SAĞLIKLI VERİCİLERİN YAŞI TOPLANAN PERİFERİK KÖK HÜCRE MİKTARI ÜZERİNDE ETKİLİ MİDİR?

Does the Age of the Healthy Donors Related With the Amount of Stem Cells Collected With GCSF?

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ÖZET

Amaç: Bu çalışmada sağlıklı kök hücre vericilerinin yaşının periferik kandan toplanan CD34+ kök hücre miktarı üzerinde etkisinin olup olmadığı incelendi.

Gereç ve Yöntemler: Bu retrospektif çalışma için, 2016 - 2018 yılları arasında gönüllü olarak merkezimizde kök hücre veren sağlıklı vericilerin dosyaları taranmıştır. Çalışma 32 erkek ve 21 kadın olmak üzere toplam 53 vericiyi kapsamaktadır. Vericiler 50 yaş altı ve 50 yaş üstü olarak iki gruba ayrıldı. Tüm vericiler lenograstim/filgrastim kullanılarak mobilize edildi. Periferik kan CD34+ kök hücre sayımları ön ölçümlere göre 20x10^6/L 'den fazla olan vericilere Fresenius (Bad Homburg, Almanya) cihazı ile mobilizasyon prosedürü uygulandı. İşlem sonrası toplanan CD34+ ler sayıldı ve vericilerin yaş grupları ile ilişkisi incelendi.

Bulgular: Çalışmaya 53 sağlıklı verici dahil edildi. CD34+ kök hücrelerin ön ölçüm değerleri açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmadı. Genç yaş grubunda (50 yaş altı olan grup) birinci ve ikinci günlerde yapılan erken ölçümler arasında istatistiksel olarak anlamlı bir fark bulunmazken, erken ölçümlerde ikinci günde yaşı 50'nin üzerinde olan grupta ilk güne göre istatistiksel olarak anlamlı derecede düşük sonuç ortaya çıktı. Vücut ağırlığı başına toplanan CD34+ kök hücre sayısı açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu. Toplanan CD34+ kök hücre sayısı açısından gruplar arasında istatistiksel olarak anlamlı fark bulunmadı. Kemik ağrısı her iki grupta en sık rastlanan yan etkiydi.

Sonuç: Sonuç olarak, verici yaşının mobilizasyonun başarısız olmasına neden olabilecek bir faktör olmadığını ve benzer miktarlarda periferik kan kök hücrelerinin hem genç hem de yaşlı vericilerde toplanabileceğini belirledik.

Anahtar kelimeler: *Kök hücre transplantasyonu; Lenograstim; Filgrastim.*

ABSTRACT

Aim: The present study aimed to investigate whether age of the healthy stem cell donors has an impact on the amount of collected CD34+ stem cells from the peripheral blood.

Material and Methods: We have scanned the medical records of the volunteer donors who donated stem cells between the years 2016 to 2018 in our instution for this retrospective study. The present study involved totally 53 donors containing 32 males and 21 females. The donors were divided into two groups as aged below and over 50 years. All the donors were mobilized using lenograstim/filgrastim. Mobilization procedure was performed by Fresenius (Bad Homburg, Almanya) device in the donors from whom CD34+ peripheral blood stem cells higher than 20x10^6/L according to the early measurement. The number of the CD34+ stem cells were counted following the procedure and the relationship between the number of the CD34+ stem cells and age of the donors was analyzed.

Results: The study included 53 healthy donors. No statistically significant difference was found between the groups with respect to early measurement values of CD34+ stem cells. No statistically significant result was found between the early measurement values obtained at the first and second days in the healthy younger group (the group aged below 50 years) whereas a statistically significant different result was obtained in the second day compared with the first day in the group aged over 50 years. No statistically significant difference was detected between the groups with respect to the amount of collected CD34+ stem cells per kg (bod weight). No statistically significant difference was determined between the groups regarding the amount of CD34+ stem cells. The bone pain was the most commonly found side effect.

Conclusion: As a conclusion, we have determined in this retrospective study that age is not a factor that may cause a failure of mobilization and that similar amounts of peripheral blood stem cells could be collected in both younger and older donors.

Keywords: *Stem cell transplantation; Lenograstim; Filgrastim.*

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Geliş tarihi/Received: 30.03.2019
Kabul tarihi/Accepted: 29.05.2019
DOI: 10.16919/bozoktip. 546993

Bozok Tıp Derg 2020;10(1):100-5
Bozok Med J 2020;10(1):100-5

INTRODUCTION

Hematopoietic stem cell transplantation is a fully-curative treatment method in many malignant and benign diseases and performed in a progressively increasing number of cases (1). Fully-matched (10/10 fully matched), one mismatched (9/10 compliant), haploidentical or umbilical cord donors may be selected as a stem cell source in the patients in whom allogeneic stem cell transplantation is planned. The impact of the age on the number of CD34+ stem cells collected from donors is not clear since the studies have presented different outcomes on this issue. Many changes may occur in human hematopoietic system with advanced age (2). With advanced age, the functionality of B and T cells diminish and consequently immune system may be weakened (3). By aging, also incidence of hematological diseases associated with bone marrow increases (4-6). Despite all these increasing negative issues due to aging, hematopoietic stem cells reinitiate hematopoiesis thanks to their continuous self-renewal and differentiation properties in the patients in whom stem cell transplantation was performed (7). The mobilization from the healthy allogeneic stem cell transplant donor (healthy donor-HD) is performed with granulocyte colony stimulating factor (G-CSF). G-CSF is administered at a dose of 2.5 mcg/kg body weight for 4 days and early measurement of CD34+ stem cells is performed from peripheral blood of the donor at the 5th day. The stem cells are collected through an appropriate peripheral venous access of the donor (commonly through antecubital vein) or otherwise via catheter (via vascular access) in absence of an appropriate venous access. Even though, apheresis procedure is commonly performed in a single session, however, donors may undergo apheresis for up to three sessions in case of inadequate mobilization. The minimum recommended dose for engraftment is 2x106 CD34+ stem cells while optimal dose is 5x106 CD34+ stem cells. Bone pain, headache, myalgia, fatigue and thrombocytopenia may be monitored during administration of G-CSF. The serious adverse effects such as pulmonary embolism, myocardial infarction, spontaneous splenic rupture, acute iritis and very rarely cerebral infarction may be encountered (8). In this retrospective study, we analyzed the relationship between donor age and CD34 + stem cell mobilization.

MATERIAL AND METHODS

This retrospective study included 53 healthy and volunteer related stem cell donors by screening patient files in the Bone Marrow Transplant Unit of Ankara Medicana International Hospital between the years 2016 and 2018 (Ethical Commitee Approval date and number 08.02.2019-27). All donors were over 18 years old (Range : 19-77 years). Because few data available comparing the age 50 years versus above 50 years we concluded to divide donors into two groups according the age 50. A hematologist from the bone marrow transplant team approved the donors by evaluating their detailed anamnesis, physical examination, complete blood count, biochemistry and infection markers, blood grouping and Rh typing, and pregnancy testing in the females of reproductive age. The donors with a chronic disease and ongoing medication were excluded from the study. All donors were mobilized using 2.5 mcg/kg lenograstim or filgrastim and underwent peripheral stem cell apheresis. The onset of G-CSF administration was accepted as the 1st day and the donors were undergone mobilization procedure with Fresenius (Bad Homburg, Germany) device if early measurement of CD34+stem cells revealed 20x10^6/L The collection of minimum 2x106/kg body weight CD34+ stem cells was targeted. The donors underwent apheresis procedure for 1 or 2 days according to that target cell dose or transplant planning of the patient. The blood volumes of the healthy donors (HD) who were decided to undergo procedure in the 2nd day were processed for 2-4 times and coagulated with 40-90 mL/minute acid-citrate dextrose as the coagulant. The healthy donors (HD) were administered 10% Calcium Gluconate.

Statistical Analysis

Data were analyzed by SPSS for Windows Version 23.0. The continuous variables were expressed as median (minimum-maximum); frequencies and percentages were used to express the categorical variables. The normal distribution is tested by One-Sample Kolmogorov Smirnov test. Probably due to the low sample size all of the data were not normally distributed. The difference between two groups in terms of continuous variables were analyzed by Mann-Whitney-U test. The repeated measurements were

compared by Wilcoxon test. Pearson Chi-square test and Fisher-Exact tests were used for the analysis of categorical variables. The statistical significance level was accepted as 0.05.

RESULTS

The present study included 53 donors. The donors were divided into two groups as subjects below 50 years old (n=30) and above 50 years old (n=23). Of the younger healthy donors (younger healthy donors, yHD) <50 years old; 40% (n=12) were female while 60% (n=18) were male. On the other side, 39% (n=9) and 60% (n=14) of the older healthy donors (older healthy donor, oHD) >50 years old were female and male, respectively. Median age of yHD was 36 years (range 19- 48 years) and median age of oHD was 55 years (range 50-77 years). Median body mass index (BMI) values in the yHD and oHD groups were 24.8 kg/m2 (range 18.94-3438 kg/m2) and 28.89 kg/m2 (range 21.45-38.71 kg/m2), respectively. BMI values of the patients aged above 50 years old were higher than those aged below 50 years old (p=0.004). (Table 1). Median processed blood volume at the first day of apheresis procedure was 333.5 mL (range (230-455 mL) in the yHD group whereas that value was 335 mL (range 240-407 mL) in the oHD group. At the second day of apheresis procedure, median processed blood volume was 305 mL (range 250-350 mL) similarly with oHD group (median 246 mL; range 220-391 mL) (p=0,753). At the first day of apheresis, early measurements revealed 64x10^6/L CD34+ and 66x10^6/L CD34+ stem cells in the yHD and oHD groups, respectively (Table 2). There was a quantitative difference between early measurement values of CD34+ stem cells in favor of oHD group but this difference was not statistically significant. Early measurement results of CD34+ stem cells at the second day were 55x10^6/L and 31x10^6/L in the yHD and oHD groups, respectively. No statistically significant difference was found between the early measurements at the first and second day in the in the yHD group whereas early measurement result of CD34+ stem cells in the oHD group was found statistically significantly lower at the second day compared with the first day. The number of the collected CD34+ stem cells per body weight was 5.05x106 in the yHD group whereas 4.4x106 CD34+ stem cells were collected in the oHD group and there was no statistically significant difference between the groups. At the second day of apheresis, 2.2x106 CD34+ stem cells were collected in the yHD group whereas 1.68x106 CD34+ stem cells were collected in the oHD group. The total numbers of the collected CD34+ stem cells in the yHD and oHD groups were 5.06x106 and 4.7x106, respectively. No statistically significant difference was found between the groups in terms of total number of collected CD34+ stem cells. The frequencies of first and second apheresis sessions were also similar between the age groups (p=0,451). The adverse effect frequency was

Table 1. Demographic characteristics of healthy donors

	Age Group		**p**
	yHD	**oHD**	
	(n=30)	**(n=23)**	
	Median (min-max) / n (%)		
Age	36 (19-48)	55 (50-77)	
Gender			
Female	12 (40%)	9 (39.1%)	0,949**
Male	18 (60%)	14 (60.9%)	
Hgb (mg/dL)	14.8 (9.5-17.3)	14.7 (12-16.3)	0,979*
WBC (x103/µL)	6.91 (4.02-11)	7.12 (4.59-11.3)	0,851*
BMI (kg/m2)	24.8 (18.94-3438)	28,89 (21.45-38.71)	**0,004***

*Mann Whitney-U test, ** Chi-square test, yHD: younger healthy donors, oHD: Older healthy donors

also found similar between the age groups (Table2).

The potential side effects that may develop due to administration of G-CSF were presented in Table 3. Bone pain was the most commonly found side effect in both groups. Also fatigue, fever, headache and insomnia may be monitored due to administration of G-CSF in the healthy donors.

Table 2 Mobilization results

	Age Group		**p**
	yHD	**oHD**	
	(n=30)	**(n=23)**	
	Median (min-max) / n (%)		
Blood volume processed (mL)			
First	333.5 (230-455)	335 (240-407)	0,773
Second	305 (250-350)	346 (220-391)	0,753
Total	350 (230-690)	340 (240-798)	0,914
CD34+ cell day 1&2 (106/L)			
First	64 (22-284)	66 (24-138)	0,802
Second	55 (27-64)	31 (16-52)	0,117
CD34 (yield/kg)			
First	5.05 (1.7-19.01)	4.4 (1.08-10.99)	0,360
Second	2.2 (1.32-2.87)	1.68 (1.05-2.24)	0,465
Total	5.06 (2.08-19.01)	4,7 (2.13-10.99)	0,456
*Mann Whitney-U test, ** Wilcoxon test yHD: younger healthy donors oHD: older health donors			

Table 3. Side effects due to administration of G-CSF

	Age Group		**p**
	yHD	**oHD**	
	(n=30)	**(n=23)**	
	n(%)		
Side effects			0,973*
Bone pain	16 (53.3%)	8 (34.8%)	0,179*
Fatigue	5 (16.7%)	3 (13%)	1**
Fever	2 (6.7%)	2 (8.7%)	1**
Headache	3 (10%)	3 (13%)	0,529**
Insomnia	-	1 (4.3%)	0,434*
* Chi-square test; **Fisher-Exact test, yHD: younger healthy donors, oHD: older healthy donors			

DISCUSSION

Hematopoietic stem cell transplantation has a curative effect in many benign and malign hematological diseases. The incidence of hematological malignancies is increasing in older adults. In contrast with autologous stem cell transplantation, allogeneic stem cell transplantation is performed with the cells obtained from the healthy donors (9). It is known that cellularity of bone marrow decreases with advancing age (10). Bone marrow stem cells of the elderly people seem to be less functional than those of younger ones. This fact can be encountered also in the hematopoietic stem cell dynamics which involve worse engraftment kinetics and outcomes encountered by autologous transplantations in the elderly patients compared with younger patients (11). Stem cell mobilization from healthy donors is a safe procedure, however, age and mobilization kinetics have been evaluated together only in a limited number of studies.

Suzuya et al. have analyzed age, gender, body mass index (BMI), white blood cell (wbc) count, platelet count prior to G-CSF and at mobilization of healthy donors and have detected that donor age is the most important predictive parameter for the mobilization induced by G-CSF (12). Various studies on donor age have presented different outcomes (13,14). De La Rubia et al. have reported that a higher number of CD34+ stem cells was collected in the younger donors (15). A retrospective study conducted on 83 healthy donors to establish a predictive model has determined that a higher amount of stem cells was collected from the donors aged below 50 years old (16). Sumithira Vasu et al. have shown in their study including 639 donors that age of the donor is strongly correlated with the amount of the collected peripheral blood stem cells (17). Motlló et al. have analyzed the results in their study conducted on donors with a median age of 50 years and figured out that apheresis of a higher amount of peripheral blood is needed to collect a sufficient amount of CD34+ stem cells from the donors aged over 55 years old. This outcome indicates that the amount of the collected stem cells per unit volume decreases by advancing age (18). In our study, the evaluation of mobilization kinetics with respect to age of healthy donor revealed that there was no statistically significant difference between the early measurements of CD34+ at the first and second days in both groups whereas early measurement at the second day was statistically significantly lower than the first days in the oHD group. Similar processed blood volumes were determined in both groups were. This outcome indicates the possibility of mobilization insufficiency with advanced age. It is considered that gender has no impact on mobilization (19). Like our study Martino et al. have divided 246 healthy donors into three age groups according as 18-49, 50-59 and 60-70 years in their retrospective study. They have compared the age groups of the healthy donors according to the number of collected CD34+ stem cells and found no statistically significant difference (20).

Several side effects may be monitored due to administration of G-CSF. Similarly with clinical observations, bone pain was the most commonly monitored side effect in also our study. We have detected no relationship between side effects and age in the healthy donors.

We have administered lenograstim or filgrastim in the healthy donors. Since our study is a retrospective study and both G-CSF products could be absent in the pharmacy of the hospital and these products could be used instead of other, we could not determine which product including G-CSF was used in the healthy donors. On the other hand, no complication developed at the stages of G-CSF administration and apheresis in the healthy donors. The retrospective design and including a small number of patients may be considered as the limitations of the study.

As a conclusion, we have determined in this retrospective study that age is not a factor that may cause a failure of mobilization and that similar amounts of peripheral blood stem cells could be collected in both younger and older donors.

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