving coefficients (SCs) of IgG and Fib using EC-4A were 0.5 and 0, respectively (7). Therefore, SePE can retain Fbg, but substances with molecular weights greater than

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that of Fbg, such as IgM, cannot be eliminated by SePE. However, there is little information regarding the removal characteristics of IgM and IgA by SePE in the literature.

Repeated plasmapheresis therapy is often necessary for the treatment of immunological disorders. At our center, three plasmapheresis sessions on alternate days in the same week are often performed because both the total amount in the body and the plasma concentration of IgG are decreased more efficiently on alternate days than on a daily basis when three plasmapheresis sessions are performed in the same week (1). Moreover, PE and SePE can be combined, resulting in both unspecific removal of pathogens by PE and retention of Fbg by SePE. There have been some reports on combination therapy with two plasmapheresis modalities, such as DFPP and PE (11), PE and IA (12), and DFPP and IA (13). However, no previous report has described combination therapy with PE and SePE.

Here, we investigated the removal dynamics of Ig and Fbg in 53 patients with immunological disorders by PE, SePE, and a combination of the two. This is the first report to investigate the removal dynamics of Ig and Fbg by PE and SePE combination therapy.

PATIENTS AND METHODS

Patients

In this retrospective, observational study, 53 patients with immunological disorders underwent plasmapheresis between October 2011 and June 2015 at the Medical Hospital of Tokyo Medical and Dental University. For this study, we reviewed previous medical charts and data related to 382 plasmapheresis sessions and evaluated the PPVs and concentrations of IgG, IgA, IgM, and Fbg before and immediately after plasmapheresis therapies in 53 patients. The causes of immunological disorders were chronic inflammatory demyelinating neuropathy, multiple sclerosis, neuromyelitis optica, myasthenia gravis, Guillain–Barré syndrome, Bickerstaff brainstem encephalitis, Lambert–Eaton myasthenic syndrome, atopic myelitis, autoimmune autonomic ganglionopathy, Isaacs' syndrome, systemic lupus erythematosus, Goodpasture's syndrome, hemophagocytic syndrome, stiff person syndrome, antiglutamic acid decarboxylase antibody-associated neurological disorders, Stevens–Johnson syndrome, bullous pemphigoid, pemphigus vulgaris, pemphigus vegetans, and cryoglobulinemic vasculitis.

The average (± standard deviation) patient age at the time of treatment was 49.0 (±18.2) years. The patient cohort included 29 (55%) females and 24 (45%) males.

Plasmapheresis therapies

Plasmapheresis therapies were performed using a Plasauto iQ21 blood purification system (Asahi Kasei Medical Co., Ltd., Tokyo, Japan). PE was performed using a Plasmaflo OP-05 W plasma separator. SePE was performed using the Evacure EC-4A10 selective plasma separator. Albumin solutions made by diluting 25% Alb in lactated Ringer's solution and 10% sodium chloride were used as supplementary fluids in all plasmapheresis sessions. The Alb concentration in the supplementary fluid was equivalent to the patient's pretreatment serum Alb levels in PE and 0.75-fold of pretreatment Alb levels in SePE because the SC of Alb using the EC-4A is reportedly 0.73 (7,8). To maintain plasma osmotic pressure of supplementary fluids, 10% sodium chloride in a 1/100 volume of diluted Alb solution was used. The final targets for plasma osmotic pressure and sodium concentration were about 280 mOsm/kg per H_2O and 138 mEq/L, respectively.

In PE and SePE, the blood flow rate was maintained at 80–120 mL/min, and the plasma separation rate was 20–30 mL/min. Unfractionated heparin was used as an anticoagulant during the plasmapheresis procedures. A double-lumen catheter was inserted into the internal jugular vein or femoral vein and was retained during therapy.

Plasma volume (PV) was calculated according to the following equation (3):

$$PV = (BW/13) \times (100 - Ht)/100 \quad (1)$$

where PV, BW, and Ht indicate plasma volume (L), body weight (kg), and hematocrit (%), respectively.

The target PPVs were set at 0.9 PV in PE and 1 – 1.25 PV in SePE (3).

Measurement of data

IgG (normal range: 868–1780 mg/dL), IgA (122–412 mg/dL), IgM (28–177 mg/dL), and Alb (3.9–4.9 g/dL) were measured using the JCA-BM2250 automatic analyzer (JEOL Ltd., Tokyo, Japan). Fbg (185–370 mg/dL) and Ht (40.8%–49.6%) were measured using an XE-2100 automated hematology system (Sysmex Corp., Kobe, Japan). IgG, IgA, and IgM immediately after plasmapheresis were corrected for hematocrit in view of the change in colloid osmotic pressure using the following equation:

Corrected substance concentration
= substance concentration × Pre-Ht/Post-Ht (2)

where Pre-Ht and Post-Ht indicate hematocrit (%) before and immediately after plasmapheresis, respectively. For multiple values, data are presented as the mean ± standard deviation.

Ethical considerations

The study protocol for retrospective data analysis was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University (approval number 1732).

RESULTS

PPVs and removal ratio of Ig and Fbg for various plasmapheresis modalities

One hundred and twenty-four sessions of PE and 258 sessions of SePE were performed. The PPVs in PE and SePE were 0.90 ± 0.09 PV and 1.10 ± 0.10 PV, respectively (Fig. 1). The percent reductions by one session of PE were 63.7% ± 6.3% for IgG, 62.4% ± 8.9% for IgA, 65.6% ± 7.1% for IgM, and 63.2% ± 7.1% for Fbg, respectively (Fig. 2). The removal ratio of all Igs and Fbg was >60%. The percent reductions by one session of SePE were 53.1% ± 5.5% for IgG, 30.1% ± 7.4% for IgA, 3.6% ± 6.1% for IgM, and 19.0% ± 7.0% for Fbg, respectively (Fig. 2). The removal ratio of IgG was >50%, while the removal ratios of IgM and Fbg were relatively low.

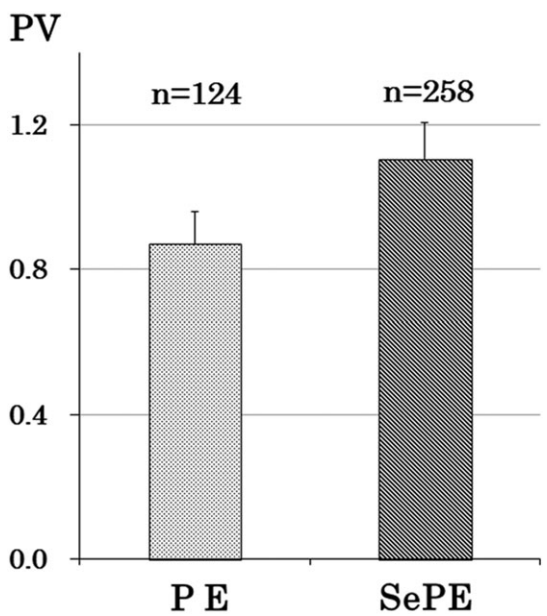

FIG. 1. Processed plasma volumes in various plasmapheresis modalities. PE and SePE indicate simple plasma exchange using a conventional plasma separator and a selective plasma separator, respectively. PV, plasma volume.

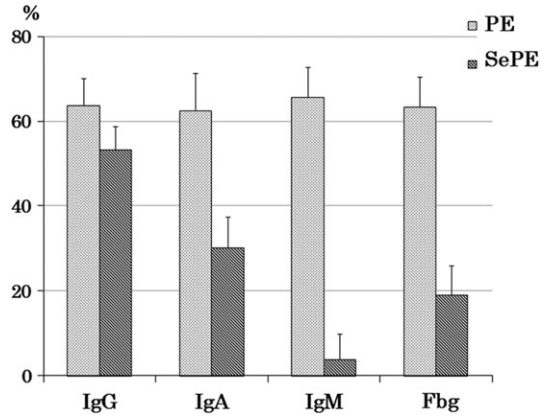

FIG. 2. Short-term changes in serum concentrations of each parameter before and immediately after plasmapheresis. PE and SePE indicate simple plasma exchange using a conventional plasma separator and a selective plasma separator, respectively. Fbg, fibrinogen; Ig, immunoglobulin.

Removal dynamics of Ig and Fbg by PE, SePE, and a combination of the two

In this study, one course of plasmapheresis therapy is defined as three plasmapheresis sessions performed on alternate days within the same week. A total of 20 courses of plasmapheresis therapy were performed in this study. We classified these courses into three categories: a group that received three PE sessions (PE group, $N=2$), a group that received three SePE sessions (SePE group, $N=14$), and a group that received PE as the first session and SePE as the second and third sessions (PE/SePE group, $N=4$). The percent reduction of Ig and Fbg following plasmapheresis therapy of each group was calculated using the equation given below.

Percent reduction by one plasmapheresis session (3)
= (concentration before the first plasmapheresis session
− concentration after the third plasmapheresis session)
/concentration before the first plasmapheresis session
× 100

Circulating Ig and Fbg dynamics during plasmapheresis therapy of each group are shown in Figures 3–6. The percent reduction in IgG for the PE, PE/SePE, and SePE groups was 82.0%, 76.4%, and 75.4%, respectively (Fig. 3). The plasma concentration of IgG decreased by >75% in all groups after three sessions of plasmapheresis on alternate days. The percent reduction of IgA in the PE, PE/SePE, and SePE groups was 80.4%, 57.7%, and 50.6%,

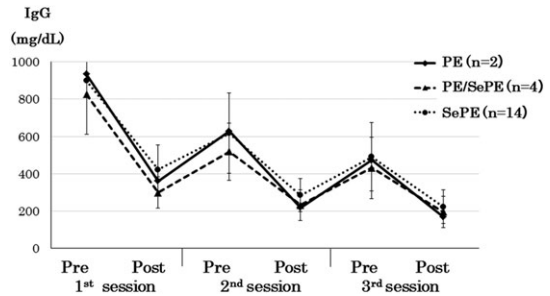

FIG. 3. Removal dynamics of immunoglobulin G (IgG) by plasma exchange, selective plasma exchange, and a combination of the two. Pre and post indicate the concentration of IgG before and immediately after each plasmapheresis session, respectively.

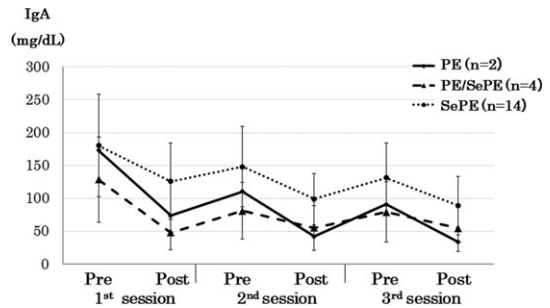

FIG. 4. Removal dynamics of immunoglobulin A by plasma exchange, selective plasma exchange, and a combination of the two. Pre and post indicate the concentration of IgA before and immediately after each plasmapheresis session, respectively.

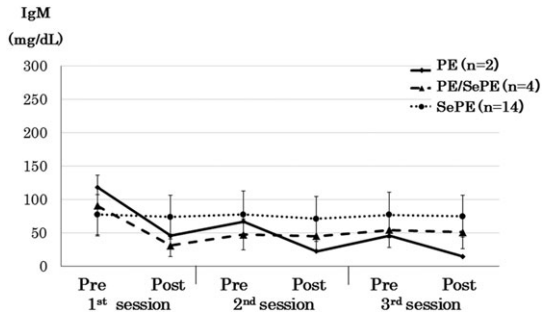

FIG. 5. Removal dynamics of immunoglobulin M by plasma exchange, selective plasma exchange, and a combination of the two. Pre and post indicate the concentration of IgM before and immediately after each plasmapheresis session, respectively.

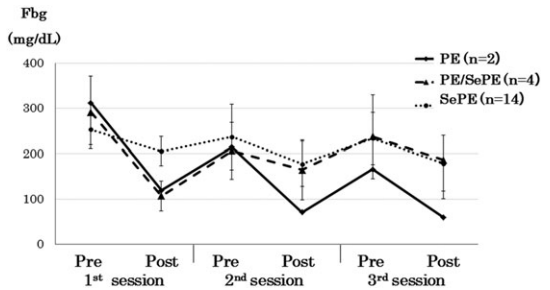

FIG. 6. Removal dynamics of fibrinogen by plasma exchange, selective plasma exchange, and a combination of the two. Pre and post indicate the concentration of Fbg before and immediately after each plasmapheresis session, respectively.

respectively (Fig. 4). For the PE group, the plasma IgA concentration decreased by >80%, similar to that of IgG, and by >50% in the PE/SePE and SePE groups. The percent reduction of IgM in the PE, PE/SePE, and SePE groups was 87.3%, 43.3%, and 3.2%, respectively (Fig. 5). The plasma IgM concentration in the PE group decreased by >80%, similar to that of IgG and IgA, and >40% in the PE/SePE group. However, IgM was not eliminated at all in the SePE group. The percent reduction of Fbg for the PE, PE/SePE, and SePE groups was 80.9%, 35.9%, and 29.3%, respectively (Fig. 6). The plasma Fbg concentration in the PE group decreased by >80%, similar to that for Ig and <40% in the PE/SePE and SePE groups.

DISCUSSION

This is the first report to reveal the removal characteristics of IgA and IgM by SePE and the removal dynamics of Ig and Fbg by the combination therapy of PE and SePE. Therapeutic PE for the treatment of immunological disorders reduces the amount of circulating antibodies through filtration (14). Meaningful depletion of harmful antibodies requires removal of 1 PV, and to prevent hypotension and peripheral edema, some form of colloid-containing fluid must be provided to replace the removed plasma (2). Alb solution is the preferred replacement fluid for PE in most instances, because of the rarity of adverse reactions, pasteurization to prevent viral infection, and convenience in storage and administration, compared with fresh frozen plasma (2,15). However, most plasma proteins, including coagulation factors, are not replaced when using Alb solution as the replacement fluid in PE.

The SCs of plasma proteins by PE were approximately 1.00 (16). Since PE can eliminate plasma proteins, including all Igs, it is considered useful for plasmapheresis even if pathogenesis is not described as solely antibody-mediated, such as with dermatomyositis (12). In this article, when the PPV was 0.9 PV, the percent reductions of Ig and Fbg by one session of PE were approximately 62%–65%. Previous studies reported that a single PE of 1.0 PPV removes approximately 63% of all solutes in plasma, and blood volume was calculated by 0.065 BW (17,18). In contrast, we calculated blood volume by BW/13 (approximately equal to 0.077 BW). Therefore, a PV of 1.0 in these previous reports was approximately equal to a PV of 0.9 in this report,

indicating that the percent reductions of the previous reports and this report were similar (17,18).

In this article, when the PPV was 1.1 PV, the percent reductions in IgG, IgA, IgM, and Fbg by one session of SePE were 53.1%, 30.1%, 3.6%, and 19.0%, respectively. The molecular weights of IgG, IgM, and Fbg are about 150 000, 950 000, and 340 000, respectively (16). The molecular weight of an IgA monomer is about 160 000, although IgA can exist as a either monomer or dimer (rarely a trimer). The SCs of IgG, IgM, and Fbg by SePE were 0.5, 0, and 0, respectively (7,19). Therefore, compared with PE, a larger PPV should be processed during SePE to improve IgG removal. Moreover, SePE could not remove IgM. However, the reduction in Fbg by SePE was approximately 19%, which was likely due to pore blockage (7).

Usually repeated plasmapheresis therapy is necessary for treatment of immunological disorders. We evaluated the removal kinetics after one course of three plasmapheresis sessions on alternate days. The percent reductions in IgG, IgA, IgM, and Fbg were 82.0%, 80.4%, 87.3%, and 80.9%, respectively, in the PE group; 76.4%, 57.7%, 43.3%, and 35.9%, respectively, in the PE/SePE group; and 75.4%, 50.6%, 3.2%, and 29.3%, respectively, in the SePE group. The percent reduction in IgG was >75% in all groups. If the substance targeted by plasmapheresis is limited to IgG, all modalities can be considered as useful for plasmapheresis therapy. However, the percent reduction of IgM in the SePE group was very low. SePE should not be chosen for plasmapheresis if the targeted substance is limited to IgM. Certainly, in some diseases, the substances targeted by plasmapheresis include both IgM and IgA antibodies (20,21). However, most IgM exists intravascularly and more than half of IgG exists outside of the blood vessels (17,18). Therefore if IgM can be decreased during the initial plasmapheresis session, as with PE/SePE, a rebound in concentration may be difficult to occur. Certainly, PE was the most effective modality to remove Ig in all groups. However, the percent reduction of coagulation factors, such as Fbg, was also >80%. Furthermore, the mean concentrations of Fbg after the second and third PEs were both <100 mg/dL, which can potentially contribute to hemorrhage and the necessity of additional treatment to restore normal hemostasis (10,12). In contrast, the mean Fbg concentration of the PE/SePE and SePE groups was maintained at >100 mg/dL. However, in this study, we did not measure concentrations of coagulation factor XIII, which has a longer half-life than Fib (1). Repeated PE and DFPP can easily reduce the concentration of factor XIII to a point that can lead to fatal bleeding (22). The SC of factor XIII by SePE was 0.17 (7); therefore SePE may retain factor XIII, as with Fbg.

There were some limitations to this study that should be addressed. First, this study was retrospective and observational. Second, the sample size was relatively small, especially in the PE group ($N=2$). Therefore, we could not perform statistical analysis. Because the remarkable reduction in Fbg by PE might be a risk factor for bleeding, consecutive PE was performed at intervals of 48 h or longer. Third, no clinical outcomes, such as therapeutic effects and complications, were assessed. Therefore, further studies to investigate the therapeutic effects and complications of PE are necessary.

When the substance targeted by plasmapheresis is limited to IgG, SePE is both a useful and safe option. When substances targeted by plasmapheresis are various Igs, PE can be combined with SePE, which results in both the unspecific removal of pathogens by PE and retention of coagulation factors, such as Fbg, by SePE. It is important to select the modality carefully and, when necessary, combine appropriate plasmapheresis modalities on the basis of the characteristics and removal kinetics of the pathogenic substances.

CONCLUSION

When the mean processed plasma volumes in plasma exchange (PE) and selective plasma exchange (SePE) were 0.9 PV and 1.1 PV, respectively, the mean percent reductions in IgG, IgA, IgM, and fibrinogen (Fbg) were 53.1%, 30.1%, 3.6%, and 19.0%, respectively, by one session of SePE, and 76.4%, 57.7%, 43.3%, and 35.9%, respectively, by the weekly combination treatment of PE/SePE. We combined PE and SePE using Alb solution as supplementary fluid, which resulted in both the unspecific removal of pathogens by PE and retention of coagulation factors, such as Fbg, by SePE.

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Conflict of Interest: All authors declare no conflict of interest.

REFERENCES

1. Hanafusa N. Theoretical basis of pathogenic substance removal during plasmapheresis. *Ther Apher Dial* 2011;15:421–30.

2. McLeod BC. Plasma and plasma derivatives in therapeutic plasmapheresis. *Transfusion* 2012;52:38S–44.
3. Ohkubo A, Okado T, Kurashima N et al. Removal characteristics of immunoglobulin G subclasses by conventional plasma exchange and selective plasma exchange. *Ther Apher Dial* 2015;19:361–6.
4. Moriya Y, Yamaji K, Kanai Y, Tsuda H. The effectiveness of intravenous human immunoglobulin treatment after plasmapheresis in restoring serum immunoglobulin levels: a preliminary study. *Ther Apher* 2002;6:154–8.
5. Shibuya N, Suenaga A. Adsorption specificity of immunoadsorbent. *Clin Eng* 1991;2:335–8(In Japanese).
6. Okamiya S, Ogino M, Ogino Y et al. Tryptophan-immobilized column-based immunoadsorption as the choice method for plasmapheresis in Guillain-Barre syndrome. *Ther Apher Dial* 2004;8:248–53.
7. Ohkubo A, Kurashima N, Nakamura A, Miyamoto S, Iimori S, Rai T. Solute removal capacity of high cut-off membrane plasma separators. *Ther Apher Dial* 2013;17:484–9.
8. Ohkubo A, Okado T, Kurashima N et al. Removal kinetics of antibodies against glutamic acid decarboxylase by various plasmapheresis modalities in the treatment of neurological disorders. *Ther Apher Dial* 2014;18:231–7.
9. Hanafusa N, Satonaka H, Doi K, Noiri E, Fujita T. Virus removal and eradication by modified double filtration plasmapheresis decreases factor XIII levels. *Ther Apher Dial* 2010;14:287–91.
10. Koessler J, Kobsar A, Kuhn S et al. The effect of immunoadsorption with the Immusorba TR–350 column on coagulation compared to plasma exchange. *Vox Sang* 2015;108:46–51.
11. Hanafusa N, Hamasaki Y, Kawasaki H et al. The effect of different apheresis modalities on coagulation factor XIII level during antibody removal in ABO-blood type incompatible living related renal transplantation. *Transfus Apher Sci* 2013;49:254–8.
12. Zöllner S, Pablik E, Druml W, Derfler K, Rees A, Peter B. Fibrinogen reduction and bleeding complications in plasma exchange, immunoadsorption and a combination of the two. *Blood Purif* 2014;38:160–6.
13. Yasuda T, Mikami T, Kawase Y. Efficacy of tryptophan immunoadsorption plasmapheresis for neuromyelitis optica in two cases. *Ther Apher Dial* 2015;19:411–2.
14. Sorgun MH, Erdogan S, Bay M et al. Therapeutic plasma exchange in treatment of neuroimmunologic disorders: Review of 92 cases. *Transfus Apher Sci* 2013;49:174–80.
15. Bouget J, Chevret S, Chastang C, Raphael JC. Plasma exchange morbidity in Guillain-Barré syndrome: results from the French prospective, double-blind, randomized, multicenter study. The French Cooperative Group. *Crit Care Med* 1993;21:651–8.
16. Hirata N, Shizume Y, Shirokaze J, Suemitsu J, Yoshida H, Yamawaki N. Plasma separator Plasmaflo OP. *Ther Apher Dial* 2003;7:64–8.
17. Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. *Am J Kidney Dis* 2008;52:1180–96.
18. Rummler S, Barz D. Plasma exchange and immunoadsorption of patients with thoracic organ transplantation. *Transfus Med Hemother* 2012;39:234–40.
19. Sueoka A, Miyahara T, Takakura K et al. Study of filtration characteristics of EVAL second filters with diseased plasma. *J Jpn Artif Organs* 1985;14:413–6(In Japanese).
20. Kaida K, Kusunoki S, Kamakura K, Motoyoshi K, Kanazawa I. Guillain–Barré syndrome with IgM antibody to the ganglioside GalNAc–GD1a. *J Neuroimmunol* 2001;113:260–7.
21. Ilyas AA, Mithen FA, Chen ZW, Cook SD. Anti-GM1 IgA antibodies in Guillain-Barré syndrome. *J Neuroimmunol* 1992;36:69–76.
22. Seishima M, Shibuya Y, Kato G, Aoki T. Decreased factor XIII activity in a patient with subcutaneous bleeding after double filtration plasmapheresis. *Ther Apher Dial* 2009;13:229–31.