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The effect of High Intensity Interval Exercise on Platelet Engraftment in Autologous Bone Marrow Transplantation (BMT)

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ABSTRACT

Background: Thrombocytopenia is a frequent complication after hematopoietic stem cell transplantation (HSCT). Although platelet transfusion is the most used treatment for severe thrombocytopenia, it is associated with well-established risks. High-intensity interval exercise (HIIE) results in thrombocytosis. Therefore, this study aimed to reduce thrombocytopenia by increasing platelet count through exercise.

Materials and Methods: Twenty lymphoma and multiple myeloma patients were divided into HIIE and control groups. To determine the maximal exercise capacity, patients in the HIIE group performed a graded exercise test. All patients received granulocyte colony-stimulating factor for 5 days, followed by a HIIE trial. After 5 min warm up at 10 to 20% of peak power, patients in the HIIE group performed an HIIE protocol that included 12 intervals of one-minute work at 100% peak power interspersed by one-minute active rest at 20% of peak power. Patients in the control group were seated for the same duration without any physical activity. Two blood samples were taken before and immediately after the trials and were analyzed for measuring complete blood count.

Results: Platelet count on the day of platelet engraftment in the HIIE group was significantly higher than in the control group (P=0.02). Single-donor platelet transfusion was significantly lower in the HIIE group than in the control group (P=0.05).

Conclusion: Based on the findings of the present study, a short bout of HIIE had a positive effect on platelet engraftment through thrombocytosis and reduced platelet transfusion and its complications, which could be a useful strategy for HSCT patients.

Keywords: HSCT; Autologous transplantation; Thrombocytosis; Thrombocytopenia; Platelet transfusion

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a type of cancer treatment using hematopoietic stem cells from the patient (autologous) or a donor (allogeneic)[1]. Thrombocytopenia, an abnormally low blood platelet count, is a consecutive complication after HSCT[2]. Nearly 40-68% of patients with a hematologic malignancy experience thrombocytopenia as a common side effect of myelosuppressive chemotherapy.[3] The incidence of thrombocytopenia was highest in patients with multiple myeloma (37.3%) and with non-Hodgkin lymphoma (24.4%)[3]. The predominant issue associated with chemotherapy-induced thrombocytopenia is the necessity for hospitalization to address active bleeding and administer platelet transfusions. Despite this, no standardized guidelines are available for the prevention or treatment of this condition[3].

Thrombocytopenia results from abnormal platelet production in the bone marrow, accelerated platelet breakdown, or sequestration of platelets in the

spleen[4]. Ineffective platelet production is found in bone marrow failure syndromes or bone marrow occupying processes[4]. Increased platelet degradation is detected in conditions such as thrombotic microangiopathy, diffuse intravascular coagulation, and immune thrombocytopenia[4]. Additionally, recent reports indicate that administering granulocyte colony-stimulating factor (G-CSF) can lead to thrombocytopenia by preventing hematopoietic progenitors from differentiating into megakaryocytes[5]. G-CSF is generally used to mobilize and collect hematopoietic stem cells from donors and treatment of neutropenic patients.[5] G-CSF is recommended after autologous HSCT and could accelerate granulocyte engraftment and recovery by 1–6 days[6]. Using marrow rather than peripheral blood as the source of stem cells and acute myeloid leukemia are significant risk factors for delayed platelet engraftment after autologous HSCT.[7]Infection with cytomegalovirus, a member of the herpesvirus family, is one of the most common complications following transplantation.[8] Positive cytomegalovirus and infection post-transplant before engraftment are additional risk factors for platelet recovery[7].

Delayed platelet recovery can be managed by transfusion of blood products[7]. When the platelet count is less than $10\times10^3/\mu L$, platelet transfusion is needed in patients with thrombocytopenia[9].The need for platelet transfusion after HSCT is less when the source of stem cells is peripheral blood rather than marrow[7]. Delayed platelet recovery has been linked to lower survival rates following HSCT. The ability to reach a certain platelet count by day 60 for autologous HSCT and day 100 for allogeneic HSCT can serve as a crucial indicator of the likelihood of survival[7].

The American College of Sports Medicine (ACSM) recommends general exercise prescriptions for cancer survivors[10]. In addition, recent suggestions indicate that physical exercise is both safe and beneficial for thrombocytopenic patients with hematologic malignancies[9]. However, the ACSM affirms the absence of experimental studies regarding exercise in patients with thrombocytopenia; thus recommendations for exercise prescription in these patients are largely subjective and not evidence-based[9].

Thrombocytosis is a non-malignant increased concentration of platelets in the blood circulation [11]. Exercise-induced thrombocytosis has been reported to occur after intense exercise[11]. Acute exercise results in a transient increase in platelet count caused by platelet release from the liver, lungs, and spleen[11]. High-intensity interval exercise (HIIE) includes frequent high-intensity physical activity combined with low-intensity or intermittent activity intervals[12]. Increases in platelet count following HIIE trial is significantly more than moderate continuous exercise[13]. Acute responses in platelet count to different HIIE modes—specifically work/rest ratios of 1:1 and 1:7—revealed that the 1:1 protocol led to a more significant increase in platelet count. This finding suggests that the work-to-rest ratio is a crucial factor when studying changes in platelet levels following HIIE[14] Besides, indicatively, catecholamine changes after HIIE are more significant than continuous exercise[15].

Since acute exercise can boost platelet count, and HIIE is a safe and viable exercise option for thrombocytopenic patients with hematologic malignancies[9], this study hypothesizes that acute HIIE might promote beneficial thrombocytosis in patients eligible for autologous HSCT. To our knowledge, no previous study has investigated the effect of HIIE on platelet engraftment after HSCT. Therefore, this study aimed to determine if exercise reduces thrombocytopenia and its complications after HSCT by increasing platelet count.

MATERIALS AND METHODS

Patients

Eleven male and nine female patients (n =20) candidates for autologous HSCT voluntarily participated in this study, and informed consent was obtained from all (Table 1). The study involved 20 patients: 13 with Hodgkin's lymphoma, two with non-Hodgkin's lymphoma, and five with multiple myeloma. These patients were randomly assigned to two homogeneous groups—HIIE and control—based on their type and history of the disease, age, and body mass index. The inclusion criteria were body mass index of less than 30, no history of

cardiovascular and pulmonary disease, diabetes, autonomic dysfunction, kidney disease, hepatitis, non-smoker, successful exercise testing up to the fourth stage of the test, and no joint or mobility problems. The exclusion criteria included inability to perform exercise protocol, failure in physician medical examination, symptoms of cessation of exercise such as chest pain, dizziness, nausea, dyspnea, and sagging ST. Prior to the study, all procedures, including exercise tests, exercise protocols, and blood sampling procedures, were thoroughly explained to patients. Additionally, written consent was obtained from participants. This study adhered to standard ethical guidelines for research in humans and received approval from the university's Ethics and Research Degree Committees (IR.SBMU.REC.1400.017).

Table 1: Patient and transplant characteristics (mean±SD)

Characteristics	Control (N=10)	HIIE (N=10)
NH L/HL/MM (number)	2/5/3	0/8/2
Age (years)	33.1±9.6	32.2±11.6
BMI (kg/m^2)	25.9±9.2	27.3±4.8
HR $_{rest}$ (bpm)	87.5±7.7	92.5±7.7
Systolic Blood Pressure (mmHg)	113±10	121±10
Diastolic Blood Pressure (mmHg)	71.0±5.7	75.0±10.8
Day of engraftment (days)	11.1±1.6	11.4±1.7
Neutrophil count in Engraftment (×10^3/uL)	733±150	740±142
No. of G-CSF administration before HSCT (days)	5.60±1.17	5.10±1.05
No. of G-CSF administration before HSCT (dose)	12.7±3.7	11.9±2.3
No. of G-CSF administration after HSCT (days)	8.80±2.37	7.60±3.31
No. of G-CSF administration after HSCT (dose)	14.1±7.5	10.9±5.3
CMV Ab (CEL)		
IgG (U/ml)	25.8±10.5	32.2±12.2
IgM (U/ml)	4.70±1.82	3.69±2.84

NHL= non-Hodgkin's lymphoma, HL= Hodgkin's lymphoma, MM=multiple myeloma, HIIE= high intensity interval exercise, BMI= body mass index, HR=heart rate, G-CSF= Granulocyte- colony stimulating factor, HSCT= Hematopoietic stem-cell transplantation, CMV Ab= Cytomegalovirus Antibody, IgG= Immunoglobulin G, IgM= Immunoglobulin A

Experimental design

To determine peak power output, patients in the HIIE group performed a graded exercise test (GXT) on the first day of hospitalization. This GXT protocol, commonly used for patients with solid tumors, follows the guidelines recommended by the ACSM.[16] After 5 min of warm-up and stretching exercises, the test began with an initial power of 20 watts, and the power was increased every minute by 10 watts until exhaustion. During the GXT, heart rate was continuously measured using a pulse oximeter. Accordingly, patients were asked to rate their perceived pressure every minute at the end of each step, based on a 6 to 20 Borg rating of perceived exertion (RPE). Peak power was determined based on a score of 20 on the Borg RPE. Five days after determining peak power (washout), patients received G-CSF for five days. HIIE protocol was performed 6 hours after the last stage of drug administration. Patients in the HIIE group performed 5 min warm up at 10 to 20% of peak power, followed by 24 min HIIE protocol. HIIE included 12 intervals of one-minute cycling at 100% of peak power interspersed by one-minute active rest at 20% of peak power. Patients in the control group were seated for the same duration without physical activity. Two blood samples were taken before and immediately after the trials.

Blood sampling and laboratory methods

Blood samples (3 mL) were taken before and immediately after the HIIE protocol and daily after HSCT in a seated position, using a catheter from the cervical vein. Blood was collected in tubes containing EDTA to test for complete blood count (CBC) using a cell counter (Cell Counter Sysmex, KX21, Japan). Anti-cytomegalovirus levels antigen antibodies (CMV-IgM, CMV-IgG) were detected via chemiluminescence analysis (CLIA, LIAISON® CMV IgG II and LIAISON® CMV IgM II, DiaSorin, Italy). Systolic and diastolic blood pressure was measured in a seated position once before exercise (Omron M3, Japan).

The day of the stem cell transplantation was defined as day 0. Engraftment was confirmed by peripheral blood counts (myeloid: peripheral absolute neutrophil count of more than $0.5\times10^3/\mu L$, megakaryocyte: peripheral platelet counts of more than $20\times10^3/\mu L$ for at least three consecutive days without requiring transfusion). Packed cell and platelet transfusions were recorded (by counting the administered units) during the hospitalization period. The packed cell was transfused in patients with hemoglobin (Hb) <7g/dL and platelet transfusions were administered when the platelet count of patients was under 20,000/µL or had clinical bleeding[17]. The platelet-rich plasma method prepared single donor platelets (SDP) with an apheresis technique and random donor platelets (RDP). One RDP unit contains platelets concentrated in 40-70 ml of plasma, and one SDP unit is concentrated in 200-300 ml – between five and six units of RDP are equivalent to one unit of SDP[18].

Statistical analyses

SPSS software version 22 was used for all data analyses. Shapiro-Wilk test was used to determine the normal distribution of data. The data for platelet count on the day of platelet engraftment and blood product transfusion in two groups were compared using an independent t-test and Mann-Whitney U test, respectively. The CBC variables (pre- and post-exercise values) in two groups were compared using repeated measures of ANOVA with between-subjects factor. Values in the text are presented as mean (±SD) noted otherwise. The significance level was set at $p\leq0.05$.

RESULTS

Statistical data analyses showed no significant differences among the pre-exercise values for patients and transplant characteristics. Even though the control group used G-CSF more frequently and at higher doses after HSCT than the HIIE group, the difference was not statistically significant (P>0.05). Furthermore, there was no significant difference in neutrophil engraftment (P=0.24, Table 1).

The platelet count on the day of platelet engraftment was significantly higher (P=0.02) in the HIIE group compared to the control group (Figure 1).

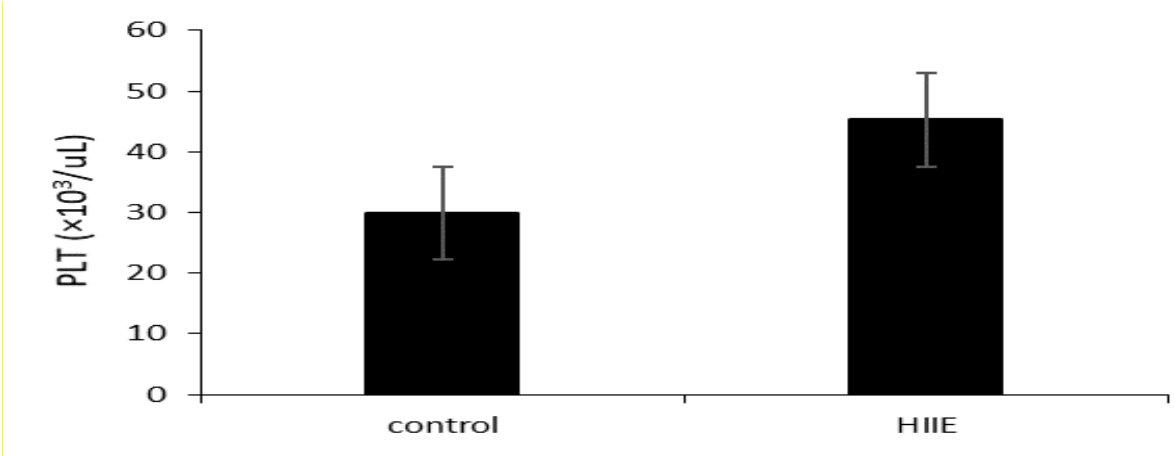

Figure 1. Platelet count (mean±SD) at the day of platelet engraftment following HSCT in HIIE and control groups. * Shows significant difference with control group (P < 0.05).

Single-donor platelet transfusion was significantly lower in the HIIE group than in the control group (P=0.05). Although random donor platelet transfusion in the HIIE group was lower than in the control group, this difference was not statistically significant (P=0.35). Packed cells were injected less in the HIIE group, though the differences did not reach to the significance level (P=0.85, Table 2).

Table 2: RBC and platelet transfusion (units)

Blood product	control	HIIE
RBC transfusion (U)	9	5
Platelet transfusion Random Donor (U)	106	77
Platelet transfusion Single Donor (U)	17	3*

*Shows significant difference with control group (P< 0.05). HIIE= high intensity interval exercise, RBC= red blood cell.

Platelet count and mean platelet volume were significantly higher in the HIIE group instantly after exercise (P<0.05), but no significant differences were found between the two groups for other blood cell indices (P>0.05, Table 3).

Table 3: The pre and post values of CBC variables (mean±SD) in HIIE and control groups

CBC	control		HIIE	
	Pre	Post	pre	post
WBC (×10³/uL)	45.0±10.6	51.4±10.9	34.4±6.2	40.4±8.5
RBC (×10⁶/uL)	3.4±0.1	4.3±0.3	4.4±0.6	4.9±0.3
HGB (g/dL)	10.8±0.5	13.4±0.5	12.7±1.8	13.8±1.2
HCT (%)	31.0±0.9	37.4±1.8	35.9±3.7	39.8±2.7
MCV (fL)	92.1±1.0	88.2±2.5	81.3±5.8	82.9±6.3
MCH (pg)	31.8±1.0	31.8±1.3	28.4±2.3	29.1±2.5
MCHC (g/dl)	34.7±1.3	35.9±0.5	33.3±3.0	35.4±1.7
PLT (×10³/uL)	156±46	167±45	159±70	199±48*
RDW (%)	14.9±1.1	14.3±0.9	14.4±1.0	15.1±1.2
PDW (%)	12.7±0.9	13.2±1.5	13.1±1.5	14.0±1.7
MPV (fL)	9.50±0.5	9.80±0.7	9.20±0.3	10.0±0.6*

* Shows significant difference with control group (P< 0.05). CBC, complete blood count; HIIE, high intensity interval exercise; WBC, white blood cell; RBC, red blood cell; HGB, Hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet; RDW, red cell distribution width; PDW, platelet distribution width; MPV, mean platelet volume.

DISCUSSION

This study is the initial one to demonstrate the beneficial impact of HIIE on platelet engraftment in patients with lymphoma and multiple myeloma following HSCT. This is due to the relationship between platelet engraftment and the quantity of CD34 cellsin the transplantation[7]. One possible explanation for the higher platelet count on engraftment day is the exercise-induced increases in the number of CD34 cells. The CD34 cells were not measured in the present study. However, previous studies had confirmed exercise-induced CD34 mobilization via activation of the sympathetic nervous system in an intensity-dependent manner[19]. Increased production of cytokines and mobilizing factors in response to exercise have been suggested as mechanisms responsible for exercise-induced CD34 mobilization[19]. Poor stem cell transplantation is the most common reason for insufficient platelet production relative to platelet demand that might be related to insufficient stem /progenitor cells or accessory cells mobilized by G-CSF for transplantation[7]. Therefore, HIIE-induced increased CD34 might have provided more stem cells for transplantation and resulted in more platelet production in engraftment days.

Moreover, increased platelet counts following HIIE could positively impact platelet engraftment in this study. This is particularly significant given that thrombocytopenia before HSCT can delay the time it takes for platelet engraftment[20]. Platelet count before HSCT can reflect the bone marrow situation, predicting hematopoietic engraftment[20]. Reportedly, G-CSF administration can result in thrombocytopenia in patients by inhibiting the differentiation of common myeloid progenitors and megakaryotic erythroid progenitors into megakaryocytes and following platelet formation[21]. The present study confirms findings from previous research that HIIE-induced thrombocytosis increases platelet count[11,13,14]. Therefore, HIIE-induced thrombocytosis may have reversed the thrombocytopenia caused by G-CSF administration. Elevated sympathetic nervous system activity during exercise is a contributing factor to the development of thrombocytosis post-exercise[22]. Increased circulating catecholamine concentrations result in spleen contraction and platelet secretion, increasing the platelet count[22]. In the current study, increased mean platelet volume after HIIE confirms that increased platelet count results from large platelets released from the spleen[14]. Since thrombocytopenia is an early indicator of bone marrow failure, HIIE may increase the likelihood of successful transplantation in this study. In addition, platelet engraftment in HIIE group was not affected by cytomegalovirus (CMV). CMV-induced thrombocytopenia through inhibiting the hematopoiesis, might be associated with platelet engraftment[20]. In addition, the blood product transfusion (SDP, RDP), associated with platelet engraftment, had a negative correlation with pre-transplant platelet count[20]. Although in this study, no significant correlation was found, the HIIE group, which had a higher pre-transplant platelet count, required fewer blood transfusions.

One of the crucial findings of the present study was lower SDP administration in the HIIE group. Indicatively, the elevated platelet count on the engraftment day in the HIIE group was not due to platelet transfusions. The current study suggests that HIIE might promote platelet engraftment by enhancing bone marrow function. This is particularly relevant for patients who need more blood components, as their bone marrow tends to be less functional[18]. Platelet transfusion is one of the main approaches to supplement platelets when the platelet count is less than 10×10^3 /μL or there are any hemorrhagic manifestations[23]. Besides, the patients undergoing HSCT use more than 50% of platelet concentrates18. Although platelet transfusions are the highly-used treatment approach for severe thrombocytopenia in post-HSCT patients, they are associated with well-established risks, such as transfusion reactions and alloimmunization[24]. Blood product transfusion is associated with allergic and immunologic reactions leading to transplant-related morbidity and mortality[18]. SDP has some benefits compared to RDP, including less donor exposure, reduced septic/infectious and non-infectious platelet transfusion reactions, and decreased febrile transfusion reactions[18]. Therefore, lower SDP administration in the HIIE group should be considered an essential finding in the present study.

The influence of exercise on hematopoiesis is not well-defined, as the mechanism or mechanisms responsible for this effect are still unclear[25]. HIIE as an acute exercise can increase spleen expression of stem cell factor and stromal cell-derived factor-1 associated with hematopoiesis[25]. In addition, transforming growth factor-β (TGF-β), which plays an essential role in regulating human hematopoietic stem/progenitor cell quiescence, proliferation, and differentiation[26] can increase after HIIE[27]. Therefore, increased TGF-β following HIIE can probably be a responsible mechanism for the accelerated hematopoiesis process.

The increase of von Willebrand factor (vWF) as a transcription factor that regulates megakaryopoiesis was confirmed in response to acute exercise[28,29]. vWF expression is identified as a discriminating marker of an HSC state primed for platelet production in response to thrombopoietin. Reportedly, enhanced vWF-GPIb interactions in patients with disease type 2B improve platelet production. Moreover, cultured megakaryocytes produced self-associated and interwoven proplatelets, and vWF was not only associated with platelets but also located on the megakaryocyte's surface[28]. Therefore, vWF may uniquely function in megakaryopoiesis and platelet production. These findings suggest that the exercise-induced increase in vWF may positively affect megakaryopoiesis. In addition, one HIIE session reduced colon cancer cell progression, probably through increased apoptosis and cytokine (TNF-α, IL-6, and IL-8) concentrations[30]. On the other hand, after HSCT, patients are at higher risk for infection if the neutrophil count (leukocytes) is less than 0.5×10^3 / μL[31]. In this study, HIIE did not affect the neutrophil count. The negative effects of acute and intense exercise, such as ROS or apoptosis of neutrophils[32,33], have possibly counteracted exercise-induced increased CD34 and then caused no effect on neutrophils. Although the neutropenia days in our study were lower in the HIIE group, this difference was not statistically significant. Prolonged neutropenia after HSCT can lead to infection, one of the vital causes of morbidity in patients[6]. G-CSF used pre-transplantation to mobilize hematopoietic stem cells into peripheral blood is commonly used post-transplantation to enhance stem cell engraftment and minimize the risk of morbidity and mortality related to prolonged neutropenia[6]. Although in most of the studies, time to neutrophil engraftment was significantly shorter when G-CSF was used after transplantation, no significant difference in platelets engraftment was reported[6]. This study confirmed this because G-CSF administration did not lead to significant differences between the two groups.

Based on the literature, increases in platelet engraftment following HIIE in the present study could be attributed to acute exercise-induced rises in CD34, platelet count, apoptosis, cytokine (TNF-α, IL-6, and IL-8), and transcription factors such as vWF. This was the first study to demonstrate a reduced need for platelet transfusion in response to acute exercise, because HIIE resulted in higher platelet count (thrombocytosis) at the day of platelet engraftment. Therefore, HIIE can reduce the risk of bleeding and the need for platelet injection in patients after HSCT.

Some limitations in this study might have affected the results. Although the groups were matched for the type of disease, their disease history and conditioning regimens were not monitored. Moreover, this investigation were not able to control the diet during hospitalization. The research investigated the influence of a solitary exercise session, yet conducting multiple exercise trials may lead to more promising results. As a result, future studies should be conducted to explore this issue further. Additionally, evaluating other factors linked to exercise-induced engraftment (including CD34, stem cell factor, stromal cell-derived factor-1, TNF-α, IL-6, IL-8, and vWF) would help solidify the conclusions.

CONCLUSION

Based on this study's key findings, patients in the HIIE group had higher platelet counts on the day of platelet engraftment and required fewer platelet transfusions. This suggests that a single session of HIIE could potentially lower the risk of platelet transfusions for patients undergoing autologous HSCT. Therefore, incorporating this type of exercise in HSCT centers might help reduce the need for transfusions and other complications related to low platelet counts in these patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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