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A Comparison of the Effect of Two Types of Continuous and Discontinuous Aerobic Exercise on Patients' Stem Cell Mobilization before Autologous Hematopoietic Stem Cell Transplantation

Kimia Kasravi[1], Farshad Ghazalian[1], Abbasali Gaeini[2], Abbas Hajifathali[3], Mandana Gholami[1]

[1]Department of Physical Education and Sport Sciences, Faculty of Literature, Humanities and Social Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran
[2]Department of Exercise Physiology, Faculty of Physical Education and Sport Sciences, University of Tehran, Tehran, Iran
[3]Taleghani Bone Marrow Transplantation Center, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author: Farshad Ghazalian, Department of Physical Education and Sport Sciences, Faculty of Literature, Humanities and Social Sciences, Science and Research Branch, Islamic Azad University, Tehran, Iran
Tel: +98 (21) 44868488
Email: f.ghazalian@srbiau.ac.ir

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ABSTRACT

Background: Transplant success largely depends on the number of hematopoietic stem cells. The release of catecholamines following exercise can, as a treatment in addition to medication, affect the mobilization of stem cells from the bone marrow into the peripheral blood. The aim of the present study is to compare two types of aerobic exercise on stem cell mobilization before autologous transplantation.

Materials and Methods: In a quasi-experimental applied study, 60 patients in the age range of 22-69 years referred to Taleghani Hospital were randomly selected and assigned into 3 groups of 20 members (continuous aerobic, discontinuous aerobic and control group). Aerobic exercise program was performed for 7 consecutive days of mobilization period including walking on a treadmill (according to the patient's ability) continuously and discontinuously for 30 minutes in the morning and afternoon. Blood samples were taken the morning before and after mobilization and the CD34 and MNC levels were counted as absolute. Chi-square test, paired t-test, analysis of covariance (ANCOA) and multiple comparison test were used for statistical analysis. All analyses were considered significant at $p \leq 0$.

Results: Moderate-intensity continuous and discontinuous aerobic activity increases the number of CD34 and MNC cells. A comparison between continuous and discontinuous aerobic activity showed an increase in the amount of these cells. The continuous aerobic activity group was found to have a statistically significant increase compared to the discontinuous group ($P \leq 0.05$).

Conclusion: Moderate intensity continuous and discontinuous aerobic exercise significantly increased hematopoietic stem cells. However, this increase was greater as a result of continuous aerobic exercise than discontinuous exercise. Regarding the potential role of these cells in transplantation, they could possibly help the transplant process.

Keywords: Aerobic exercise; Mobilization; Hematopoietic stem cells; Autologous transplantation

INTRODUCTION

Cancer is the second leading cause of death in the world, and in Iran, 100 people die every day because of this[1]. Malignant neoplasm is medically known as a malignant that has an uncontrollable growth process in cell reproduction[2]. Transplantation of hematopoietic stem cells is required for the treatment of many malignant and non-malignant blood diseases[3]. In hematopoietic stem cell transplantation, patients' hematopoietic cells and immune system are removed and replaced with stem cells from another person (allogeneic) or from the patients' themselves (autologous), some of which have already been collected from peripheral blood[4]. The success of the transplant depends largely on the size of the CD34 and MNC cells. The higher the number of cells, the faster the transplant and the sooner the patient is discharged[5]. Stem cells make up 1% of bone marrow nucleated cells and 0.1% of peripheral blood mononuclear cells[6]. Mobilization is the process of moving these cells into the peripheral blood, which is mostly present in the bone marrow[6]. Granulocyte-colony-stimulating factor (G-CSF) is used to stimulate the proliferation of bone marrow CD34 and MNC cells into the peripheral blood. However, the use of this drug is associated with many side effects such as severe bone pain and nausea[7]. On the other hand, getting enough cells during apheresis is very important. Hematopoiesis is a complex process that is influenced by several hormones, cytokines and growth factors[8]. Exercise affects the concentrations of several cytokines and hormones that stimulate self-division, proliferation, and hematopoietic stem cell proliferation. Increased concentrations of Tumor Necrosis Factor-α, Interleukin 1 beta, interleukin 6 and interleukin receptor antagonist and granulocyte colony stimulating factor (G-CSF) were observed after exercise[8-11]. Exercise, which causes these changes in the activity of these factors, affects bone marrow function. The secretion of catecholamines during and after exercise is completely independent of G-CSF and increases stem cell mobilization[12]. Some studies show that exercise sends hematopoietic stem cells from the bone marrow to the peripheral circulation and can significantly increase the number of CD34 cells in the peripheral circulation[13]. In a study, Cheng et al. showed an increase in the incidence of hematopoietic factors under the influence of low-intensity physical activity in transplant patients[14]. Van Kerinenbrook et al. reported an increase in stem cells after a period of increased exercise activity on a work bike [15]. Mobius Winkler et al. showed that CD34 cells increased in patients after 4 hours of cycling[16]. In contrast, Adams et al. reported that hematopoietic stem cells decreased immediately after the marathon[17]. In another study, Bansignor et al. showed that CD34 cell counts remained unchanged after the marathon, but increased by 1.5 km after a field test[18]. However, in a study by Locardo et al., examining the effect of a one-time exercise on a treadmill for 30 minutes observed no significant changes in stem cells[19]. A review of previous research shows that according to the above points, there are contradictory results in the field of exercise and its effect on the number of stem cells, and most studies have focused on the effect of exercise on cell count. Therefore, a research on different types of exercise programs with different protocols and comparing its effect on the number of cells can solve one of the problems of this defect and answer the question whether there is a difference between the effect of two types of continuous and discontinuous aerobic exercise on stem cell mobilization of patients before autologous hematopoietic stem cell transplantation.

MATERIALS AND METHODS

In a clinical trial with trial code IRCT20140818018842N18, ethics code of Shahid Beheshti University of Medical Sciences IR.SBMU.REC.1398.152 and clinical trial ID 44758 in 1398, 60 patients were candidates for autologous hematopoietic stem cell transplantation for cancer treatment in Taleghani Hospital, Tehran, Iran. According to the inclusion criteria, patients were randomly assigned into three groups of 20 members (continuous aerobic group of 20 people, discontinuous aerobic group of 20 people and control group of 20 people). Written informed consent was also obtained from all participants. Patients had mean age of 50.28±12.11 years and a mean body mass index of 26.16±3.47 kg/m2.

Inclusion criteria for patients were as follows: a) diagnosis of leukemia based on cellular pathology b) the ability to walk on a treadmill. C) absence of chronic diseases such as hypertension, heart disease, respiratory and allergies, diabetes and kidney failure, etc. d) no previous history of treatment and radiotherapy. e) Mobilization with a single drug and same injection method (In all patients, GCSF was used to stimulate cells during the mobilization period). The treatment protocol was performed uniformly (The use of the main drug Melphalan at a dose of 100 to 120 mg). Exclusion criteria were as follows: a) patient's request to exclude the study b) discontinuation of continuous aerobic exercise more than one consecutive session c) discontinuation of interval aerobic exercise for more than one consecutive session d) failure to perform at least continuous aerobic training sessions daily during the mobilization period, e) hemoglobin drop below 8 f) decreased platelet below 5,000 g) indication of fever and neutropenia. Aerobic exercise program included 30 minutes walking on a treadmill (depending on the patient's ability, in a three 10-minute boot or two 15-minute boot) in the morning and afternoon for 7 consecutive days of mobilization. RPE (rating of perceived exertion) of the intensity of exercise activity based on the Borg scale is equivalent to the average intensity and speed of 50 to 60% of the most oxygen consumption. In order to perform the treatment, First, the patient became familiar with treadmill walking, RPE scale to measure maximum speed, and ability to report his condition on the treadmill to find out the degree of fatigue (i.e., if he is very tired, the RPE score is 20, and if there is no pressure, the RPE score is 6). The report received from the patient entered at any time on a sheet placed next to the treadmill. Then, the patient started walking on a treadmill without a slope. A 6-point RPE scale indicates very, very light activity. In each step, the speed was increased. During the work, the researcher talked with the patient regularly until he complained of feeling *breathless.* Afterwards, the moderate-intensity exercise was considered for the patient and the patient's RPE and speed were recorded. In fact, RPE 12 to 14 for each patient is the intensity of activity in which the patient is out of breath and the maximum oxygen consumption is approximately equal to 50 to 60 percent. Based on the latest speed and scale recorded, the person's speed on the treadmill was determined on the following days. The next stage, which is the first day of mobilization, the patient began to walk on the treadmill at a certain speed with full awareness and moderate intensity (continuous samples, depending on the patient's ability for approximately 30 minutes, in a three10-minute boot or two 15-minute boot and discontinuous samples, one15-minute boot in the morning and one 15-minute boot in the afternoon under the supervision of the relevant official). At the beginning of the movement, the patients warmed up their body for a few minutes at a speed of 2 kilometers per hour or less, and then started moving at a certain speed. Five minutes after the movement, the patient reduced the speed, and then after one minute of rest, he continued at the same speed as before. This process continued until the end. (As the condition of these patients are precarious, the length of the activity was based on each individual's ability.) in clinical centers, an abnormal response to exercise stress leads to its discontinuation. At this stage, the intensity of the exercise was specific to each subject and was adjusted for each individual by the researcher and assistants. The subjects can use the water bottle provided to them, if necessary. Due to the presence of a tape recorder in the blood isolation section during the 7-day mobilization period, each subject performed a separate movement, and then a blood sample was taken immediately after the test. On the last day, blood sample, 5 cc in amount, was taken from participants. Similar to the continuous and discontinuous aerobic exercise groups, 5 cc blood samples were taken from the control group in the same period of time (7 days) before and after test. After training tasks and mobilization period (It should be noted that no drug side effects were observed in patients), patients were connected to the cell separator. Absolute number of CD34 and MNC cells in the peripheral blood were calculated using flow cytometer in the beginning of the study, after mobilization period (7 days) and training tasks. Blood samples, 5 cc in amount, were taken from the subjects in two stages: before and after the test. In addition, after collecting the cells, apheresis samples were sent to the transplant laboratory to measure the level of CD34 and MNC. MNC and CD34 levels reported in the graft were recorded by the laboratory.

Statistical analysis

In this research, SPSS statistical software version 24 has been used for statistical analysis. In addition to using descriptive statistics to estimate the mean, range of changes and standard deviation, Chi-square test was used to evaluate the homogeneity of the three intervention groups and control variables of age, weight, height, blood group, body mass index, disease type, marital status and education in the Intervention group and control group. To evaluate the natural distribution of data Shapiro-Wilk test, to compare pre-test and post-test of each group paired T-Test, to compare pre-test and post-test changes of groups with each other analysis of covariance (ANCOVA) test, to compare groups in time General test of linear model and to detect differences between the two groups, multiple comparison (Post-Hoc Test) test were used. All analyses were considered significant at $p \leq 0.05$.

RESULTS

Based on the research findings between intervention and control groups, the characteristics of the subjects are presented in the following Tables.

Table 1: The characteristics of the subjects are presented in the following tables. Based on the research findings, between the intervention and control groups

The significance level	The amount of P		Control	Experimental			Group
P≤0.05	Chi-Square Tests	General (number) percent	(number) percent	Discontinuous aerobics (number) percent	Continuous aerobics (number) percent		characteristic
0.262	2.679	37(61.7%)	10(50%)	12(60%)	15(75%)	Male	Gender (number) percent
		23(38.3%)	10(50%)	8(40%)	5(25%)	Female	
0.725	7.008	2(3.3%)	2(10%)	0(0%)	0(0%)	A-	Blood type (number) percent
		14(23.3%)	6(30%)	4(20%)	4(20%)	A+	
		5(8.3%)	2(10%)	2(10%)	1(5%)	AB+	
		15(25%)	4(20%)	6(30%)	5(25%)	B+	
		2(3.3%)	0(0%)	1(5%)	1(5%)	O-	
		22(36.7%)	6(30%)	7(35%)	9(45%)	O+	
0.641	0.891	11(18.3%)	3(15%)	5(25%)	3(15%)	Single	Marital status (number) percent
		49(81.7%)	17(85%)	15(75%)	17(85%)	Married	
0.469	9.685	23(38.4%)	10(50%)	7(35%)	6(30%)	Diploma and under diploma	Education (number) percent
		37(61.6%)	10(50%)	13(65%)	14(70%)	collegiate	
0.650	2.471	19(31.7%)	5(25%)	7(35%)	7(35%)	Hodgkin's lymphoma	Diagnosis of disease (number) percent
		41(68.3%)	14(70%)	13(65%)	14(70%)	Multiple myeloma	

In terms of gender (P = 0.262), mean age (P = 0.621), body mass index (P = 0.793), blood type (P = 0.725), marital status (P = 0.641), level of education (P = 0.469) and Diagnosis (P = 0.650), there was no statistically significant difference.

Table 2: Anthropometric characteristics of autologous transplant patients of Taleghani Hospital

The significance level	The amount of P F		Control	Experimental		Group
P≤0.05	* ANOVA test	General		Discontinuous aerobics	continuous aerobics	characteristic
0.621	0.480	12.110±50.28	9.534±52.45	13.121±48.95	13.594±49.45	Age (years)
0.793	0.233	3.477±26.16	3.668±25.72	3.914±26.37	2.911±26.39	Body mass index (kg / m2)

Numbers are expressed in terms of standard deviation ± mean.

According to the findings of the study, there was no significant difference among three intervention and control groups.

Table 3: Characteristics of the variables CD34, MNC before training (1) and after training (2)

	Control	**Experimental**			**Group**
Total(60)	Control	Discontinuous aerobics	continuous aerobics		characteristic
0.013±0.043	0.011±0.045	0.015±0.044	0.014±0.041	Before training	CD34 (Cells/ml)
16.36±24.13	7.55±16	9.83±22.15	22.27±34.25	After exercise	
0.732±2.044	0.961±2.163	0.605±2.030	0.591±1.939	Before training	MNC (Cells/ml)
4.50±14.45	3.17±12.36	3.55±13.98	5.34±17.02	After exercise	
	Control	Discontinuous	continuous		
	-7.55±15.95	-9.84±22.10	-22.27±34.20		CD34 mean difference before and after exercise(Cells/ml)
	0.000	0.000	0.000	P≤ 0.05	Significance level (paired t test)
	-3.42±10.19	-3.75±11.95	-5.65±15.08		MNC mean difference before and after training(Cells/ml)
	0.000	0.000	0.000	P≤ 0.05	Significance level (paired t test)

Numbers are expressed in terms of standard deviation ± mean.

Paired t-test was used to detect intergroup differences. There was a statistically significant difference in the number of MNC and CD34 among continuous, discontinuous and control group (p<0.0001) before and after training test.

According to the means, cell counts increased more in the continuous group compared to the discontinuous group.

Table 4: Multiple comparison analysis for separate evaluation of both groups

The significance level	**Mean difference**	**The significance level**	**Mean difference**		**Group**
P≤ 0.05	Group 1 and 2 differences MNC(Cells/ml)	P≤ 0.05	Group 1 and 2 differences CD34(Cells/ml)	2	1
0.028	3.135	0.012	12.103	Discontinuous	continuous
0.001	4.888	0.000	18.253	Control	
0.028	-3.135	0.012	-12.103	continuous	continuous
0.212	1.753	0.192	6.150	Control	
0.001	-4.888	0.000	-18.253	continuous	Control
0.212	-1.753	0.192	-6.150	Discontinuous	

Using Post-Hoc Test analysis (multiple comparison), the exact difference between the two groups in terms of CD34 variable (mean difference between the two groups) was determined. In this way, there was a significant difference between continuous and discontinuous groups (P = 0.012). Moreover, a significant difference was observed between the continuous and control groups (P = 0.000), but no significant difference was observed between the discontinuous and control groups (P = 0.192). There was a significant difference between the continuous and discontinuous groups in terms of MNC variable. (P = 0.028). There was also a significant difference between the continuous and control groups (P = 0.001), but no significant difference was observed between the discontinuous group and the control group (P = 0.212).

Table 5: Analysis of covariance (ANOVA) changes of CD34 and MNC variables according to other variables after transplantation

The significance level P≤ 0.05				Examined variables
MNC.2(Cells/ml)		CD34.2(Cells/ml)		
Comparison between 2 groups	Comparison between 3groups	Comparison between 2groups	Comparison between 3groups	
0.0497	0.0045	0.3203	0.0103	Groups
0.9024	0.10	0.2546	0.0156	Gender
0.8406	0.6389	0.4913	0.8094	Type of disease
0.2090	0.086	0.0076	0.0003	education
0.7275	0.8681	0.3286	0.5082	marital status
0.7523	0.5861	0.0542	0.0191	Blood Type
0.8811	0.9998	0.4523	0.6858	Age
0.0715	0.3229	0.4716	0.8324	Body mass index
0.6284	0.7023	0.8030	0.4297	Number of hospitalization days
		0.5393	0.6400	CD34.1(Cells/ml)
0.1252	0.1817			MNC.1(Cells/ml)

The results of covariance analysis of CD34 variable after transplantation showed that there is a statistically significant difference in CD34 cells among the three study groups after adjusting for confounding variables (P=0.0103). There was a significant difference in CD34 levels after transplantation in terms of sex, education and blood group. Age, body mass index, marital status, body mass index, length of hospitalization, disease status and CD34 before transplantation had no effect on CD34 after transplantation, but analysis indicated an effect of time. As shown in Figure 1, the level of CD34 cells changed after transplantation but no similar changes were observed in all three study groups. Also, there is no significant difference between the two groups, continuous and discontinuous, in terms of CD34 (P = 0.3203). There is a statistically significant difference in the level of CD34 after transplantation in terms of education and blood type. Gender, age, body mass index, marital status, body mass index, length of hospitalization, disease status and CD34 before transplantation had no effect on CD34 after transplantation; only time had positive effect. Moreover, there was a statistically significant difference between the continuous and discontinuous groups in the number of CD34 cells before and after transplantation.

The results of covariance analysis of MNC variable after transplantation showed that this variable after adjusting confounding variables, there was a significant difference between the three groups in terms of MNC (P=0.0045)(Figure 2). In terms of sex, education, blood type, age, body mass index, marital status, number of hospital days, disease status and MNC amount before transplantation had no effect on MNC after transplantation. Only time had effect. As a result, before and after, it has changed in terms of MNC, which means that although it has changed in all three groups before and after transplantation, it has not been the same in all three groups as shown in the chart. There is also a significant difference between the two groups of continuous and discontinuous in terms of MNC (P = 0.0497). In terms of sex, education, blood type, age, body mass index, marital status, number of hospitalization days, disease status and MNC before transplantation had no effect on MNC after transplantation. Only time had effect. As a result, before and after transplantation, they changed in terms of MNC, which means that although they changed before and after transplantation in both groups, it was not the same in both groups.

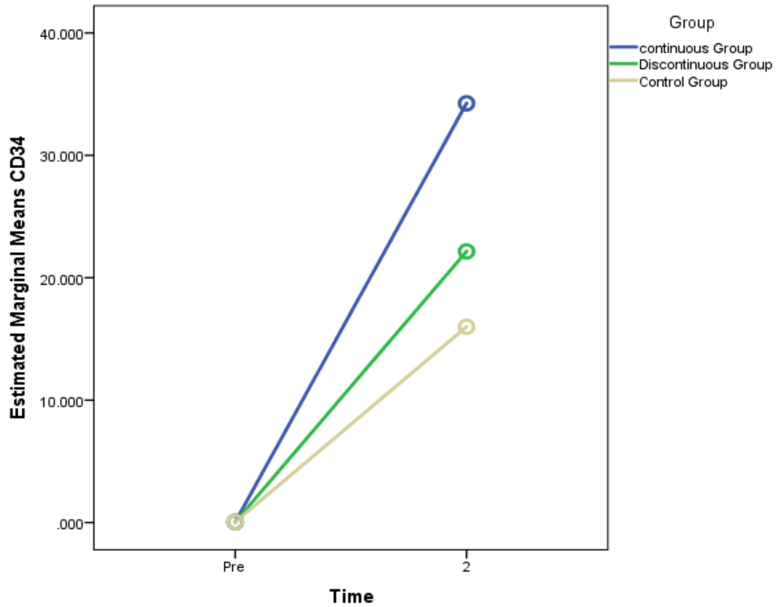

Figure 1. According to the means, Cd34 counts increased more in the continuous group than in the discontinuous group.

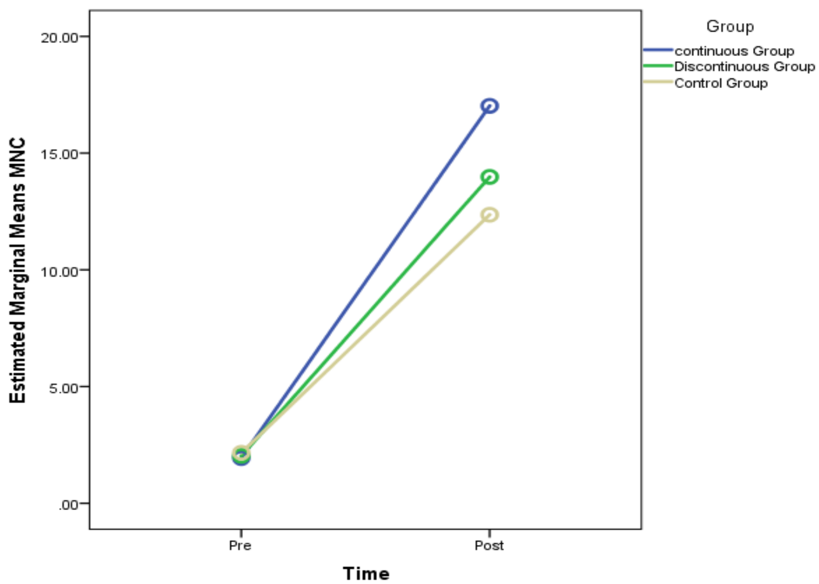

Figure 2. According to the means, MNC counts increased more in the continuous group than in the discontinuous group.

DISCUSSION

Based on the objectives and hypotheses of the study, the parameters of CD34 and MNC in the training group compared to the control group in both continuous and discontinuous aerobic states were significantly increased. The present study compared the effect of two types of continuous and discontinuous aerobic exercise on stem cell mobilization of patients before autologous hematopoietic stem cell transplantation, which showed that these cells as a result of continuous and discontinuous aerobic physical activity significantly increased in both training groups compared to the control group. It can be said that this increase is due to exercise and could be an effective factor in patients who were candidates for autologous transplantation. Moreover, the comparison of continuous and discontinuous aerobic activity revealed that the continuous group had a significantly higher increase than the discontinuous group and was better overall. The success of the transplant depends largely on the amount of CD34 and MNC cells (markers that represent hematopoietic stem cells as measured by a flow cytometer). The higher the number of hematopoietic stem cells, the faster the donor cell replacement in the recipient bone marrow engraftment and the earlier the patient is discharged. Hematopoiesis is a complex process that is influenced by several hormones, cytokines and growth factors[8]. Exercise affects the concentration of several cytokines and hormones that have a stimulating effect on self-division, proliferation and maturation of hematopoietic stem cells. Increased concentrations of tumor necrosis factor alpha, interleukin beta, interleukin 6 and antagonist interleukin receptor and granulocyte colony stimulating factor (G-CSF) were observed after exercise [8-11]. Exercise, which causes these changes in the activity of these factors, affects bone marrow function. Growth hormone is significantly increased in patients with anemia after exercise. Growth hormone (directly or indirectly) stimulates erythroid and myeloid generative colonies through insulin-like growth factor[20-21]. Granulocyte-Macrophage colony stimulating factor (GM-CSF), which acts as a growth factor for white blood cells, interleukins (including interleukins 3 and 6) that stimulate the growth of lymphoid cells and thrombopoietin (TPO) which induce the production and differentiation of megakaryocytes are among the cytokines involved in the proliferation of hematopoietic stem cells. It is also used for the proliferation and differentiation of hematopoietic cells[21]. Meanwhile, G-CSF has been hypothesized to induce the release of specific proteases, which causes decomposition and destruction of the adhesion molecules and chemokines. In particular, CXCL-12 (SDF-1) and its receptor (CXCR4) are considered as key ligands / receptors responsible for the maintenance of HSCS in bone marrow[22]. The secretion of catecholamines increases stem cell mobilization during and after exercise, completely independent of G-CSF[12]. Dynamic exercise as an adjuvant therapy along with drug therapy to increase the mobilization of these cells from the bone marrow to the peripheral blood and increase the number of these cells in the sample of transplant candidates has attracted much attention of researchers in recent years. The findings of this study on CD34 cell proliferation are consistent with the findings of Cheng et al., Van Krinenbrook et al., Gickins et al., and Mobius et al. Cheng et al. (2015) in a study showed that hematopoietic stem cells inside the bone marrow, especially CD34 cells, are called up under the influence of low-intensity physical activity in transplant patients, which is in parallel with the increased incidence of hematopoietic factors [14]. Van Krinen-Brook et al. (2008) reported an increase in stem cells after a period of increased exercise on the bike ergometer, noting that the increase in CD34 cells was less than the increase in CD34 + / KDR + cells, indicating the change and transfer of CD34 multipotent cells to CD34 + / KDR + due to exercise stimulation. Mobius Winkler et al. showed an increase in CD34 cells after 4 hours of cycling with a 70% anaerobic threshold in patients, and therefore found that endurance exercise releases vascular endothelial growth factor and interleukin-6, which are effective in growth and release of CD34 cells. Interleukin-6 is one of the most important factors in increasing the expression of vascular endothelial growth factor and its receptors. Vascular endothelial growth factor plays an important role in the proliferation, migration and differentiation of CD34, as well as the production and release of nitric oxide. It has also been shown that vascular endothelial growth factor receptor expression in CD34 stem cells occurs as a result of exercise-induced stimulation. Expression of these receptors on the surface of stem cells as CD34 + / KDR + allows these cells to differentiate into endothelial cells [16].

In contrast, Adams et al. (2008) reported that CD34 blood progenitor cells decreased immediately after a marathon [17]. In another study, Bansignor et al. (2009) showed that CD34 cell counts remained unchanged after the marathon, but increased by 1.5 km after a field test [18].

One of the significant reasons for the consistency of these studies with the present study could be due to the timing of sample collection after the end of the exercise test, so that it seems that some stress factors and hormones secreted by exercise can affect the functional levels and the number of CD34 stem cells[23,24], but more research is needed in this area. Another reason for the consistency of the studies is the appropriate and similar flow cytometry method. Therefore, more research is needed in this area. Checking the appropriate number of blood mononuclear cells in flow cytometry for CD34 cell count according to laboratory instructions is another reason. Data supported by direct evidence in laboratory conditions show that catecholamines released by sympathetic nerve activity can directly affect the number of hematopoietic stem cells (HSPC). It has recently been shown that circadian release of norepinephrine (NE) is associated with concentration (HSPC) in the peripheral circulation. Also, overnight NE fluctuations are associated with changes in HSPC function[25]. Plasma cortisol level may be effective in this case. In this study, plasma cortisol was significantly increased 10 minutes after the end of exercise and returned to rest baseline 120 minutes after the end of exercise. It is noteworthy that the kinetics of cortisol and catecholamines are interconnected and the hematopoietic stem cell cycle has the same kinetics as plasma cortisol level[23,26], although further research is necessary in this area. The results of the present study are inconsistent with the results of a number of studies in this field. The contrary results of the mentioned studies with the present study may be due to the inability of comparing the study groups in these studies and the obvious difference in age, sex and level of readiness of the subjects to participate in the present study. For instance, marathon runners of have high aerobic capacity, and the adaptations achieved in the body of these people to the stress caused by exercise probably affect the secretion of CD34 cells. So that the subjects of the present study were non-athletes and an aerobic exercise session with moderate intensity and duration is considered an acute stress for them. Of course, the comparison of athletes and non-athletes in the field of CD34 stem cell mobilization needs to be investigated specifically according to the same training conditions. A wide variety of flow cytometric methods, training variables (volume, duration and intensity), and the type of training can be considered as factors causing different results in previous studies.

CONCLUSION

Aerobic exercise can increase hematopoietic stem cells in patients who are candidates for autologous transplantation and continuous aerobic training has relative superiority over discontinuous aerobic training. Sampling methods and Training protocols and are not similar in various studies. So, further investigation on different groups of transplant patients with different conditions at various stages of transplant period are beneficial.

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