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Association between Activated Partial Thromboplastin Time and the Amount of Infused Heparin at Bone Marrow Transplantation

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A B S T R A C T

The actual heparin concentration of harvested allogeneic bone marrow varies among harvest centers. We monitor the activated partial thromboplastin time (APTT) of the patient during bone marrow infusion and administer prophylactic protamine according to the APTT. We retrospectively reviewed the charts of consecutive patients who underwent bone marrow transplantation without bone marrow processing at our center between April 2007 and March 2016 (n = 94). APTT was monitored during marrow transfusion in 52 patients. We analyzed the relationship between the APTT ratio and several parameters related to heparin administration. As a result, the weight-based heparin administration rate (U/kg/hour) seemed to be more closely related to the APTT ratio ($r = .38$, $P = .005$) than to the total amount of heparin. There was no significant correlation between the APTT ratio and renal or liver function. Bleeding complications during and early after infusion were seen in 3 of 52 patients, and included intracranial, nasal, and punctured-skin bleeding. The APTT ratio during transfusion was over 5.88 in the former 2 patients and 2.14 in the latter. All of these patients recovered without sequelae. In conclusion, slow bone marrow infusion is recommended to decrease the weight-based heparin administration rate when the heparin concentration per patient body weight is high.

INTRODUCTION

Thomas et al. [1] performed bone marrow transplantation for the first time in 1957, and then established technical methods in the late 1960s. In their method, 4 mL of heparin-containing 1000 U/mL are added to each 100 mL of tissue culture medium, and the aspirated bone marrow is poured into the medium. The medium accounts for 20% to 40% of the overall product, and results in a final heparin concentration of 9 to 15 U/mL. The Japan Marrow Donor Program currently recommends a final concentration of unfractionated heparin in the harvested bone marrow fluid of around 10 U/mL. However, the actual heparin concentration varies among harvest centers.

Although unfractionated heparin has been replaced by low-molecular-weight heparin (LMWH) for many indications, both are considered an anticoagulant of choice for the treatment and prophylaxis of acute venous thrombosis. Some factors that predict bleeding complications have been reported, such as poor performance status, a history of a bleeding tendency, and recent trauma or surgery [2]. There have also been some reports on the relationship between intravenous heparin concentrations in excess of .7 or .8 U/mL anti-Xa and bleeding complications [2,3]. Williamson et al. [4] reported prolonged bleeding in a diabetic female bone marrow transplantation recipient after bone marrow infusion containing 26,000 U (287 U/kg) of heparin over 84 minutes. The patient bled continuously from a finger injury for 4 hours after marrow infusion. Other than this case report, however, little is known about the relationship between the amount of

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heparin in bone marrow graft and bleeding events in the setting of bone marrow infusion.

The most widely used laboratory assay for monitoring intravenous heparin therapy is the activated partial thromboplastin time (APTT) [5]. In our practice, we check the APTT during bone marrow infusion and administer prophylactic protamine according to the APTT value during marrow infusion and the amount of heparin. In this retrospective study, we analyzed the relationship between the amount of heparin in bone marrow graft and the APTT value during bone marrow infusion. As the parameters of the amount of heparin, we used not only total amount of infused heparin, but also parameters related to heparin infusion such as infusion speed and those based on patient's body weight or body surface area. We also evaluated the influence of liver and kidney function on APTT during bone marrow infusion.

PATIENTS AND METHODS

Study Patients

We retrospectively reviewed the charts of consecutive patients who underwent bone marrow transplantation without bone marrow processing at the Division of Hematology, Saitama Medical Center, Jichi Medical University between April 2007 and March 2016 (n = 95). Among these patients, this study included 52 in whom serial monitoring data of their APTT values during marrow infusion were available (Table 1).

This study was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University. According to the Japanese ethics guidelines for clinical studies, informed consent was not obtained from each participant. However, we provided information about this retrospective cohort study on a website and allowed patients to be excluded from the study if they did not wish us to use their data.

Bone Marrow Infusion Procedures

Bone marrow infusion was performed through a central venous catheter in most cases. Patients were monitored during infusion by electrocardiography and pulse oximetry. We confirmed a negative crossmatch test between the donor and the recipient before starting marrow infusion. Thirty minutes before infusion, hydrocortisone at 100 mg was administered as premedication. Next, marrow graft was infused at 50 mL/hour for the first 10 minutes, and the infusion rate was then increased to 200 to 300 mL/hour in a step-by-step manner. Vital signs were checked every 10 minutes for the first 30 minutes and every 30 minutes thereafter. Urine volume and occult blood in urine were checked every 4 hours.

In principle, APTT during marrow transfusion was checked when the bone marrow fluid contained more than 10,000 U of heparin, although there were some exceptions. In most cases, APTT was checked when about half of the bone marrow fluid was infused. Prophylactic protamine was administered according to the APTT value before restarting marrow infusion. We usually use protamine in cases with APTT ratio during bone marrow infusion ≥2.5. The dose of protamine was decided on based on the initial amount of heparin. We used 10 to 15 mg of protamine for 1000 units of heparin. In most of the cases, 50 to 100 mg of protamine was administered at one time and repeated according to APTT ratio and the total amount of heparin.

Table 1
Patient Characteristics (n = 52)

Age, y	38.5 (23–55)
Sex	
Male	38 (73.1)
Female	14 (26.9)
Body weight, kg	67.5 (50–91)
Underlying diseases	
Acute leukemia	34 (65.4)
Bone marrow failure disorders	10 (19.2)
Lymphoma	6 (11.5)
Multiple myeloma	2 (3.8)
Disease status	
Early or non-neoplastic	43 (82.7)
Advanced	9 (17.3)
GVHD prophylaxis	
CSA+sMTX	42 (80.8)
TAC+sMTX	8 (15.4)
CSA+sMTX+ATG	1 (1.9)
TAC+sMTX+ATG	1 (1.9)
Conditioning regimen	
CY/TBI	22 (42.3%)
BU/CY	4 (7.7%)
Other myeloablative regimens	3 (5.8%)
Fludarabine-based RIC	23 (44.2%)
Hepatic and renal function *	
ALT, IU/L	22 (8–177)
AST, IU/L	24 (8–199)
Cre, mg/dL	.54 (.25–1.27)

Data are presented as median (range) or n (%).
GVHD indicates graft-versus-host disease; CSA, cyclosporine; sMTX, short-term methotrexate; TAC, tacrolimus; ATG, antithymocyte globulin; CY, cyclophosphamide; TBI, total body irradiation; BU, busulfan; RIC, reduced-intensity conditioning; ALT, alanine transaminase; AST, aspartate transaminase; Cre, creatinine.
* Data at bone marrow infusion.

APTT Measurement, Indexes Associated with the Volume or Rate of Heparin Infusion, and Liver and Kidney Function

APTT was measured with PlaterineLS II (Kyowa Medex, Tokyo, Japan) using a Coapresta 3000 (Sekisui Medical, Tokyo, Japan). The APTT control was 34 seconds. The normal range of APTT is 20 to 35 seconds. We used the APTT ratio (patient/control APTT values) to analyze the effect of heparin on APTT during marrow infusion, as recommended by the American Heart Association.

With regard to the volume or rate of heparin infusion, we analyzed the following indexes: volume of infused heparin (referred to as the cumulative heparin volume) at the time of APTT measurement, volume of infused heparin per patient's body surface area (m^2), volume of infused heparin per patient's body weight (kg), rate of heparin infusion (volume of infused heparin per hour), rate of heparin infusion per patient's body surface area, and rate of heparin infusion per patient's body weight (kg).

Because liver and kidney function may affect the clearance of heparin, we checked serum albumin (mg/dL), aspartate transaminase (U/L), alanine transaminase (U/L), and total bilirubin (mg/dL) levels as indicators of liver function, and creatinine clearance (mL/minute) and serum creatinine (mg/dL) as indexes of kidney function.

Statistical Considerations

We mainly used descriptive statistics to summarize the patient characteristics, information on bone marrow fluid and APTT, and bleeding events. The associations between the APTT value and parameters related to heparin infusion, and between the APTT value and organ function were evaluated using Spearman's rank correlation test. All statistical analyses were performed with EZR version 1.34 [6], which is a graphical user interface for R (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of the Study Patients

Table 1 shows the characteristics of the study patients (n = 52). All of the included patients (n = 52) received bone marrow from unrelated donors collected in other institutions. The median age was 38.5 years (range, 23 to 55 years). None of the patients were receiving anticoagulant or antiplatelet drugs, or had coagulopathy such as disseminated intravascular coagulation at the time of bone marrow infusion. Table 2 shows the information on infused bone marrow and APTT ratio before, during, and after bone marrow infusion. The median heparin concentration in the bone marrow was 14.05 U/mL, but exceeded 20 U/mL in some cases. The median APTT ratio during marrow infusion was 4.1 (range, 1.19 to 5.88).

Relationship between APTT Ratio and Indexes Associated with Heparin Infusion, and Liver and Kidney Function

Spearman's correlation test was used to evaluate the relationship between the APTT ratio and parameters related to heparin infusion including infused volume (U) and infusion speed (U/hour), and those divided by the patient's weight (U/kg, U/hour/kg) and body surface area (U/m^2, U/hour/m^2).