Am J Transl Res 2022;14(3):1729-1736
www.ajtr.org /ISSN:1943-8141/AJTR0138869

Original Article

Prophylaxis use of vitamin K1 improves coagulation function in hematopoietic stem cell transplantation patients: a retrospective cohort study

Yi Zhang, Xuan Lu*, Liang V Tang*

*Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. *Equal contributors.*

Received September 4, 2021; Accepted February 6, 2022; Epub March 15, 2022; Published March 30, 2022

Abstract: Objectives: This study aimed to investigate the efficacy of vitamin K1 in patients undergoing HSCT and find a feasible and safe option for HSCT patients to prevent bleeding. Methods: A retrospective analysis was performed on 96 HSCT patients admitted to the Department of Hematology of Wuhan Union Hospital from January 2018 to July 2019. Patients were divided into two groups (the vitamin K1 group and the control group) based on the administration of vitamin K1. All patients were reexamined for coagulation function during their hospitalization. The prothrombin time (PT), activated partial thromboplastin time (APTT), and plasma fibrinogen (FIB) were measured. The relationship between plasma infusion volumes were also analyzed. Results: In the independent sample T-test analysis, PT and APTT of the vitamin K1 group were significantly shorter than that of the control group after transplantation. There was no obvious difference in plasma FIB levels between the two groups. Total plasma infused volume in the vitamin K1 group was significantly lower than that in the control group. Conclusions: Prophylactic intravenous drip of vitamin K1 has a good therapeutic effect on improving the coagulation function in HSCT patients without significant side effects and decreases the plasma transfusion.

Keywords: Vitamin K1, hematopoietic stem cell transplantation, hemostasis, blood coagulation, blood transfusion

Introduction

Hematopoietic stem cell transplantation (HSCT) is an aggressive therapeutic procedure that infuses the precursor hematopoietic stem cells after a conditioning regimen, a short term of high-dose chemoradiotherapy treatment. It is an increasingly used treatment modality for a variety of hematologic malignancies, and some benign lesions [1]. Chemotherapy and radiation therapy in conditioning regimens can damage not only cancer cells but also healthy cells, especially the rapidly dividing cells, such as hair follicles, myelopoietic bone marrow precursor cells, intestinal epithelial cells, and colonic epithelial cells. The disturbances to these cells can adversely impact immunity and the gastrointestinal system, which is important to nutrition and metabolism [2]. In recent years, HSCT has become a radical treatment for many malignant hematologic diseases, such as genetic metabolic and autoimmune diseases [1]. Bleeding is a common complication in HSCT patients. Gastrointestinal bleeding occurs in 5% to 15% HSCT patients. Several patients may undergo hemorrhagic cystitis, intracerebral bleeding, and pulmonary bleeding after transplantation [3, 4]. Recently, the reported incidence of early hemorrhagic events in adult HSCT patients ranges from 15.4% to 32% [5-7].

Vitamin K1 is mainly stored in the liver, where it plays an important role in the production of the major coagulation factors, such as factor II, VII, IX, and X, which are essential to the coagulation system. The body itself cannot synthesize and secrete vitamin K1. The main vitamin K1 for humans is obtained through food intake [8]. In HSCT patients, the ingestion of vitamin K1 may be strongly influenced by the altered metabolic and nutritional status of patients. Since the amount of vitamin K1 stored in the body is lim-

ited, HSCT patients may have a deficiency of vitamin K1. In general, decreased plasma levels of vitamin K1 leads to increased levels of vitamin K1 epoxide, appearance of noncarboxylated protein (PIVKA), decreased levels of vitamin K-dependent coagulation factors, and coagulation disorders [9].

The objective conditioning regimens for HSCT patients may disturb their digestive and nutritional status, reduce the intake of vitamin K1, lead to a clotting factor deficiency, and increase the risk of bleeding. Prophylactic vitamin K1 supplementation in HSCT patients can improve the coagulation factor deficiency, which can reduce the risk of hemorrhage and decrease the volume of preventive plasma infusion. The aim of our study was to retrospectively assess the effect of vitamin K1 supplementation on coagulation function and plasma infusion requirement of HSCT patients, providing a new thought in reducing the risk of bleeding in HSCT patients.

Methods

In this retrospective study, a total of 96 patients who underwent HSCT between January 2018 and July 2019 at the Department of Hematology of Wuhan Union Hospital were included. All patients' data was obtained from the digital medical record database of the hospital. This study was only based on archival data. All patients provided informed consent to use their clinical data for research purposes. This study was approved by the Ethics Committee of Wuhan union Hospital.

Inclusion criteria: All transplantation patients admitted into the hematopoietic stem cell transplantation chamber (aged 8-65 years, male or female) were enrolled in this study.

Exclusion criteria were as follows: (1) patients with allergy to vitamin K1, (2) patients with obvious abnormal coagulation function on admission, (3) patients with an explicit history of vitamin K1 deficiency, (4) patients with abnormal coagulation factor, (5) patients who were recently taking vitamin K antagonists.

Subgroup: Patients enrolled in this study were divided into two groups based on whether they had received the supplementary vitamin K1. The two groups were known as vitamin K1 group and control group.

Methods: We appointed the day that the patients underwent HSCT as Day 0. All the positive and negative numbers respectively represented the days after and before HSCT. The following variables were recorded: recipient characteristics (age, gender, main diagnosis, coagulation indexes, and risk level) and transplant characteristics (type of graft, CD34+ cells graft count, and total nucleated cells count). The blood coagulation function tests, such as PT, APTT, and FIB, were detected for each patient at 5:00 am every 3 days after their admission to the hospital and every 3 days after their transplantation. All adverse effects of the vitamin K1 injection, such as hypersensitivity at the point of the vitamin K1 injection, liver function impairment, and elevated bilirubin were documented throughout this study. In this study, the end point was the predetermined study time (16 days after patients' graft), the date of a patient's death, discharge from the hospital, or re-transplantation. The rate of intravenous vitamin K1 was controlled at less than 1 mg/min (1 mL 10 mg/ml vitamin K1 injection was diluted in 100 mL 0.9% sodium chloride solution, and the speed of intravenous drip was 5 mL/min).

Definition: We defined the normal value of APTT as 28.0 s-43.5 s, the normal value of PT as 11.0 s-16.0 s, and the normal value of FIB as 2.0 g/l-4.0 g/l. We defined the indications for plasma infusion as a prolongation of APTT to more than 53.5 s, or an extension of PT to more than 19 s, or a reduction of FIB to less than 1.5 g/L. Frozen fresh plasma was transfused based on the coagulation function tests of the patient and the British Committee for Standards in Hematology guidelines. A total of 400 ml plasma would be administrated to improve the coagulation function when the patient's coagulation tests reached the above indications of blood transfusion.

Instrument and equipment: Coagulation tests including PT, APTT, and FIB were detected using a STA-Revolution coagulation analyzer and original reagents (Diagnostica Stago, Saint-Denis, France). All laboratory tests were assayed in the core laboratory at the Wuhan Union Hospital according to standard laboratory procedures.

Statistical method: All statistical analysis was conducted with IBM SPSS Statistics 22 statisti-

Table 1. The characteristics of the patients

Characteristics	Vitamin K1 group	Control group	*P* value
Age (years)	*32.42±11.92*	*33.33±15.68*	*0.748*
Sex			*0.536*
Male	*26 (54.2%)*	*29 (60.4%)*	
Female	*22 (45.8%)*	*19 (39.9%)*	
Diagnosis			*0.272*
Aplastic anemia	*9 (18.8%)*	*12 (25%)*	
Acute Leukemia	*28 (58.3%)*	*19 (39.6%)*	
Lymphoma	*5 (10.4%)*	*5 (10.4%)*	
Myeloproliferative disorder	*5 (10.4%)*	*7 (14.6%)*	
Myeloma	*1 (2.1%)*	*5 (10.4%)*	
Type of HSCT			*0.241*
Auto-PBSCT	*3 (6.3%)*	*2 (4.2%)*	
PBSCT	*26 (54.2%)*	*34 (70.8%)*	
PBSCT+BMT	*19 (39.6%)*	*12 (25%)*	
Criticality			*0.021*
High risk	*35 (72.9%)*	*24 (50%)*	
Middle and low risk	*13 (27.1%)*	*24 (50%)*	
CD34+ cell count (*10^6)	*8.74±9.28*	*9.23±5.19*	*0.772*
Nucleated cell count (*10^8)	*13.37±4.28*	*14.60±5.18*	*0.25*
APTT (s)	*36.89±3.04*	*36.46±4.62*	*0.756*
PT (s)	*13.93±1.25*	*13.86±0.87*	*0.59*
FIB (g/l)	*3.09±1.83*	*2.85±0.74*	*0.411*

HSCT, Hematopoietic Stem Cell Transplantation; PBSCT, Peripheral Blood Stem Cell Transplantation; BMT, Bone Marrow Transplantation.

cal software. Continuous variable data of normal distribution were expressed as mean and standard deviation. The between-group comparisons were performed using an independent sample T test. The classification variables were recorded as percentage (%). The Chi-square tests were used for comparison between groups.

Results

Baseline data of the patients

The basic clinical characteristics of all 96 patients were listed in **Table 1**. This study involved 48 HSCT patients who underwent vitamin K1 injection (vitamin K1 group) and 48 HSCT patients who were not injected with vitamin K1 (control group). There were no statistically significant differences in age, gender, main diagnosis, type of transplantation, risk degree, CD34+ cell count, and total nucleated cell count of the graft between the vitamin K1 group and the control group. No significant differences in APTT, PT, and FIB were observed between the two groups at admission and before transplantation.

Coagulation function and the need of transfusion in vitamin K1 group and control group

From the time of patient admission, blood coagulation tests were detected every 3 days on admission to the hospital and every 3 days after their transplantation for 28 consecutive days, as shown in **Table 2**. PT of 7^{th} days after transplantation were 13.73±1.02 s in the vitamin K1 group and 14.30±0.96 s in the control group (P= 0.0056). PT of 10^{th} days after transplantation were 14.06± 1.05 s in the vitamin K1 group and 14.98±1.30 s in the control group (P=0.0002). PT of 13^{rd} days after transplantation were 14.19±0.96 s in the vitamin K1 group and 15.38±1.71 s in the control group (P< 0.0001). PT of 16^{th} days after transplantation were 14.28± 1.11 s in the vitamin K1 group and 15.35±1.74 s in the control group (P=0.0005). APPT of 13^{rd} days after transplantation were 41.14±5.85 s in the vitamin K1 group and 44.08±7.65 s in the control group (P=0.0381). The total volume of plasma infusion of the vitamin K1 group was 775.0±196.2 ml, and the volume of the control group was 341.7±85.9 ml (P=0.0459). The PT of the vitamin K1 group on the 7^{th}, 10^{th}, 13^{rd}, and 16^{th} days after transplantation was significantly shorter than that of the control group. The APTT of the vitamin K1 group on the 13^{rd} days after transplantation was significantly shorter than that of the control group. All these differences were statistically significant (P< 0.05). The statistical analysis showed no significant difference in the FIB level between the two groups (P>0.05) for 28 consecutive days. The volume of plasma infusion in the vitamin K1 group was significantly fewer when compared to the control group. The difference was statistically significant (P<0.05). And the **Figure 1** showed the coagulation function and the

Table 2. Coagulation function and plasma infusion volume in vitamin K group and control group

Testing item	Time	Vitamin K1 group	Control group	*P* value
PT (s)				
	Day -9	*13.93±1.25*	*13.86±0.87*	*0.7555*
	Day -6	*13.81±0.96*	*13.76±0.82*	*0.7756*
	Day -3	*13.61±0.93*	*13.46±0.80*	*0.3924*
	Day 0	*13.12±0.93*	*13.46±0.80*	*0.3915*
	Day 1	*13.00±0.76*	*13.32±0.86*	*0.052*
	Day 4	*13.44±0.88*	*13.62±0.75*	*0.2702*
	Day 7	*13.73±1.02*	*14.30±0.96*	*0.0056*
	Day 10	*14.06±1.05*	*14.98±1.30*	*0.0002*
	Day 13	*14.19±0.96*	*15.38±1.71*	*<0.0001*
	Day 16	*14.28±1.11*	*15.35±1.74*	*0.0005*
APTT (s)				
	Day -9	*36.89±3.04*	*36.46±4.72*	*0.5905*
	Day -6	*36.53±3.70*	*36.24±4.74*	*0.7395*
	Day -3	*36.46±4.03*	*35.73±5.27*	*0.4505*
	Day 0	*37.10±4.43*	*37.85±7.32*	*0.5452*
	Day 1	*34.99±6.50*	*35.97±7.24*	*0.4874*
	Day 4	*39.93±6.16*	*39.58±6.84*	*0.7904*
	Day 7	*41.45±7.00*	*43.58±7.38*	*0.1506*
	Day 10	*42.30±6.66*	*44.62±7.47*	*0.111*
	Day 13	*41.14±5.85*	*44.08±7.65*	*0.0381*
	Day 16	*40.47±8.34*	*42.95±8.00*	*0.1444*
FIB (g/l)				
	Day -9	*3.09±1.83*	*2.85±0.74*	*0.4105*
	Day -6	*2.88±1.06*	*2.81±0.93*	*0.7437*
	Day -3	*2.99±1.03*	*3.02±0.91*	*0.8776*
	Day 0	*3.44±1.04*	*3.39±1.00*	*0.8081*
	Day 1	*3.57±1.79*	*3.03±0.86*	*0.0619*
	Day 4	*3.81±1.13*	*3.66±1.12*	*0.5463*
	Day 7	*3.95±1.10*	*4.08±1.15*	*0.597*
	Day 10	*3.72±1.12*	*3.91±1.26*	*0.4507*
	Day 13	*3.38±0.99*	*3.58±1.91*	*0.5197*
	Day 16	*3.10±1.01*	*3.06±1.09*	*0.8819*
Plasma infusion (ml)		*775.0±196.2*	*341.7±85.9*	*0.0459*

Day 0: the day the patient underwent transplantation.

transfusion requirement in vitamin K1 group and control group. No adverse effect associated with vitamin K1, such as vitamin K1 hypersensitivity, liver function injury, and the elevated bilirubin was observed during the study.

Discussion

Our study showed that, the PT and APTT of HSCT patients in the vitamin K1 group were shorter than that of the control group. There were no markedly differences in the FIB level between the two groups. The vitamin K1 group had a lower demand of plasma than the control group. HSCT patients in the vitamin K1 group were not observed significant adverse effects related to vitamin K1 at a daily dose of 10 mg and at an intravenous drip speed of less than 1 mg/min. Our study suggested that continuous prophylactic vitamin K1 intravenous injection can ensure stable coagulation function, reduce the need for plasma infusion, and save blood products in patients with HSCT.

HSCT has been an effective and potentially curative treatment for many malignant and non-malignant hematopoietic diseases. Its usage has increased markedly over the past decades. The widespread application of it inevitably leads to various complications, among which the most frequently encountered complications are graft-versus-host disease (GVHD), infection (including invasive fungal infection, sepsis, and viremia), and recurrence of malignant tumors and hemorrhage. Recent studies have shown that a large number of HSCT recipients had encountered at least one bleeding event [10], as high dose chemotherapy, radiotherapy, anti-thymocyte immunoglobulin, GVHD, infection, thrombotic microangiopathy (TMA), thrombocytopenia, and other transplant-related complications can cause coagulation dysfunction [11]. Many studies have shown that bleeding complications after transplantation might shorten the survival time of patients. The following mechanisms may have something to do with it: (a) Conditioning regimen or other complications of HSCT can contribute to long-term severe thrombocytopenia and damage the tissue vessel [12]. (b) FXIII levels are reduced in patients with gastrointestinal GVHD, and FXIII activity is correlated with the serious GVHD. Some patients may develop a rare acquired FVII deficiency after HSCT, leading to the asymptomatic

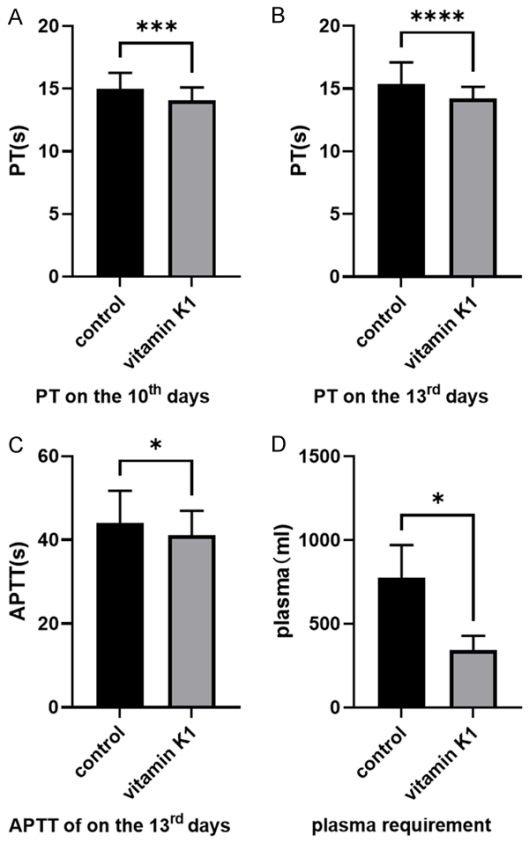

Figure 1. The coagulation function and the transfusion requirement in vitamin K1 group and control group. A. The PT of vitamin K1 group on the 10th days after transplantation is shorter than that of the control group (P=0.0002). B. The PT of vitamin K1 group on the 13rd days after transplantation is shorter than that of the control group (P<0.0001). C. The APTT of vitamin K1 group on the 13rd days after transplantation is shorter than that of the control group (P=0.0381). D. The plasma requirement of vitamin K1 group is fewer than that of the control group (P=0.0459). Vitamin K1 group: patients with continuous prophylactic use of vitamin K1 injection, control group: patients without prophylactic use of vitamin K1 injection. "*": P<0.05, "***": P<0.001, and "****": P<0.0001.

course, severe life-threatening bleeding diathesis and fatal bleeding [13]. (c) Severe infections after HSCT can activate the coagulation system, characterized by increasing the production of thrombin through an exogenous coagulation pathway, impairing the downregulation of thrombin as systemic physiological anticoagulants are consumed, and inhibiting the fibrinolysis system [14]. Based on the pathogen and the severity of clinical infection, the effects on hemorrhage and coagulation may range from minor laboratory changes to disseminate intravascular coagulation (DIC) that is associated with intravascular fibrin deposition and depletion of platelets and coagulation factors [15].

Studies have found that patients with HSCT are also at an increased risk of thrombosis. The thrombotic complications after HSCT mainly consist of hepatic veno occlusive disease or sinusoidal obstruction syndrome (VOD/SOS) [16] and transplant-associated thrombotic microangiopathy (TA-TMA) [17]. VOD/SOS is a potentially serious complication following the conditioning regimens of HSCT. The vascular endothelium is a key mediator of such complication [18]. Blood flow imbalance after HSCT is a consequence of interaction among endothelial damage, thrombocytopenia, and the dysfunction of the coagulation and fibrinolysis system [19]. The pathogenesis of thrombosis-related complications after HSCT may include as follows: (a) Conditioning therapy induces thrombocytosis and endothelial injury, which in turn stimulates the local coagulation system, and activates the coagulation cascade by increasing the expression of tissue factor and other main coagulation promoters. (b) Infection after HSCT could cause different degrees of coagulation dysfunction, which was also related to the severity of the complications of HSCT. For example, bacterial infection can rescue thrombin generation, enhance the FVIII activation, and reduce the activity of physiological anticoagulant [20]. (c) Allogenic reactivity may also play a role in endothelial injury and coagulation changes. Previous studies have shown that after transplantation the coagulation system is activated. Several activated coagulation markers levels, such as increasing fibrinogen, thrombin-antithrombin complex (TAT), and D-dimer (DD) are elevated in adult HSCT patients. It has also been established that the ability of anticoagulant substances to respond to the increased thrombin generation after HSCT may be damaged in children, such as antithrombin III (ATIII) and protein C (PC) [21]. Some scientists believe that venous thromboembolism (VTE) is mainly catheter-related in HSCT patients, of which the incidence is 3-fold less common than clinically significant bleeding. The patients with high risks of VTE, such as GVHD and infection, are also a high bleeding risk. Hemorrhage is a common and severe complication of HSCT. VTE can take place during severe thrombocytopenia. The prevention of VTE in patients after HSCT should be carefully considered.

In general, most treatments at present in the severely bleeding are proposed as antifibrinolytic drugs, transfusion of platelets, fresh frozen plasma (FFP), fibrinogen, cryoprecipitate, or recombination-activated clotting factors. These measures can manage bleeding, but the more severe bleeding is usually difficult to be controlled [22]. Since HSCT is a complex clinical issue, it may be a good approach to face it from the perspective of improving the coagulation function, which can reduce the risk of bleeding, cut down the use of blood products, and improve the clinical outcome.

Vitamin K1 has an essential role in coagulation, serving as a cofactor for the ribosomal synthesis of clotting factors II, VII, IX, and X. As a coenzyme for glutamate carboxylase, vitamin K1 can assist carboxylase to converse the glutamate of coagulation factor precursor into gamma-carboxyglutamate which has a high-affinity binding of calcium ion. The coagulation factor is allowed to interact with negatively charged phospholipid membrane areas. Inactive coagulation factor precursors are transformed into activated coagulation factors which perform the crucial coagulation function and maintain hemostasis [23, 24]. The deficiency of vitamin K1 can result in abnormal and defective vitamin K1-dependent clotting factors that cannot normally participate in coagulation. Vitamin K1 in the body is mainly obtained from green leafy vegetables in the diet and absorbed in the digestive tract by small intestine epithelial cells. In this process, vitamin K1 is packaged into chyle particles, and utilized by the liver [25]. In the liver, vitamin K1 can assist the carboxylation and cleavage of clotting factors, and then be eliminated rapidly in the circulation. Some studies have proposed that the normal intestinal flora of humans can produce some vitamin K1 homologues [26]. The vitamin K1 level in a healthy adult ranges from 200 to 800 pg/ml after fasting, but it would fall rapidly after a continuous low intake, with a development of subclinical vitamin K1 deficiency [27]. Factors contributing to vitamin K1 deficiency include poor diet, malabsorption, antibiotic treatment, excessive renin, liver dysfunction, recent major surgery, failure to obtain the supplement of vitamin K1 on time, and pregnancy. Vitamin K1 deficiency can result in coagulation disorders. Some abnormal results of hemostatic analysis can reflect the partially or completely deficiency of vitamin K-dependent coagulation factors (factor II, VII, IX, and X). Patients with vitamin K1 deficiency are often overlooked and develop into severe bleeding, which can cause serious clinical outcomes [28]. It can be prevented by prophylactic vitamin K1 administration in severely ill patients with inadequate diet and receiving antibiotics. A recent study demonstrated that vitamin K could lead to a slightly large decrease of PT-INR in critically ill patients compared to controls. Vitamin K might be a better alternative to improve PT-INR before non-emergent invasive procedures than plasma or prothrombin complex concentrate [29]. For patients undergoing HSCT, high-dose chemotherapy, total body irradiation, and other conditioning regimens before HSCT may bring about loss of appetite and disorders of digestion, which in turn leads to less intake and absorption of vitamin K1. HSCT patients are more easily infected. Intravenous antibiotics may kill part of the normal intestinal flora, which may reduce the production of vitamin K1 in this pathway and aggravate the deficiency of vitamin K1. Currently, the supplementation of vitamin K1 is used in the following situations: (a) anticoagulation-induced prothrombin deficiency (anticoagulant reversal), (b) prothrombin deficiency secondary to other medications that may limit the absorption or synthesis of vitamin K1, (c) the prevention or treatment of neonatal hemorrhagic diseases. The recommended dosage and the administration route of vitamin K1 vary from indication to indication. There is inadequate evidence to support any one clinical practice. The commonly used dose of vitamin K1 is 10 mg, 1-2 times a day with the total dose administered less than 40 mg [30]. As a prophylactic medication, this study chose 10 mg once a day to avoid severe adverse reactions of vitamin K1 infusion, such as severe allergic reactions (facial flushing, sweating, fever, syncope, and anaphylactic shock), cardiovascular system damage (severe hypotension, arrhythmia, and cardiac arrest), and respiratory system damage (chest tightness, dyspnea, and bronchospasm) [31].

Our study is the first to propose that prophylactic use of vitamin K1 is a simple and cost-effective way to improve coagulation function, reduce the blood transfusion requirements, and decrease the incidence of transfusion-related adverse events and hemorrhage, which may lower the mortality of HSCT patients. Within the limitations of this retrospective anal-

ysis, other concomitant treatments may partially influence the final outcomes. Our study provides a preventive measure for coagulation dysfunction and bleeding complications for the first time in HSCT patients. The prophylactic use of vitamin K1 in HSCT patients could shorten their APTT and PT and reduce the plasma infusion volume. Based on our study, we suggest that physicians should routinely use vitamin K1 in patients with HSCT during their hospitalization. Early prophylactic use of vitamin K1 can improve patients' coagulation function, reduce coagulopathic bleeding, and decrease plasma transfusion requirement in HSCT patients.

Conclusion

Our study is the first, to share the experience of vitamin K1 injection in HSCT patients, providing promising data on its efficacy and safety in real-clinical practice. Our preliminary experience suggested that prophylactically intravenous administration of vitamin K1 can be considered a safe, effective, feasible, and reproducible option for HSCT patients. Future research is warranted to standardize the technical aspects of vitamin K1 injection, including an appropriate dose, modality of dispensing, and timing of administration. Future randomized control studies are needed to assess the value of vitamin K1 supplementation in other forms of hemorrhage and determine whether it should be recommended as a routine therapy for primary or secondary prevention in different clinical settings.

Acknowledgements

This work was supported by Program for HUST Academic Frontier Youth Team (No. 2018QYTD14) and National Natural Science Foundation of China (No. 81973995).

Disclosure of conflict of interest

None.

Address correspondence to: Xuan Lu and Liang V Tang, Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277 Jiefang Avenue, Wuhan 430022, China. Tel: +86 27 85726387; Fax: +86 27 85726387; E-mail: luxuan20@163.com (XL); lancet.tang@qq.com (LVT)

References

[1] Bazinet A and Popradi G. A general practitioner's guide to hematopoietic stem-cell transplantation. Curr Oncol 2019; 26: 187-191.

[2] Jones KS, Bluck LJ, Wang LY and Coward WA. A stable isotope method for the simultaneous measurement of vitamin K1 (phylloquinone) kinetics and absorption. Eur J Clin Nutr 2008; 62: 1273-1281.

[3] Schwartz JM, Wolford JL, Thornquist MD, Hockenbery DM, Murakami CS, Drennan F, Hinds M, Strasser SI, Lopez-Cubero SO, Brar HS, Ko CW, Saunders MD, Okolo CN and McDonald GB. Severe gastrointestinal bleeding after hematopoietic cell transplantation, 1987-1997: incidence, causes, and outcome. Am J Gastroenterol 2001; 96: 385-393.

[4] Sun X, Su Y, Liu X, Zhang Y, He Y, Han W, Chen Q, Chen H, Wang Y, Cheng Y, Liu F, Wang F, Chen Y, Zhang G, Mo X, Fu H, Chen Y, Wang J, Zhu X, Xu L, Liu K, Huang X and Zhang X. Overt gastrointestinal bleeding following haploidentical haematopoietic stem cell transplantation: incidence, outcomes and predictive models. Bone Marrow Transplant 2021; 56: 1341-1351.

[5] Labrador J, Lopez-Anglada L, Perez-Lopez E, Lozano FS, Lopez-Corral L, Sanchez-Guijo FM, Vazquez L, Perez Rivera JA, Martin-Herrero F, Sanchez-Barba M, Guerrero C, del Cañizo MC, Caballero MD, San Miguel JF, Alberca I and Gonzalez-Porras JR. Analysis of incidence, risk factors and clinical outcome of thromboembolic and bleeding events in 431 allogeneic hematopoietic stem cell transplantation recipients. Haematologica 2013; 98: 437-443.

[6] Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ and Streiff MB. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. Blood 2008; 112: 504-510.

[7] Pihusch R, Salat C, Schmidt E, Göhring P, Pihusch M, Hiller E, Holler E and Kolb HJ. Hemostatic complications in bone marrow transplantation: a retrospective analysis of 447 patients. Transplantation 2002; 74: 1303-1309.

[8] Shearer MJ, Fu X and Booth SL. Vitamin K nutrition, metabolism, and requirements: current concepts and future research. Adv Nutr 2012; 3: 182-195.

[9] Sinhadri BCS, Jin DY, Stafford DW and Tie JK. Vitamin K epoxide reductase and its paralogous enzyme have different structures and functions. Sci Rep 2017; 7: 17632.

[10] Labrador J, López-Corral L, Vazquez L, Sánchez-Guijo F, Guerrero C, Sánchez-Barba M, Lozano FS, Alberca I, Del Cañizo MC, Caballero D and González-Porras JR. Incidence and risk factors for life-threatening bleeding after allogeneic stem cell transplant. Br J Haematol 2015; 169: 719-725.
[11] Bacigalupo A. Haemopoietic stem cell transplants: the impact of haemorrhagic complications. Blood Rev 2003; 17 Suppl: S6-10.
[12] Dumler JS, Beschorner WE, Farmer ER, Di Gennaro KA, Saral R and Santos GW. Endothelial-cell injury in cutaneous acute graft-versus-host disease. Am J Pathol 1989; 135: 1097-1103.
[13] Franchini M, Frattini F, Crestani S and Bonfanti C. Bleeding complications in patients with hematologic malignancies. Semin Thromb Hemost 2013; 39: 94-100.
[14] Antoniak S and Mackman N. Multiple roles of the coagulation protease cascade during virus infection. Blood 2014; 123: 2605-2613.
[15] Levi M and van der Poll T. A short contemporary history of disseminated intravascular coagulation. Semin Thromb Hemost 2014; 40: 874-880.
[16] Coppell JA, Richardson PG, Soiffer R, Martin PL, Kernan NA, Chen A, Guinan E, Vogelsang G, Krishnan A, Giralt S, Revta C, Carreau NA, Iacobelli M, Carreras E, Ruutu T, Barbui T, Antin JH and Niederwieser D. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. Biol Blood Marrow Transplant 2010; 16: 157-168.
[17] Batts ED and Lazarus HM. Diagnosis and treatment of transplantation-associated thrombotic microangiopathy: real progress or are we still waiting? Bone Marrow Transplant 2007; 40: 709-719.
[18] Eissner G, Multhoff G, Gerbitz A, Kirchner S, Bauer S, Haffner S, Sondermann D, Andreesen R and Holler E. Fludarabine induces apoptosis, activation, and allogenicity in human endothelial and epithelial cells: protective effect of defibrotide. Blood 2002; 100: 334-340.
[19] Långström S, Koskenvuo M, Huttunen P, Lassila R, Taskinen M, Ranta S, Heikinheimo M and Mäkipernaa A. Haematopoietic stem cell transplantation in children shifts the coagulation system towards a pro-coagulant state. Thromb Haemost 2018; 118: 1390-1396.
[20] Carreras E and Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. Bone Marrow Transplant 2011; 46: 1495-1502.
[21] Pinomäki A, Volin L, Joutsi-Korhonen L, Virtanen JO, Lemponen M, Ruutu T and Lassila R. Early thrombin generation and impaired fibrinolysis after SCT associate with acute GVHD. Bone Marrow Transplant 2010; 45: 730-737.
[22] Pihusch M, Bacigalupo A, Szer J, von Depka Prondzinski M, Gaspar-Blaudschun B, Hyveled L and Brenner B. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. J Thromb Haemost 2005; 3: 1935-1944.
[23] Araki S and Shirahata A. Vitamin K deficiency bleeding in infancy. Nutrients 2020; 12: 3.
[24] Lippi G and Franchini M. Vitamin K in neonates: facts and myths. Blood Transfus 2011; 9: 4-9.
[25] Schurgers LJ and Vermeer C. Differential lipoprotein transport pathways of K-vitamins in healthy subjects. Biochim Biophys Acta 2002; 1570: 27-32.
[26] Goncalves A, Margier M, Roi S, Collet X, Niot I, Goupy P, Caris-Veyrat C and Reboul E. Intestinal scavenger receptors are involved in vitamin K1 absorption. J Biol Chem 2014; 289: 30743-30752.
[27] Vermeer C and Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. Hematol Oncol Clin North Am 2000; 14: 339-353.
[28] Alperin JB. Coagulopathy caused by vitamin K deficiency in critically ill, hospitalized patients. JAMA 1987; 258: 1916-1919.
[29] Dahlberg S, Schött U and Kander T. The effect of vitamin K on prothrombin time in critically ill patients: an observational registry study. J Intensive Care 2021; 9: 11.
[30] Britt RB and Brown JN. Characterizing the severe reactions of parenteral vitamin K1. Clin Appl Thromb Hemost 2018; 24: 5-12.
[31] Fan J, Armitstead JA, Adams AG and Davis GA. A retrospective evaluation of vitamin K1 therapy to reverse the anticoagulant effect of warfarin. Pharmacotherapy 2003; 23: 1245-1250.