

PROSPECTIVE STUDY ON THE EFFECT OF BLOOD DONATION IN THE IRON STATUS

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Abstract

Introduction: blood donation can generate iron metabolism imbalance and deficiency of this micronutrient, mainly in frequent donors. **Objective:** to evaluate the effect of blood donation in the iron status in repeat donors of a blood bank in Medellín. **Methods:** prospective study with 70 repeat donors randomly selected. Ferritin, erythrogram, reticulocytary haemoglobin, coprological, physical activity, and iron ingestion tests were carried out; previous blood donations was collected of the blood bank database. Summary measures, frequencies, results of Friedman test, McNemar's test, Student's t-test for paired samples, and the Spearman correlation were calculated on the SPSS 25.0® software. **Results:** the physical activity frequency, the prevalence of intestinal parasites, the parameter of leuko-plateletgram, and the iron ingestion in the diet did not show statistically significant differences between the two moments of the study, unlike the MCV (Mean Corpuscular Volume), MCHC (Mean Corpuscular Hemoglobin Concentration) and ferritin. In the second stage, ferritin (which decreases as the amount of donations increases) decreased 10% in women and 15% in men. **Conclusion:** blood donation decreases storage iron and the plundering of the reserves becomes more serious as the amount of donations increases, and also as the period of time between donations decreases. It is necessary to implement strategies to reduce the prevalence of iron deficiency, which include nutritional education, pre-donation iron deficiency determining, and medical guidance on the ingestion of dietary iron supplements.

Keywords: blood donors, ferritins, hemoglobins, iron deficiency, iron dietary.

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Introduction

Iron is a useful micronutrient for cytochromes, enzymes, and oxygen-carrier molecules such as myoglobin and haemoglobin, and it is indispensable for the erythropoiesis, the oxidative metabolism, and the immune cell response. Iron presents in the organism a concentration of 40-50mg/kg of weight, with 65% in haemoglobin, 10% in muscle fibers and other tissues, and 25% in the liver, the bone marrow, and the reticular-endothelial system. Every day, 1-2 mg of iron are absorbed and excreted, and the requirement for an adequate erythropoiesis is 20-30mg/day, which come from the phagocytosis of senescent erythrocytes [1,2].

In normal conditions, there is a balance between iron absorption, transportation, and storing; nevertheless, women in child-bearing age, children, blood donors and hemodialyzed patients suffer highly frequent metabolism alterations: basically iron deficiency with subsequent anemia, characterized by the mobilization of reserve iron towards the bone marrow and other tissues, which generates decreased serum ferritin values, and normal haemoglobin values [3].

According to the World Health Organization (WHO), this disease is a public health problem of epidemic proportions [4], with a world prevalence of 25% [5]. This deficiency can be caused by an increase of the iron requirements, insufficient ingestion and/or absorption, or an increase in blood losses such as the ones attributed to intestinal parasites, and frequent and repeated blood dona-

tions [6,7]. In women, main causes include menstrual losses (approximately 22mg per cycle) and the increase in the iron requirements during the pregnancy, which is equivalent to approximately 840mg, assuming adequate reserves of the micronutrient [8].

Blood donors are a population segment at risk due to the loss of 450-500ml of blood that contain between 200 and 250mg of iron. This can cause a decrease of ferritin and anemia due to iron deficiency, which is a situation responsible for 16%-40% of the deferrals of potential donors, among which 75% has low ferritin levels [9].

Prior studies have reported divergent iron deficiency prevalence in donors; however, a systematic revision of studies that were published between 2001 and 2011 showed a global prevalence of 13% [10]. This revision and other reports concur that there is a greater prevalence in women and repeat donors. A 14,1% prevalence in 5,006 donors was reported in New Zealand, with 20% in women and 8% in men. Also, it was observed that 25% of the affected donors were repeat donors, with 3 to 4 blood donations per year, in whom the repeated donation increased the iron deficiency frequency in 77,3% [11]. Studies performed in Europe reported a 14% deficiency in the first donation and 30,7% in the third, which indicated a 119,3% increase after three blood donations in 8 months [12]. In Colombia, a high prevalence related to the amount of donations was found: 78% in women and 44% in men [13].

All these facts demonstrate that repeated blood donations increase the risk of iron deficiency, which translates into a

serious problem for the sufficient and timely supply of hemocomponents and hemoderivatives because the deferral results in negative implications. The most notable implications are the fact that donors will not be willing to give blood again, the decrease of the amount of donations and the time extension between donations, added to the negative consequences related to the health of the individuals (mainly fatigue, and a decrease in physical performance) [14,15].

The situation described above can be even worse in people without an adequate ingestion of this micronutrient, as its absorption is an indispensable factor for compensating the loss caused by blood donation, which in women corresponds to almost 100% of the iron reserves. Despite the relevance of this aspect, the studies available in our sector that approach iron ingestion in blood donors are meager.

Thus, a study was carried out with the objective of evaluating the effect of blood donation in the iron status in repeat donors of a blood bank in Medellín. This study allowed discovering the iron status in repeat blood donors and, in perspective, it could improve the process of its selection by evidencing the need to add to the screening of anemia, the iron deficiency assessment by means of ferritin, and it would result in the prevention of iron deficiency, the progression of anemic statuses, and deferral due to low haemoglobin levels.

2. Materials and Methods

2.1. Type of study: prospective.

2.2. Subjects: 70 randomly-selected repeat blood donors (with two or more blood donations registered in a year) of whole blood or platelets through apheresis, from the Universidad de Antioquia blood bank. Sample sizes were calculated for the dependent variables (those related to iron status), the highest value was obtained with the following parameters: deviation expected of 15, difference of paired means 10, 95% confidence and 85% power, with which a minimum of 41 pairs was required to be compared.

The study was performed in two stages: the first was the recruitment of the subject for the donation; and the second stage was carried out 3 or 4 months after the first one. The inclusion criteria were the following: the fulfillment of the requirements established in Resolution 0901/1996 [16], and the signing of the informed consent form. The exclusion criteria were the following: i) difficult vein access; ii) incomplete procedures; and iii) demand for compensation.

2.3. Clinical and laboratory assessment: In every single donation, two blood samples were collected: one for the erythrogram and another for the ferritin. These measurements were carried out in the laboratory of the León XIII Clinic, which complies with all the internal and external (RIQAS) quality control regulations. Ferritin was determined through electrochemiluminescence (Cobas® E601-Roche S.A); the biological reference intervals were 30-400ng/ml in men, and 13-150ng/ml in women. The erythrogram was carried out with the Sysmex XE2100 system (Roche, SA), and it included reticulo-

cytary haemoglobin (Ret-He), which biological reference interval was 28,3 – 35,7pg.

The information analysis related to haemoglobin was performed considering the measurement of the Sysmex because, in a preliminary study in the same population, the concordance between the results of the Compolab and the state-of-the-art hematology analyzer was evidenced [17].

For controlling confounding variables, it was also necessary to perform: i) a parasite assessment through direct coprological and formalin-ether concentration techniques, due to the fact that the subjects parasitized especially with uncinaria or some protozoa can have decreased haemoglobin and ferritin [18]; ii) a poll about the iron-rich food ingestion frequency, because the dietary contribution is an indispensable source for recovering the iron loss caused by blood donation (the poll consisted of 31 questions, it was validated with criteria of appearance, content, construct, and reliability, and it was applied as described by Manjarrés [19]; and iii) an IPAQ questionnaire (short format), categorizing physical activity as follows: physically inactive, minimally active, and healthy physical activity, according to the amount of METs/min/week (Metabolic Equivalent Task) [20,21]. The physical activity measurement was carried out with the purpose of control this variable, as athletes present higher haemoglobin values in comparison to the people that do not practice any physical activity or do it irregularly [22].

This information was complemented with data (from the blood bank) related to previous donations, pre-donation haemoglobin values, the amount of donations, and the period of time between donations.

2.4. Information analysis: summary measures and frequencies were used for the description of study group. The variables of the study were compared in both stages as follows: i) the degree of physical activity with the Friedman test; ii) the prevalence of intestinal parasites with McNemar's test; and iii) the findings of the complete blood count, the iron ingestion in the diet, the haemoglobin, the reticulocytary iron, and the ferritin with the Student's t-tests for paired samples and Wilcoxon. The correlation between the ferritin and the donations was carried out by Spearman coefficient. The selection of parametric or non-parametric tests was based on the fulfillment of the normality assumption, assessed with the Kolmogorov-Smirnov tests with correction by Liliefors, and Shapiro-Wilk. The analyses were performed in SPSS 25.0[®] with a significance of 0,05.

2.5. Ethical aspects: According to Resolution 8430/1993 from the Republic of Colombia Ministry of Health, this is a minimum risk study, approved by University of Antioquia - University Research Campus (*en español SIU Sede de Investigación Universitaria*) ethics committee. Each donor signed an informed consent form authorizing the collection of samples and the use of the results for research purposes, ensuring the confidentiality of the information.

3. Results

Mean age was 33,1 years \pm 12,5 and the interquartile range was 23-44 years. 60% were women, the most frequent age group was the young adults group (63%), with university degrees (63%), and employees (43%). In the hematologic characteristics, it was observed that the component that was donated

the most was whole blood (81%), the average amount of donations was 6,4 over a lifetime, and 2,4 over the last year, with an average time since the last donations which ranged from 4,3 to 6,6 months (Table 1). In the components donated in prior occasions, platelets and 2RBC (double blood cell package) were recorded for an individual, and whole

Table 1. Study group description

Variable	Category	#	%
Gender	Feminine	42	60,0
	Masculine	28	40,0
Age group	Adolescent	10	14,3
	Young adult	44	62,9
	Mean adult	16	22,9
Social stratum	Low (1-2)	27	38,6
	Mean (3-4)	43	61,4
Education level	Primary	4	6,3
	Secondary	8	12,7
	Technical	11	17,5
	University	40	63,4
Occupation	Student	18	28,6
	Worker	27	42,9
	Student and worker	9	14,3
	Housewife	4	6,3
	Unemployed	5	7,9
Donated component	Platelets	13	18,6
	Whole blood	57	81,4
Donated components history	Only whole blood	52	74,3
	Platelets-whole blood	9	12,9
	Only platelets	4	5,7
	Whole blood and 2RBC	3	4,3
Donations amount	Mean \pm SD	Me (IR)	Range
Lifetime N=70	6,4 \pm 4,9	5 (3 - 7)	2 - 32
Year 2011 N=70	2,4 \pm 0,8	2 (2 - 3)	2 - 5
Platelet N=15	7,7 \pm 6,0	5 (4 - 13)	1 - 19
Directed donation N=22	1,5 \pm 1,0	1 (1 - 2)	1 - 5
Voluntary donation N=63	4,6 \pm 3,3	4 (3 - 6)	1 - 22

Variable	Category	#	%
Double red blood cell N=5	1,4 ± 0,5	1 (1 - 2)	1 - 2
Months between last 4 donations*			
Fourth and third N=70	4,3 ± 1,3	4,2 (3,5-4,7)	2,3-10,3
Third and second N=70	5,5 ± 2,4	5,4 (3,9-6,9)	0,9-10,6
Second and first N=52	6,6 ± 2,9	6,5 (4,3-8,8)	1,9-12,8
Haemoglobin in last 4 donations*			
Fourth N=70	15,0 ± 1,3	14,8(14,0-16,0)	12,5-17,6
Third N=70	14,8 ± 1,2	14,6(14,0-15,7)	12,4-17,8
Second N=70	14,7 ± 1,4	14,5(13,4-15,7)	12,1-17,9
First N=52	14,7 ± 1,3	14,6(13,6-15,5)	12,7-17,9

SD: Standard deviation. Me: Median. IR: Interquartile Range. *Prior to the inclusion to the study. Source: elaboration of the authors.

blood, platelets, and 2RBC were recorded for another individual.

In the second moment, only 45 donors were accepted, 11 were excluded due to iron deficiency, which is equivalent to a 15,7% prevalence. 10 were deferred by the blood bank because they did not fulfill the requirements for blood donation, and 4 donors decided to voluntarily withdraw from the research study.

The physical activity frequency, the prevalence of intestinal parasites, the parameters of the leukogram and the plateletgram, and the dietary iron ingestion did not show statistically significant differences between the two moments of the study (Table 2). It is worthwhile to note that the parasites identified in both moments of the study corresponded to commensals and protozoa.

Table 3 show the results comparison of the haemoglobin, the hematocrit, the corpuscular constants, the reticulocytary haemoglobin, and the ferritin in both stages of the study for all the

individuals and detailed by gender. In the latter, statistically significant differences were found for the MCV and the MCHC, while there were no such differences for haemoglobin.

The other parameters showed the following status: the hematocrit, the MCH, and the Ret-He did not exhibit statistical differences when separated by gender; the percentage and the absolute reticulocyte count exhibited statistically significant differences in women; and ferritin levels, in both women and men, were lower in the second assessment, although it was statistically significant only in women.

When ferritin was compared in both moments, a 10% decrease in women and a 15% decrease in men were observed. Despite the greater decrease in men, it was not statistically significant due to the small sample size (n= 17 in the second stage). Additionally, ferritin quantification showed an inverse and statistically significant correlation, which evidences the decrease of its values as the amount

Table 2. Comparison of the hematological, parasitological and physical activity profile in both stages of the assessment

Physical activity	Stage of the project % (#)		p value
	Donation 1 N=70	Donation 2 N=45	
Physically inactive	29,9 (20)	46,3 (19)	0,90a
Minimally active	35,8 (24)	34,1 (14)	
Healthy physical activity	34,3 (23)	19,5 (8)	
Intestinal parasites	53,7 (29)	64,4 (29)	0,28b
Hemogram	X ± SD	X ± SD	
Erythrocytes (mm ³)	4,87±0,4	4,8±0,9	0,35c
Platelets(mm ³)	271,1±65,6	263,9±67,0	0,17c
Leukocytes (mm ³)	7,5±2,5	7,3±1,9	0,91d
Lymphocyte (%)	31,9±6,4	34,0±7,4	0,14c
Monocytes (%)	7,87±2,6	7,7±1,8	0,28d
Neutrophils (%)	57,0±7,6	55,5±8,5	0,52c
Eosinophils (%)	2,5±2,1	2,1±1,6	0,14d
Basophils (%)	0,5±0,5	0,4±0,3	0,03d*
Erythrocyte sedimentation (mm/h)	3,6±2,3	12,2±11,0	0,00d**
Iron ingestion in diet			
Daily ingestion (mg)	12,4±8,0	10,3±12,2	0,80d
Absorbed iron (mg)	4,1±3,1	2,9±4,3	0,35d
Hem iron (mg)	4,7±4,0	3,6±4,9	0,43d
Non-hem iron (mg)	7,7±7,2	4,8±7,3	0,71d

^aFriedman Test. ^bMcNemar's Test. ^ct paired. ^dWilcoxon. *p<0,05. **p< 0,01. X: Mean. SD: Standard Deviation.

Source: elaboration of the authors.

of donations increases (Spearman's correlation coefficient = 0.35; p value = 0.003).

Discussion

Statistically significant changes in the MCV, MCHC, and ferritin parameters subsequent to the blood donation were observed in this study. These changes can be attributed to the donation due to the homogeneity observed in other factors related to the iron decrease, such as the physical activity degree, the ab-

sence of infections (indirectly measured through the Erythrocyte Sedimentation as acute phase reagent and with the leukogram as orientation in viral, bacterial, or inflammatory processes), the intestinal parasites, and the daily dietary ingestion of iron. In addition, it was observed that ferritin decreases as the amount of donation increases.

The donors included in this study were mostly women and young people, who mainly donated whole blood. A decrease in the time period between donations was found as subjects became repeat do-

Table 3. Iron marker comparison in both stages of the study.

Haemoglobin (gr/dl)	Total		Women		Men	
	Donation 1	Donation 2	Donation 1	Donation 2	Donation 1	Donation 2
Mean ± SD	14,4±1,3	14,5±1,2	13,9±0,9	13,8±0,8	15,5±1,0	15,7±1,0
Median	14,4	14,3	13,6	14,1	15,5	15,7
p value	0,778a		0,598a		0,801a	
Hematocrit (%)						
Mean ± SD	42,1±3,0	43,1±2,8	40,6±2,4	41,6±1,9	44,5±2,4	45,5±2,5
Median	41,8	42,8	40,7	42,0	44,8	45,5
p value	0,011a*		0,068a		0,090a	
MCV (fl)						
Mean ± SD	86,7±4,3	88,1±4,2	86,2±4,4	87,6±4,5	87,4±4,3	89,0±3,4
Median	87,0	88,2	86,3	87,4	87,5	89,8
p value	0,000a**		0,003a**		0,001a**	
MCH (pg)						
Mean ± SD	29,7±1,9	29,7±1,9	29,1±1,9	29,2±1,9	30,6±1,8	30,6±1,6
Median	29,8	29,7	29,4	29,3	30,4	30,1
p value	0,028a*		0,083b		0,301a	
MCHC (pg)						
Mean ± SD	34,3±1,1	33,7±1,1	33,8±1,0	33,3±1,0	35,0±0,8	34,4±0,9
Median	34,4	33,7	33,9	33,6	34,8	34,5
p value	0,000b**		0,000b**		0,005b**	
Ret-He (pg)						
Mean ± SD	32,6±2,1	33,1±2,4	32,4±2,2	33,0±2,6	33,1±2,1	33,4±2,1
Median	33,1	33,6	32,8	33,5	33,5	33,9
p value	0,047b*		0,085b		0,795a	
% Reticulocytes						
Mean ± SD	0,8±0,4	0,9±0,4	0,8±0,3	1,0±0,4	0,9±0,5	0,8±0,5
Median	0,8	0,8	0,8	0,9	0,7	0,7
p value	0,058b		0,029b*		0,795b	
# Reticulocytes						
Mean ± SD	4,0±1,8	4,4±1,9	3,7±1,4	4,5±1,6	4,4±2,4	4,3±2,3
Median	3,8	4,3	3,7	4,4	4,0	3,8
p value	0,020b*		0,011b*		0,636b	
Ferritin (ng/ml)						
Mean ± SD	61,7±56,8	63,7±64,3	50,8±49,5	59,2±71,2	78,0±63,8	71,2±52,3
Median	37,1	38,9	34,0	30,6	58,2	49,5
p value	0,014b*		0,046b*		0,102b	

^at paired. ^bWilcoxon. *p<0,05. **p< 0,01.

Source: elaboration of the authors.

nors, which is a fact that is in accordance to the observations of Ownby et al. [23], who reported a donor return rate of 57% in subjects with 4 prior donations, and 72% in individuals with more than 6 donations.

The foregoing facts evidence the need to implement educational strategies for donors, which would facilitate to build donor loyalty and, thus, the following: i) the reactivity decrease in serological markers; ii) a greater opportunity and safety in the supply of hemocomponents; and iii) the fulfillment of the goals suggested by the Pan American Health Organization (PAHO) [24] to adequately respond to the increase of the blood transfusion use, which (according to the PAHO) in 2008 recorded a total of 130.444 red blood cells units used, 6.096 more units than the total used between 1999 and 2000 [25].

Iron ingestion levels were below the value recommended by the Colombian Family Welfare Institute for the Colombian population (19mg/day for women from ages 18 to 24, and 14mg/day for women above the age of 24 and for men) and by Resolution 288, 2008, “which establishes the technical regulations regarding the nutritional labeling requirements that shall be complied with by all packaged food products for human consumption” (18mg/day for both genders). But it was slightly superior to the value reported since 2005 in the National Poll of the Nutritional Situation in Colombia (11,1mg) [26-28]. Low iron ingestion levels have been mainly reported in cities such as Bogotá and Barranquilla [29] locally, and abroad in populations such

as young adult Chilean women [30] and adolescent Korean-Americans [31].

This situation could explain the high deficiency prevalence of this micronutrient in a worldwide context, and it reflects the need to implement more and better nutritional education strategies, as well as to promote the increase in availability, production, and consumption of safe food products. These facts are indispensable in donors with iron deficiency, which prevalence in this study was 15,7% in the first stage, since the dietary iron ingestion becomes the only source of the micronutrient for recovering the losses caused by blood donation.

Haemoglobin, hematocrit, MCH, and Ret-He did not exhibit any change between donations, which concurs with the RISE study (the REDS-II Donor Iron Status Evaluation) [32]. The constant values of haemoglobin and reticulocytary haemoglobin indicate the adequate supply of iron towards the functional iron compartment, whether it is due to the mobilization of enough iron reserves (found in 84,3% and 91% of the donors in the first and second stages, correspondingly), or due to the increase of iron absorption from the diet (specifically in the case of donors with iron deficiency), which is immediately used for an adequate erythropoiesis, and not for the recovery of the exhausted reserves.

MCHC and Ret-He are haemoglobin concentration measurements of mature erythrocytes and reticulocytes, respectively, and they have a direct correlation; however, MCHC was the only measure-

ment that presented a statistically significant variation between donations. These parameters have been used for the screening of iron deficiency, and some authors have stated that MCHC exhibits a better performance in comparison to the reticulocytary haemoglobin. Specifically, Kiss et al. [33] found ROC curves of 0,74 for MCHC, and 0,66 for the reticulocytary haemoglobin, regarding the screening of iron deficiency. Nevertheless, further studies are required in order to exactly determine the diagnostic performance of reticulocytary haemoglobin in the detection of iron deficiency in blood donors.

With regard to the gradual decrease of the ferritin values after the blood donations, the results obtained in this study concur with what has been reported by different authors in the worldwide context [34,35]. Richard Cable [36] informs that an individual with 4-6 donations in the last two years has 9,2 times more probabilities of develop iron deficiency than a first-time donor; and Abdullah [37] has found a 16,2% increase in the iron deficiency prevalence in donors with 10 to 12 blood donations in the last three years in comparison to first-time donors. According to the abovementioned facts, the amount of blood donations and a short period of time between them are the most important predictive variables for the development of iron deficiency and iron deficiency anemia in the mentioned population.

Moreover, other authors, such as Rosvik [38], concur in the negative effect of repeated blood donations on the iron metabolism, taking into account biochemi-

cal markers such as the soluble receptor of the transferrin, hepcidin, and erythrocyte indices, such as the hypochromic erythrocyte percentage (%Hypo) [39,40].

These findings carry practical implications for blood banks, which have the responsibility to take care of the health of their donors [41], including the prevention of iron deficiency and anemia. Especially, repeat donors are very important since they contribute to the safe obtaining of blood and a sufficient hemocomponents supply, because they imply a low risk regarding the transmission of infections through the human immunodeficiency virus, the human T-lymphotropic virus, and hepatitis B and C viruses, in comparison to directed and paid donors [42].

Another relevant finding was that men had a more noticeable decrease in ferritin levels between donations in contrast to women, a situation that could be explained by the fact that women keep low ferritin values since the first donation due to the physiological losses during the menstruation or the pregnancy, while men (as they do not have physiological risk factors and they keep adequate reserves) respond with a marked decrease of ferritin levels to a significant blood loss. This fact was evidenced by a meta-analysis carried out with 10 studies in diverse countries, in which the same status regarding both genders was observed [43].

It is important to specify that donors show adequate iron metabolism regulating mechanisms that do not allow a com-

promise of erythropoiesis. However, it is necessary to take into consideration the low daily iron ingestion, a quantity only sufficient for supplying the functional iron compartment requirements, but not to recover the reserves, which is why such reserves can decrease after repeatedly blood donation, and consequently it will cause repeat donors to be anemic.

It is fundamental to highlight that iron reserves decrease after blood donation, and this could be considered as an additional risk factor towards developing iron deficiency in donors, since the plundering of the reserves becomes more serious as the amount of donations increases, and the period of time between donations decreases, as it was demonstrated in this study, and in the ones carried out by Cable [36] and other authors [44]. In accordance to what has been presented in this study, it is essential to implement strategies such as nutritional education, exploring the possibility to increase the time period between donations in the case of some donors with the purpose of allowing the recovery of iron reserves, medical guidance for iron-deficient or anemic donors, recommending iron supplements, serum ferritin determination as a pre-donation exam, or other measures according to the clinical and epidemiological profile of each blood bank, and fully complying with the blood donation and transfusion ethical code [41].

Conclusion

Blood donation decreases storage iron and the plundering of the reserves becomes more serious as the amount of

donations increases, and also as the period of time between donations decreases. It is necessary to implement strategies to reduce the prevalence of iron deficiency, which include nutritional education, pre-donation iron deficiency determining, and medical guidance on the ingestion of dietary iron supplements.

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