Chapter 18
Bleeding Complications and Reduction of Coagulation Factors

Norio Hanafusa

Main Points

- Bleeding diathesis during apheresis can be caused by anticoagulant drugs, removal of endogenous coagulating factors, or primary diseases.
- Monitoring is necessary; activated coagulation time as well as direct measurement of fibrinogen and factor XIII levels is indispensable during plasmapheresis with albumin supplementation including double filtration plasmapheresis.

18.1 Introduction

Hemorrhage is an important complication of apheresis. Bleeding diathesis can originate from the use of anticoagulant drugs, the removal of endogenous coagulation factors, or

N. Hanafusa (✉)
Department of Hemodialysis & Apheresis, University Hospital, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: hanafusa-tky@umin.ac.jp

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certain diseases. The complication is well known, but its actual incidence is not high and is reported to be between 0.02 % and 0.2 % [1, 2].

18.2 Use of Anticoagulants

Anticoagulation is indispensable for procedures utilizing extracorporeal blood circulation. The blood flow rate is lower in apheresis procedures than in hemodialysis, and the plasma flow rate in double filtration plasmapheresis or in plasma adsorption is slower still, thus the plasma transit time is long. Subsequently the dosage of anticoagulant drugs tends to be larger than that seen with hemodialysis. Certain diseases also might cause an increased bleeding risk, and in these situations extra care should be taken.

Heparin is usually used for anticoagulation. The ability to remove heparin during plasmapheresis is limited and the half-life of heparin is quite long. Therefore most of the infused heparin enters the systemic circulation. Nafamostat mesylate is often used in Japan as an anticoagulant. The drug works almost exclusively in the hemodialysis circuit because it can be eliminated during dialysis and has a short half-life. However, plasmapheresis removes only a small amount of the drug and it can prolong the coagulation time of systemic blood.

Vascular access site bleeding is sometimes observed during apheresis procedures because a central vein catheter is often inserted just before the session or because native arteries are sometimes used for vascular access. Patients should be carefully monitored during apheresis sessions for bleeding at the puncture site or deep hematomas because anticoagulation agents may promote such complications.

18.3 Removal of Coagulation Factors

Many plasmapheresis modalities, by their nature, are nonspecific in their removal of plasma substances. If such nonspecific therapies do not include supplementation with

fresh plasma, levels of coagulation factors are often decreased. For example, plasma exchange with albumin supplementation causes a uniform relative decrease of plasma substances other than albumin.

Double filtration plasmapheresis (DFPP) removes molecules larger than albumin. Figure 18.1 lists the molecular weights and half-lives of coagulation factors [3], as well as of albumin and IgG. Many coagulation factors have a larger molecular weight than albumin and can be removed through DFPP therapy. However, most of them have short half-lives and they recover rapidly before the next session, therefore even with albumin supplementation, the deficiency of such factors may not be obvious.

Fibrinogen and factor XIII (FXIII) have the distinct property of a long half-life, or in other words, a slow production rate, and therefore frequent therapies can decrease levels of these factors [4, 5]. Moreover, reduced production in such cases as liver failure, or increased consumption in such cases as hemorrhage or disseminated intravascular coagulation (DIC), can result in a longer recovery time for such substances by the body.

18.3.1 Importance of Monitoring

Attention should be paid to the reduction of coagulation factors such as fibrinogen or FXIII during plasmapheresis with albumin supplementation. When performing frequent procedures on a patient, physicians should perform direct measurements of fibrinogen and factor XIII as well as coagulation tests such as prothrombin time or activated partial thrombin time.

DFPP is used for the removal of hepatitis C virus (see Chap. 3), and it is recommended that the frequency of therapy be modified according to the fibrinogen concentration. When fibrinogen is decreased to <100 mg/dL, the procedure should be suspended and be postponed until there is recovery of the factor. FXIII does not affect coagulation time

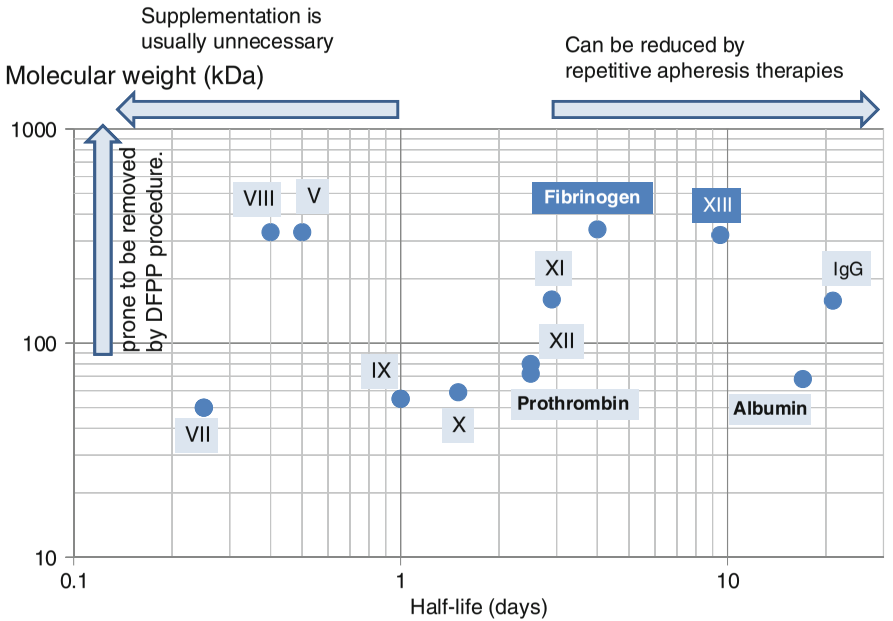

FIGURE 18.1 Half-lives and molecular weights of coagulation factors. Most coagulation factors weigh more than albumin and can be removed through a DFPP procedure. Fibrinogen and FXIII have longer half-lives and can be reduced during frequent apheresis procedures

or bleeding time, but a profound decrease of FXIII is usually observed during frequent apheresis [4]. Therefore direct measurement of the factor is recommended in such circumstances.

The dosage of anticoagulation agents should be carefully modified during the procedures. The removal of coagulation factors results in a decreased requirement for heparin, while the removal of antithrombin III results in an increased requirement for heparin. Activated coagulation time should be monitored for appropriate anticoagulation dosing during procedures.

18.3.2 Measures for Reduced Coagulation Factors

Fibrinogen levels should be maintained at more than 100 mg/dL before the session, while FXIII concentrations should be maintained at more than 5 % after the session. A FXIII level less than 60 % of baseline can be related to an increased incidence of perioperative bleeding complications [6].

The interval between procedures can be increased to wait for recovery of the factors, if possible, when fibrinogen or FXIII levels are reduced. FFP infusion or plasma exchange with FFP supplementation can be considered [7] when the severity of the target disease limits prolonging the interval between procedures.

In chronic conditions where an isolated FXIII reduction is observed, 1 dose (20 mL) of FXIII concentrate (Fibrogammin P) is useful for the recovery of FXIII levels. For example, a patient with a body weight of 60 kg can regain 50 % of FXIII activity after infusion of 1 dose. Patients with a profound decrease of the factor, with levels as low as 10 % before the procedure without a reduction of other factors, may also benefit from FXIII concentrate supplementation [8].

18.4 Bleeding Complications due to Primary Diseases

The target diseases of apheresis include vasculitis (antineutrophil cytoplasm antibody associated), thrombocytopenic disorders (thrombotic thrombocytopenic purpura, systemic lupus erythematosus, or liver failure), and coagulopathies (liver failure). Hemorrhage or bleeding diathesis can be observed in such conditions.

Nafamostat mesylate should be used and the dosage itself should be made as little as possible. Simple plasma exchange with FFP supplementation should be considered as a therapeutic modality, because modalities with albumin supplementation can reduce coagulation factors by the end of the session.

FFP or platelet infusion might be considered according to laboratory test results, before placing vascular access, especially for patients requiring central venous access.

Note: Reduction of FXIII Levels During Apheresis Therapies
FXIII makes cross bridges between fibrin molecules and tightens the clot that forms as a result of the coagulation cascade. A profound decrease to less than 5 % of normal values often causes fatal bleeding. Even a modest decrease causes postoperative bleeding and prolongation of wound healing. FXIII is not a member of the coagulation cascade, and does not affect coagulation time or bleeding time. Therefore direct measurement of either the antigen or its activity is necessary to monitor its decrease.

A decrease of FXIII to 10–20% of normal values is often observed during a DFPP course [4]. If major bleeding occurs under such conditions, a further reduction due to bleeding can result in a vicious cycle that can sometimes be fatal [9].

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