혈소판성분헌혈자의 체내 페리틴 함량 분석

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Assessment of Serum Ferritin Levels in Plateletpheresis Donors

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Background: While plateletpheresis donation results in less red blood cell loss and therefore less depletion of storage iron, repeated plateletpheresis can also lead to iron depletion. To determine the safety of regular plateletpheresis donations, this study estimated donor's iron status according to age, gender, number of donations, and donation interval.

Methods: The study population included 5,109 plateletpheresis donors (4,824 males, 285 females), who passed the hemoglobin (Hb) criteria for plateletpheresis donation of 12.0 g/dL or more in an inclusion period (September 2013 ~ November 2013). During donor screening, serum ferritin levels were measured for assessment of iron status of plateletpheresis donors.

Results: Mean age of donors was 30.4 years (range: 17 ~ 59). Donors with a history of donation of more than 3 years accounted for 89.3% and 74.0% in males and females, respectively. Mean donation interval and annual donation number in male (female) donors was 11.9 (7.2) weeks and 4.2 (8.7) times, respectively. Approximately 37.8% of male donors and 64.2% of female donors had a serum ferritin level of less than 15 ng/mL. Serum ferritin levels showed correlation with donation interval, as the percentage of donors with a low ferritin level decreased with increase in donation interval (ρ : 0.191 ~ 0.438, $P < 0.001$). Serum ferritin levels also showed correlation with annual plateletpheresis number (ρ : -0.261 ~ -0.411, $P < 0.001$).

Conclusion: Depleted iron store was observed in nearly 40% of donors who had acceptable Hb levels for plateletpheresis donation. Hb pre-donation screening is not sufficient to reduce the risk of iron deficiency in regular plateletpheresis donors. (Korean J Blood Transfus 2015;26:282-290)

Key words: Blood donors, Plateletpheresis, Iron-Deficiency anemia, Ferritin

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Introduction

Iron deficiency can lead to fatigue, reduced work capacity, reduced endurance, cognitive impairment, pica, and restless leg syndrome (RLS) and may progress to iron deficiency anemia.¹⁾ A 450~500 mL whole blood donation results in the loss of 213 to 236 mg of iron and loss of iron by blood donation can contribute to iron deficiency.^{2,3)} The lost iron is not readily replenished. Loss of 200~250 mg iron requiring the donor to absorb 4~5 mg of iron each day to replace that lost within 56 days inter-donation interval.⁴⁾ Thus, anyone who donates one unit of whole blood requires 50 days or longer for positive impact to body iron levels. While plateletpheresis donation results in less red blood cell loss and therefore less depletion of storage iron, repeated plateletpheresis can also lead to iron deficiency. Blood losses within the chamber of apheresis machine and 30 mL of samples for laboratory test every time are between 60 and 80 mL resulting an annual blood loss of up to 1,900 mL in someone donating by apheresis 24 times a year. This is the equivalent of four to five time whole blood donations per annum.^{5,6)}

To ensure donor's safety and quality of blood collected, guidelines exist for manage the iron status to blood services worldwide but they vary among different countries. The present guidelines to manage the iron status of Korean whole bloods include a donation interval of 12 weeks with eligibility cutoffs for hemoglobin (Hb) of 12.5 g/dL for both men and women. In the case of apheresis blood donations, the current strategies for plateletpheresis and plasmapheresis donations are limited to 24 times for plateletpheresis and unlimited for plasmapheresis per year,

if the interval between apheresis donations is no less than 2 weeks and satisfy the minimum Hb level of 12.0 g/dL for apheresis donors in both men and women. However unfortunately, the current method to screen donors for eligibility to donate based on a hematologic assessment, the finger stick Hb, is a poor predictor of a donor's iron status.⁷⁾ Because Hb values do not necessary reflect donor iron stores, some donors are being deferred who have adequate iron stores, and others who are donating may have inadequate iron stores. Although other indicators for assessment of the iron status are available, such as zinc protoporphyrin (ZPP) levels⁸⁾ and the soluble transferrin receptor concentration,⁹⁾ serum ferritin measurement seems appropriate as a routine screening test for blood donors.¹⁰⁻¹³⁾

The main objective of this study was to investigate the iron status according to age, gender, number of donations and donation interval of plateletpheresis donors.

Materials and Methods

1. Study population

This study was performed among a cohort of Korean plateletpheresis donors whose blood samples were tested on Korean Red Cross Central Laboratory Center in an inclusion period (September 2013~ November 2013). The study population comprised 5,109 plateletpheresis donors (4,824 males, 285 females) and the donor criteria of Hb level for plateletpheresis donation is 12.0 g/dL or more. All these donors also fulfilled the other eligibility criteria for donation according to the Korean Blood Management

Act. As the study population consists of donors providing both plateletpheresis and whole blood, we only considered plateletpheresis donations to contribute to the iron depletion. As a result, annual number of donations and the lifetime number of donations represents either amount of plateletpheresis or the total amount of blood donations per donor. Annual number of donations were categorized into <5 donations, 5~10 donations, 11~15 donations, 16~20 donations, 21~24 donations and ≥ 25 donations. Lifetime number of donation were stratified by <5, 5~10, 11~15, 16~20, 21~24, 25~29, 30~39, 40~49, 50~74, 75~99, 100~149, 150~199 and ≥ 200 donations. To analyzes correlation between serum ferritin levels and donation intervals, donors were stratified by 2, 3, 4, 5, 6~7, 8~9, 10~13, 14~16 and >16 weekly donations.

2. Laboratory testing and definitions

Donor information including blood donation history was compiled Blood Information Management System (BIMS) of Korean Red Cross Blood Service Headquarters. Hb determination of the donors has

been performed on Korean Red Cross Blood Donation Centers by Sysmex KX-21N hematology analyzer (Sysmex, Kobe, Japan). During donor screening, serum ferritin levels were measured additionally in venous samples from diversion pouch of the blood bag using a Beckman Coulter AU640 analyzer (Beckman Coulter, Brea, CA, USA) and HiSens Ferritin LTIA reagent (HBI, Seongnam, Korea). A ferritin level at less than 15 ng/mL was considered as suggestive of depleted iron store in female and male according to WHO defines iron deficiency.¹⁴⁾ While iron store was considered as small or reduced at ferritin levels from 15~30 ng/mL.¹⁵⁾ Iron overload is defined as a ferritin level of more than 150 ng/mL in females and more than 200 ng/mL in males.¹⁶⁾

3. Statistical analysis

Descriptive statistical analyses were performed for the donor's characteristics and serum ferritin levels obtained. Spearman correlation coefficient tests were used to determine any degree of relationship in subgroup analysis and *P* values <0.05 were considered

Table 1. Demographic characteristics of plateletpheresis donors

Characteristics	Females (n=285)	Males (n=4,824)	All donor (n=5,109)
Age (years)	17~19	53	320
	20~29	169	2,272
	30~39	59	1,351
	40~49	4	641
	50~59	0	240
Donation history	≥ 3 years	211	4,310
	<3 years	72	506
Mean donation interval (weeks)	7.16	11.89	11.6
Mean donation number/year	8.7	4.2	5.1

significant. The magnitude of Spearman correlation coefficients (ρ) were considered as follows: 0.7~1.0, highly correlated; 0.3~0.7, substantially correlated; 0.1~0.3, moderate correlated; and 0~0.1, no straight-line relationship. Wilcoxon rank sum tests (WRSTs) were carried out to establish the significance of blood donation history including apheresis and whole blood in the features for serum ferritin levels. All statistical analyses were performed using R software version 2.13 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The study population comprised 5,109 plateletpheresis donors, who were accepted to donations by Hb screening. Of 5,109 plateletpheresis donors, 285 (5.6%) were females and 4,824 (94.4%) were males. Table 1 shows the general demographic characteristics of the plateletpheresis donors in this study.

Donor's ages were ranged from 17 to 59 years (mean: 30.9 years). The mean donation number of the donors per year was 8.7 times for females and 4.2 times for males. The percents of regular donors who had donated for more than 3 years were 74.0% (211/285) for females and 89.3% (4,310/4,824) for males.

We investigated the association of mean serum ferritin levels and number of plateletpheresis donors with serum ferritin level below normal reference range according to donor's ages. The average Hb measurements were 14.57 ± 1.16 g/dL and the mean serum ferritin levels were 33.2 ± 36.5 ng/mL for all donors (Table 2). Fig. 1 shows the distribution of Hb and ferritin levels of plateletpheresis donors in this study. The percentage of donors who had less than 15 ng/mL of serum ferritin level was 50~68% for females and 35~52% for males according to donor's age. We also examined the iron status by the blood donation experience to determine whether the

Table 2. Hemoglobin and serum ferritin levels of plateletpheresis donors according to donor's age and gender

Donor age	Hemoglobin mean $\pm$ SD (g/dL)	ρ age vs. mean Hb (P value)	Serum ferritin mean $\pm$ SD (ng/mL)	ρ age vs. mean serum ferritin (P value)	No. Serum ferritin < 15 ng/mL
Females 17~19	12.79 $\pm$ 0.69		11.9 $\pm$ 11.9		36 (67.9%)
20~29	12.87 $\pm$ 0.73		15.3 $\pm$ 16.0		108 (63.9%)
30~39	12.80 $\pm$ 0.76	-0.030	14.9 $\pm$ 17.2	0.069	37 (62.7%)
40~49	12.75 $\pm$ 0.5	(P=0.614)	13.4 $\pm$ 9.9	(P=0.249)	2 (50.0%)
50~59	N/A		N/A		0
Males 17~19	14.74 $\pm$ 1.05		24.3 $\pm$ 22.1		138 (43.1%)
20~29	14.82 $\pm$ 1.04		35.9 $\pm$ 36.4		798 (35.1%)
30~39	14.65 $\pm$ 1.16	-0.155	38.0 $\pm$ 43.6	-0.046	508 (37.6%)
40~49	14.40 $\pm$ 1.06	(P<0.001)	29.5 $\pm$ 31.6	(P=0.001)	252 (39.3%)
50~59	14.03 $\pm$ 1.14		22.9 $\pm$ 24.7		125 (52.1%)
Total	14.57 $\pm$ 1.16		33.2 $\pm$ 36.5		2,004 (39.2%)

Abbreviations: ρ , Spearman correlation coefficient; N/A, not applicable.

blood donation experience difference in participating could be attributed to an iron status. Donors with a history of donation more than 3 years accounted for 74.0% in females and 89.3% in males. Table 3 shows the serum ferritin and Hb levels of plateletpheresis donors according to donation history. Wilcoxon rank sum tests showed that within the female blood donors group who donated more than 3 years

and those who donated less than 3 years did not differ in both serum ferritin ($P=0.314$) and Hb levels ($P=0.482$). On the other hand, between male blood donors group who donated more than 3 years and those who donated less than 3 years was differ not in serum ferritin ($P=0.716$) but in Hb levels ($P=0.019$). However, about 64.2% (183/285) female and 37.8% (1,822/4,824) of male plateletpheresis donors had iron stores below 15 ng/mL of serum ferritin.

Table 4 summarized correlations between donation intervals and Hb or serum ferritin levels of plateletpheresis donors. As shown in Table 4, serum ferritin levels decreased as donation intervals increased ($\rho=0.262$ for females and 0.420 for males, $P<0.001$). However, Hb levels were less correlated with donation intervals in both sexes (females: $\rho=0.159$, $P=0.007$; males: $\rho=0.194$, $P<0.001$).

Results were considered in terms of the annual number of plateletpheresis donation and lifetime number of plateletpheresis donation made. Table 5 shows substantial negative correlations between annual number of plateletpheresis donation and serum ferritin levels either in female ($\rho=-0.261$, $P<0.001$) and male donors ($\rho=-0.411$, $P<0.001$). As well as

Fig. 1. Distribution of hemoglobin (●) and serum ferritin (■) levels of plateletpheresis donors in this study (n=5,109).

Table 3. Serum ferritin and Hb levels of plateletpheresis donors according to donation history

Donation history	No. of donors	Hemoglobin mean $\pm$ SD (g/dL)	Serum ferritin mean $\pm$ SD (ng/mL)	No. Serum ferritin <30 ng/mL	No. Serum ferritin <15 ng/mL
Females ≥ 3 years	211 (74.0%)	12.86 $\pm$ 0.74	15.3 $\pm$ 16.4	181 (85.8%)	131 (62.1%)
Females < 3 years	74 (26.0%)	12.78 $\pm$ 0.69	12.5 $\pm$ 12.4	64 (86.5%)	52 (70.3%)
Females Total	285 (5.6%)	12.84 $\pm$ 0.72	14.6 $\pm$ 15.5	245 (86.0%)	183 (64.2%)
Males ≥ 3 years	4,310 (89.3%)	14.66 $\pm$ 1.11	34.4 $\pm$ 37.4	2,541 (59.0%)	1,644 (38.1%)
Males < 3 years	514 (10.7%)	14.79 $\pm$ 1.00	33.0 $\pm$ 33.6	309 (60.1%)	177 (34.4%)
Males Total	4,824 (94.4%)	14.67 $\pm$ 1.10	34.3 $\pm$ 37.1	2,850 (59.1%)	1,822 (37.8%)
All donors	5,109	14.57 $\pm$ 1.16	33.2 $\pm$ 36.5	3,095 (60.6%)	2,004 (39.2%)

annual number plateletpheresis donations, substantial correlation between low serum ferritin levels and lifetime number of donations ($\rho = -0.332$, $P < 0.001$) was also observed in this study. Notably, the mean Hb levels did not changed according to annual number and lifetime number of plateletpheresis donations.

Discussion

Before blood donation, the iron status is assessed in blood donors. Most commonly, the iron status is assessed by measuring Hb levels to prevent donors from becoming anemic after subsequent blood dona-

tions, but also because iron deficiency affects various other cellular processes as iron an important of many enzymes.¹⁵⁾ However, donors that meet the Hb criterion for blood donation may have depleted iron stores or even iron-deficiency erythropoiesis.^{3,4,17)} This condition is what we called subclinical iron deficiency that in early stages in the development of iron deficiency and may proceed to iron deficiency anemia.^{18,19)}

In this study, we investigated the prevalence of depleted iron store (defined as serum ferritin levels < 15 ng/mL) by measuring serum ferritin levels in plateletpheresis donors that met the Hb criteria for blood donation. Based on the used definitions of iron deficiency, the results from the study reported here show that reduced iron stores correlated with the donation interval and also with the annual number of donations. The prevalence of iron deficiency increased with increasing number of plateletpheresis donation and donation frequency. An unexpected finding was the high prevalence of iron deficiency in the participants that observed in nearly 60% of donors who had acceptable Hb values for plateletpheresis donation. However, estimated prevalence

Table 4. Correlations between donation intervals and Hb or serum ferritin levels of plateletpheresis donors

Correlation with donation intervals		Spearman correlation coefficient (ρ)	P value
Female	Hemoglobin	0.159	0.007
	Ferritin	0.262	< 0.001
Male	Hemoglobin	0.194	< 0.001
	Ferritin	0.420	< 0.001

Donation intervals were stratified by 2, 3, 4, 5, 6~7, 8~9, 10~13, 14~16, and 16 weekly donations.

Table 5. Correlations between number of donations and Hb or serum ferritin levels

Correlation with number of donations			Spearman correlation coefficient (ρ)	P value
Annual No. of donations	Female	Hemoglobin	-0.148	0.012
		Ferritin	-0.261	< 0.001
	Male	Hemoglobin	-0.186	< 0.001
		Ferritin	-0.411	< 0.001
Lifetime No. of donations	All donors	Ferritin	-0.332	< 0.001

Annual numbers of donations were categorized according to < 5 donations, 5~10 donations, 11~15 donations, 16~20 donations, 21~24 donations, and ≥ 25 donations; Lifetime numbers of donations were stratified by < 5 , 5~10, 11~15, 16~20, 21~24, 25~29, 30~39, 40~49, 50~74, 75~99, 100~149, 150~199, and ≥ 200 donations.

rates varied wildly, similar results were also reported by Marks et al.,²⁰⁾ who observed 55% of Hb criteria eligible donors in Australian study had a serum ferritin level of less than 15 ng/mL. Importantly, none of the donors in our study deferred from donation even their iron stores were depleted, highlighting that Hb screening alone is not sufficient to reduce the risk of iron deficiency in blood donors. In this regard, more recently there has been interest in using a ferritin test, which is considered a reliable indication of iron status, to reduced iron deficiency and low hemoglobin deferrals in blood donors.²¹⁾

A limitation of our study is that as the donor population consists of donors providing both apheresis and whole blood, we did not considered donation types to contribute amount of iron deficiency. A second limitation is the reference ranges for serum ferritin have not been universally adopted. The diversity in cutoffs in the published work also shows there is a broad range of thresholds and approaches to their definition.²²⁾ Without universal and functional reference ranges the exact scale of the existence of subclinical iron deficiency in blood donors is unclear. Prevalence rates may be under- or overestimated. Nevertheless, the results of our study do provide indications for the presence of subclinical iron deficiency among whole blood donors with Hb levels above cutoff levels for donation.

In conclusion, about 40% of plateletpheresis donors were found to have depleted iron store status despite the fact that their Hb levels are still acceptable to donate by the Korean Blood Management Act. Iron depletion correlated with the donation interval and also with the number of donations. We demonstrated that Hb pre-donation screening is not

sufficient to reduce the risk of iron deficiency in regular plateletpheresis donors. However, further controlled and comprehensive studies are needed to evaluate the effectiveness of prolongation inter-donation interval, as well as restriction of total allowable number of donations per year for the donors with subclinical iron deficiency.

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요약

배경: 혈소판성분헌혈은 전혈 헌혈에 비해 실혈이 적어 체내 저장철의 손실이 적지만, 반복되는 혈소판성분헌혈 역시 철 결핍을 초래할 수 있다. 본 연구에서는 다회 혈소판성분헌혈자의 건강을 보호하기 위해 헌혈자의 연령, 성별, 헌혈 횟수 및 간격에 따른 체내 철 상태를 분석하였다.

방법: 2013년 9월부터 11월까지 혈액소 검사결과 혈소판성분헌혈 가능 기준인 12.0 g/dL 이상을 통과하여, 실제 혈소판성분헌혈에 참여한 헌혈자 5,109명(남성 4,824명, 여성 285명)을 대상으로 헌혈혈액선별검사 과정 중 추가적으로 혈청 페리틴 농도를 측정하여 체내 저장철 상태를 분석하였다.

결과: 헌혈자의 평균 연령은 30.4세(범위: 17세~

59세)이고, 남성의 89.3%, 여성의 74.0%가 3년 이상의 헌혈 경력을 갖고 있었다. 이들 헌혈자의 연간 평균 헌혈 횟수는 남성이 4.2회, 여성이 8.7회이었으며, 평균 헌혈 간격은 남성이 11.9주, 여성이 7.2주이었다. 남성 헌혈자의 37.8%, 여성 헌혈자의 64.2%가 페리틴 수치가 15 ng/mL 미만으로 나타났으며, 혈청 페리틴의 농도는 헌혈 간격이 길어질수록 페리틴 저하 헌혈자의 비율이 감소되어, 헌혈 간격과 상관관계(ρ : 0.191~0.438, $P < 0.001$)가 있었다. 또한 연간 혈소판성분헌혈 횟수와도 상관관계(ρ : -0.261~-0.411, $P < 0.001$)가 있었다.

결론: 혈소판성분헌혈을 위한 혈액소 기준을 통과한 헌혈자의 약 40% 에서 체내 저장철 고갈이 있는 것으로 나타나 혈소판성분헌혈 다회헌혈자의 철결핍 위험을 감소시키기 위해서 헌혈 전 혈액소 농도 검사만으로는 충분하지 않다.

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