적혈구증다증 환자의 최적의 사혈술 주기

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Optimal Phlebotomy Interval to Change Hematocrit Levels in Patients with Polycythemia

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Background: Phlebotomy is used to maintain hematocrit levels <45% to prevent polycythemia-related thrombotic events. However, guidelines for the phlebotomy intervals are lacking. Therefore, we analyzed post-phlebotomy changes in hematocrit and determined the optimal phlebotomy intervals for patients with polycythemia.

Methods: Between March 2009 and August 2016, we performed 441 phlebotomies for 48 patients with polycythemia. Patients with high-risk polycythemia vera (PV) or secondary polycythemia with hypertension or arrhythmia were medicated with hydroxyurea. We divided the patients into three groups based on phlebotomy interval: <2 weeks, 2~4 weeks, and >4 weeks.

Results: No patients with secondary polycythemia and 25.8% of the patients with PV had thrombotic events pre-phlebotomy. Post-phlebotomy, none of the patients experienced a thrombotic event. The average decrease in hematocrit level was significantly different between the three groups, being $1.98 \pm 1.90\%$ (<2 weeks), $0.73 \pm 2.53\%$ (2~4 weeks), and $-0.46 \pm 4.80\%$ (>4 weeks).

Conclusion: To prevent thrombotic events, phlebotomy is a safe and effective treatment to reduce hematocrit levels in patients with polycythemia, regardless of medication. For the maximum effect, a <2-week phlebotomy interval to reduce and <4-week phlebotomy interval to maintain hematocrit levels could be effective. (Korean J Blood Transfus 2016;27:220-228)

Key words: Polycythemia, Thrombosis, Phlebotomy

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Introduction

Polycythemia is characterized by an increased number of red blood cells (RBCs), based on laboratory tests, and is divided into primary polycythemia, including polycythemia vera (PV), and secondary polycythemia. PV is a myeloproliferative neoplasm with a *JAK2* (9p24) mutation, and excess RBCs are produced as a result of a bone marrow abnormality. Secondary polycythemia is caused by either natural or artificial increases in the production of erythropoietin, resulting in increased production of erythrocytes, and can be caused by a variety of conditions that are related with hypoxia-driven events such as cardiac or pulmonary disease, smoking, and renal artery stenosis or with oxygen-independent events such as renal transplantation and malignant tumors.¹⁾

Despite the different etiologies between PV and secondary polycythemia, the clinical symptoms are similar, such as high hematocrit levels; both primary PV and secondary polycythemia also share common clinical manifestations such as thrombosis and organ damage. The increased blood viscosity with both conditions is likely to result in thrombus and is a major cardiovascular risk factor. Increasing the blood viscosity by affecting nitrous oxide levels or enhancing platelet-vessel wall interactions could increase the risk of thrombosis.²⁾ However, the risks for thromboembolism differ between PV and secondary polycythemia; the most common cause of death with PV is thrombosis, accounting for 21~29%.³⁾ In contrast, there is no definitive evidence that secondary polycythemia increases the risk of thromboembolism, based on five observational studies.⁴⁾

To prevent the complications of PV, therapeutic

maintenance of hematocrit levels <45% has been recommended.⁵⁾ Phlebotomy is the primary method of treatment for erythrocytosis and can reduce RBC mass, improve the symptoms related to high blood viscosity, and lower the risk of thrombosis and hemorrhage.²⁾ Phlebotomy should be started daily or every other day until a hematocrit level of 0.4~0.45 (40~45%) is obtained. After normalization of the hematocrit obtained, blood counts at every 4 to 8 weeks are recommended.^{6,7)}

We analyzed the post-phlebotomy change in hematocrit levels and determined the optimal phlebotomy intervals for patients with polycythemia, regardless of medication.

Materials and Methods

1. Patients

Between March 2009 and August 2016, we performed 441 phlebotomies for 48 patients with polycythemia in Pusan National Yangsan Hospital, Korea. We reviewed their age, sex, diagnosis, medication, associated disease(s), symptoms, phlebotomy volume, and number of phlebotomies. Advanced age (>60 years), an previous arterial or venous thrombotic event, hypertension, and diabetes mellitus are the risk factors for thrombosis in patients with PV. The patients were sub-grouped into low risk (no risk factors) and high risk (>1 risk factor) groups according to the risk factors for cardiovascular disease. PV diagnosis was based on the 2008 World Health Organization diagnostic criteria.⁸⁾

The procedures were also separately divided into 3 groups based on phlebotomy interval: <2 weeks, 2

~4 weeks, >4 weeks.

2. Routine hematologic assays

Hematocrit levels were measured in whole blood using an XE-2100 (Sysmex, Kobe, Japan) just before the next phlebotomy.

3. Treatment

Patients with PV were medicated with hydroxyurea and aspirin. For patients with secondary polycythemia, only those with hypertension or arrhythmia were treated with hydroxyurea, aspirin, or warfarin, because hypertension is a proven risk factor for thrombosis in secondary polycythemia. In patients with secondary polycythemia but without hypertension, only phlebotomy was performed to lower hematocrit levels. Phlebotomies were only done when clinicians request them to blood bank. 17 patients were stopped phlebotomy due to follow up loss (8 patients) and getting medication only (9 pa-

tients).

Whole-blood phlebotomy was performed using the traditional technique, by removing 200~800 mL whole blood during each procedure, not to exceed 13% of total blood volume [TBV (mL)=(68 mL/kg [men] or 62 mL/kg [women]) $\times$ weight (kg)].

4. Statistical analysis

All analyses were performed using SPSS v.21.0 (IBM Corp., Armonk, NY, USA). Chi-square tests, Fisher's exact tests, Student *t*-tests, or Mann-Whitney tests were used for intergroup comparisons. Differences in the mean change in hematocrit levels among the 3 groups were evaluated using one-way ANOVA. A *P* value <0.05 was considered significant.

Results

The median age of the 48 patients (32 men, 16

Table 1. Characteristics of patients with polycythemia who underwent phlebotomy treatment

Variables	Total (N=48)	Polycythemia vera (N=31)	Secondary polycythemia (N=17)	<i>P</i> values
Age (years)	56 (18~79)*	59 (31~79)*	54 (18~70)*	0.036 [†]
Sex (male/female)	32/16	19/12	13/4	0.350 [†]
Thrombotic event	8	8	0	0.052 [†]
Cardiovascular accident	3	3	0	0.543 [†]
Cerebral infarction	5	5	0	0.146 [†]
Risk factors for cardiovascular disease	18		5	
Diabetes mellitus	5 (3 [†])	4	1	0.643 [†]
Hypertension	16	12	4	0.344 [†]
Atrial fibrillation	2 [†]		2	0.121 [†]
Hematocrit (%)		58.5	53.3	0.001 [§]

*Values are reported as the medians (range); [†]with hypertension; [†]*P* values were calculated using Fisher's exact test; [§]*P* values were calculated using a Mann-Whitney test.

women) was 56 (18~79) years; 31 patients had PV, and 17 patients had secondary polycythemia. Pre-phlebotomy thrombotic events occurred for 25.8% of the patients with PV and none of the patients with secondary polycythemia (Table 1). The initial hematocrit level ($P=0.036$) and age ($P=0.001$) were significantly different between the patients with PV and

secondary polycythemia. The diseases associated with secondary polycythemia are shown in Table 2. There were no significant differences in the number of procedures or phlebotomy intervals between the patients with PV who were classified as low risk, patients with PV who were classified as high risk, and patients with secondary polycythemia (Table 3).

Table 2. Associated diseases or conditions in patients with secondary polycythemia

Diagnosis	N	Combined with hypertension
Post-kidney transplantation	3	
Arrhythmia	2	1
Hypertension	2	
Eisenmenger syndrome	1	
Neurofibromatosis	1	
Chronic kidney disease	1	1
Diabetes mellitus	1	
Hemochromatosis, liver	1	
CADASIL	1	
Polycythemia only	4	

Abbreviation: CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

After dividing each procedures into three phlebotomy interval group, the average change in decreased hematocrit levels was significantly different between the three phlebotomy interval groups (Fig. 1A). $1.98 \pm 1.90\%$ (<2 weeks), $0.73 \pm 2.53\%$ (2~4 weeks), and $-0.46 \pm 4.80\%$ (>4 weeks) ($P=0.000$, <2 weeks vs >4 weeks; $P=0.004$, <2 weeks vs 2~4 weeks; and $P=0.005$, 2~4 weeks vs >4 weeks). The average change in platelet levels was not significantly different between the three phlebotomy interval groups (Fig. 1B): -10.59 ± 72.36 K (<2 weeks), 4.43 ± 117.42 K (2~4 weeks), and 21.23 ± 112.11 K (>4 weeks) ($P=0.154$).

The average change in hematocrit levels was not significantly different between the three phlebotomy interval groups according to presence of medication. Diagnosis did not affect on the hematocrit change

Table 3. Mean (range) of phlebotomy procedures for patients with polycythemia

	Polycythemia vera		Secondary polycythemia	P values
	High risk*	Low risk*		
Number of patients	18	13	17	0.360 [†]
Number of procedures	9.12 (1~22)	9.8 (1~30)	9.0 (1~32)	0.190 [†]
Phlebotomy interval (weeks)	21 (0.1~207)	7 (0.1~96.2)	17 (0.3~106.7)	0.555 [†]
Volume removed (mL)	378.9 (400~800)	376.9 (300~400)	387.8 (215~800)	0.288 [†]

*The patients were sub-grouped into low risk (no risk factors) and high risk (>1 risk factor) groups according to the risk factors for cardiovascular disease; [†]P values were calculated using Fisher's exact test; [†]P values were calculated using a Student's T test.

Fig. 1. Change in hematocrit levels (A) and platelet levels (B) according to phlebotomy interval in patients with polycythemia. P values were calculated by one-way ANOVA.

Abbreviations: Hct, hematocrit; PLT, platelet.

Table 4. Average change in hematocrit between three phlebotomy interval groups according to medication and diagnosis

Phlebotomy interval	Change of hematocrit			Total (N)	P values*
	<2 weeks	2~4 weeks	>4 weeks		
Medication					0.154
Yes	1.38 $\pm$ 1.93	0.27 $\pm$ 2.94	-0.43 $\pm$ 3.73	241	
No	2.16 $\pm$ 1.58	0.59 $\pm$ 3.02	-0.16 $\pm$ 8.31	136	
Diagnosis					0.58
Polycythemia vera	1.39 $\pm$ 1.90	0.22 $\pm$ 2.88	-0.27 $\pm$ 3.59	247	
Secondary polycythemia	2.30 $\pm$ 1.64	0.75 $\pm$ 3.17	-0.32 $\pm$ 8.25	130	

* P values were calculated by one-way ANOVA.

(Table 4).

The average proportion of depleted blood volume to total blood volume by one phlebotomy between three phlebotomy interval groups are not significantly different (Table 5).

Side effects of phlebotomy were observed in 2 patients with vasovagal reaction, which included nausea and dizziness. There were no post-phlebotomy thrombotic events.

Discussion

Preventing thrombotic events in patients with polycythemia is important for achieving superior survival without complications.^{9,10)} In the present study, patients with secondary polycythemia did not experience thrombotic events, while 25.8% of the patients with PV did experience a thrombotic event.

To deplete RBCs, therapeutic erythrocytapheresis

Table 5. Average proportion of depleted blood volume by one phlebotomy between three phlebotomy interval groups

Phlebotomy interval	< 2 weeks	2~4 weeks	>4 weeks	Total (N)	<i>P</i> values*
Depleted blood volume/TBV (%)	8.71±1.36	8.64±1.54	8.82±1.59	377	0.605

**P* values were calculated by one-way ANOVA.

Abbreviation: TBV, total blood volume.

(TE), usually conducted once, is recommended in the guidelines on the use of therapeutic apheresis from the American Society for Apheresis (ASFA).¹¹⁾ TE removes a larger volume of RBCs than phlebotomy and returns the plasma to the patients. In patients with erythrocytosis, TE reportedly decreased a greater RBC mass by selectively removing greater RBC volume than single phlebotomy.¹²⁾ In addition, the effect of TE lasts considerably longer than that of classic phlebotomy. In a previous study that compared the treatment intervals between TE and phlebotomy in patients with erythrocytosis, the treatment interval was 20 days to 2 months for 80% of the patients who underwent phlebotomy, compared with a treatment interval of 4~7 months for 70% of the patients who underwent TE.¹³⁾ Furthermore, to maintain optimal hematocrit levels, TE requires fewer procedures, and the effects last longer than phlebotomy; however, it is more expensive.¹⁴⁾ Considering the difference in the number of procedures, the total treatment cost is not significantly different between TE and phlebotomy when treating patients.¹⁵⁾

In Korea, TE is not covered by insurance; therefore, classic phlebotomy is used to reduce hematocrit levels in patients with erythrocytosis. Classic phlebotomy is a simple, safe, and low-cost method for both PV and secondary polycythemia, based on various conditions. Conventional therapeutic options

aim at reducing vascular and thrombotic risks; low-dose aspirin and phlebotomy are the first-line recommendations for patients at low risk of thrombotic events, and cytoreductive therapy (usually hydroxyurea or interferon alpha) is recommended for high-risk patients. Several targeted therapies, including JAK inhibitors and histone deacetylase inhibitors, were also recently developed.¹⁶⁾ In the present study, all of the patients who underwent phlebotomy, even those with a previous thrombotic event, did not have a thrombotic event after phlebotomy, regardless of medication. In addition, only 2 patients experienced mild side effects, and the symptoms were relieved after rest. Although phlebotomy reduces RBCs with plasma, it results in hypovolemic side effects, including fatigue, bruising, dehydration, dizziness, fainting, and loss of appetite.¹⁷⁾

To predict the amount of packed RBCs for transfusion, we used the following equation: hematocrit (dL)=infused hemoglobin (g)/circulating blood volume (dL). The circulating blood volume can be calculated as: body weight (kg)×70 mL/kg/100. A normal adult weighing approximately 65 kg has 45.5 dL of circulating blood volume; 250 mL packed RBCs from 400 mL whole blood would then increase hemoglobin by 1 g/dL.¹⁸⁾ Therefore, we could expect an approximate 1-g/dL decrease in hemoglobin after 1 unit phlebotomy. In a previous study, one phlebot-

omy session decreased hematocrit levels approximately 3~4% right after phlebotomy.¹⁹⁾

A retrospective study demonstrated a progressive increase in the incidence of vascular complications at hematocrit levels >44%.²⁰⁾ Therefore, phlebotomy should be started daily or every other day until a hematocrit level of 40~45% is obtained; once normalization of hematocrit levels has been obtained, blood counts at regular intervals will establish the frequency of future phlebotomies.^{6,7)} However, only two patients undergoing phlebotomy every other day reached the target hematocrit level (<45%) in the present study. The remaining patients underwent phlebotomy according to their outpatient follow-up schedule, at a mean interval of 79 days. The permitted minimal interval between whole blood donations is 2 months to maintain appropriate hemoglobin levels,²¹⁾ and a previous study reported that 80% of patients with erythrocytosis undergoing phlebotomy had 20 days to 2 months between treatments.¹⁴⁾ Given this evidence, phlebotomy should be conducted more frequently than every 2 months to reach the target hematocrit levels. In the present study, the average change in the hematocrit level was different according to phlebotomy interval.

The limitation of this study was that hematocrit levels immediately after phlebotomy were not analyzed; these should be evaluated in future studies.

In summary, phlebotomy is a safe and effective treatment to reduce hematocrit levels with the aim of preventing thrombotic events in patients with polycythemia, regardless of medication. For maximal effect, the phlebotomy interval should be <2 weeks to reduce hematocrit levels or <4 weeks to maintain hematocrit levels.

요 약

배경: 사혈술은 적혈구증가증과 관련된 혈전증 관련 부작용 예방을 목표로 헤마토크릿을 45% 이하로 유지하기 위해 이용된다. 그러나, 사혈술 주기에 관한 가이드라인은 없다. 이에, 본 연구자들은 적혈구증가증 환자들의 사혈술의 주기를 결정하기 위해 사혈술 후의 헤마토크릿변화를 분석하였다.

방법: 2009년 3월부터 2016년 8월까지 적혈구증가증 48명의 환자에서 441건의 사혈술을 시행하였다. 고위험군의 진성적혈구증가증 환자와 고혈압이나 부정맥이 동반된 이차성 적혈구증가증 환자들은 hydroxyurea 약물 치료도 병행하였다. 사혈술을 시행한 간격이 2주 미만, 2주에서 4주 사이, 4주이상인 3군으로 나누어 분석하였다.

결과: 진성적혈구증가증환자의 25.8%에서 사혈술 치료를 시작하기 전 혈전증 관련 부작용을 경험하였고 가성적혈구증가증 환자는 부작용이 없었다. 사혈술 치료 후에는 모든 환자에서 혈전증 관련 부작용이 일어나지 않았다. 감소한 헤마토크릿의 평균 변화는 세 군에서 유의한 차이가 있었다: $1.98 \pm 1.90\%$ (<2 weeks), $0.73 \pm 2.53\%$ (2~4 weeks), and $-0.46 \pm 4.80\%$ (>4 weeks).

결론: 적혈구증가증 환자에서 혈전증 관련 부작용을 예방하기 위해 약물치료 유무와 상관없이 사혈술은 안전하고 효과적인 방법이다. 헤마토크릿을 낮추기 위해서는 2주 미만, 헤마토크릿을 유지하기 위해서는 4주 미만의 간격으로 사혈술을 시행하는 것이 효과적이다.

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