Research Article

Mean Corpuscular Volume and Red Cell Distribution Width Changes in Uncorrected Cyanotic Congenital Heart Disease with Repeated Phlebotomy

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Received on: 25-Nov-2022 Accepted for Publication: 20-Mar-2023

Cyanotic congenital heart disease (CCHD), which according to its prevalence is accounted around 0.608 per 1000 live births. One of the most common problem among CCHD patients is secondary erythrocytosis leading to polycythemia and hypervsicosity that can be overcomed temporarily by phlebotomies. Although phlebotomy is proven to reduce the risk of coagulopathy and thrombosis among patients with polycythemia, removing the circulating red blood cells (RBCs) that contain high amounts of iron-containing hemoglobin could lead to iron deficiency anemia.

Objective: To evaluate mean corpuscular volume (MCV) and red cell distribution width (RDW) changes among children with uncorrected cyanotic congenital heart disease (CCHD) who underwent phlebotomy procedure.

Method: A prospective study with a pre-post design was conducted with inclusion criteria was children with CCHD who came for phlebotomy procedure (hematocrit level >65%) and observed within 6 months since initial phlebotomy. MCV and RDW levels were measured before and after the phlebotomy procedure.

Result: From January 2016 to December 2020, 42 patients participated in this study. The subjects who underwent phlebotomy procedure in 6 months more than 2 times were 54.8% with median age was 7 years and the most subject was female (52.2%). MCV level decreased from 78.4 fL became 71.9 fL and RDW level became increase from 18.28% to 20.53%. Mean difference of MCV in initial measurement was 1.45 (P=<0.05, 95%CI 0.78 to 2.12) compare to 0.72 (P=0.31, 95% CI -0.70 to 2.23) at last measurement. Meanwhile, mean difference of RDW was 0.75 (P=<0.05, 95% CI 0.32 to 1.17) compare to 0.71 (P=0.04, 95%CI 0.04 to 1.39) in the last measurement.

Conclusion: Phlebotomy procedure could lower the level of MCV and increase the RDW level among children with uncorrected CCHD that indicates of iron deficiency anemia. Further study should be performed to evaluate the causes and effects of these changes.

Keywords: pediatric, cyanotic congenital heart disease, phlebotomy, mean corpuscular volume, red cell distribution width

INTRODUCTION

The prevalence of cyanotic congenital heart disease (CCHD), is accounted for 5.7% until 19% with incidence around 0.608 per 1000 live births.[1-3] One of the most common problem among CCHD patients is secondary erythrocytosis policythemia and hyperviscosity with prevalence around 22% - 37%.[4-6] Phlebotomy, which means the removal of patient's blood is the way to overcome this problem temporarily.[5-8] In the case of uncorrected CCHD, *European Society of Cardiology* (ESC) suggests that phlebotomy performed in patients with the initial hematocrit (HCT) level is at least more than 65%. Although phlebotomy is proven to reduce the risk of coagulopathy and thrombosis among patients with polycythemia, removing the circulating red blood cells (RBCs) that contain high amounts of iron-containing hemoglobin could lead to iron deficiency anemia.[7]

Iron deficiency anemia (IDA) in CCHD can diagnosed by affordable criteria including mean corpuscular

volume (MCV) and red cell distribution width (RDW).[9] A study conducted by Barton and Bottomley showed that children with CCHD have significant high value of MCV due to rapid hematopoiesis stimulated by prolonged hypoxic condition.[10] On the contrary, a previous study showed that 11.1% of children with CCHD had low MCV caused by iron deficiency anemia but the cause of this phenomenon is unknown.[11] Similar study conducted in Sanglah Hospital showed that children with uncorrected CCHD who undergone phlebotomy procedures in 6 months had a lower level of MCV.[12] Children with CCHD who experienced IDA, also had RDW level >14.5%.[13] As far as we know, study about repeated phlebotomy among children with uncorrected CCHD especially the impact on alteration of MCV or RDW is still limited and not well known. Based on that background, we want to know MCV and RDW changes in children with uncorrected CCHD who underwent phlebotomy procedures.

METHODS

This prospective study with pre-post scheme that was executed from January 2016 until December 2020 in Sanglah General Hospital Bali. The inclusion criteria of this study were children aged 0-18 years old with CCHD, have not undergone any corrective surgery for the defect yet, and undergone phlebotomy procedure due to policytemia (hematocrit level >65%). Exclusion criteria were incomplete medical records, children with history packed red cell transfusion and undergone phlebotomy before. The sample size of this study was 42 subjects.

Cyanotic congenital heart disease was defined as a congenital heart malformation that has mixed shunting, thus making the amount of oxygen circulating lower than normal, which visible clinically as cyanosist or oxygen saturations measured by pulse oxymeter. The cardiac diagnosis was classified into two major groups which increase pulmonary blood flow (including transposition of the great arteries (TGA) and Double outlet right ventricle (DORV)) and decrease pulmonary blood flow (including tetralogy of Fallot (TOF), tricuspid atresia, pulmonary atresia, and complex CCHD). The frequency of repeat episodes of phlebotomy was defined by how many times the subjects undergoing the phlebotomy procedure within 6 consecutive months from the initial procedure. MCV and RDW levels were measured before and after the phlebotomy procedure. Decreased MCV was defined if MCV level <80 fL and RDW increased if RDW level >14.5%. Iron deficiency anemia (IDA) in CCHD defined by Hb <15 gr/dL and MCV <80 fL.

Continuous data will be presented in mean and standard deviation if distributed normally, or median and range if not distributed normally. Categorical data will be presented in percentage. Differences between quantitative groups with normal distribution were evaluated with the paired t-test. P-value below 0.05 was considered statistically significant, with 95% confidence interval. All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 26. This study was approved by the Ethics Committee of Sanglah Hospital number 1790/UN14.2.2.VII.14/LT/2021

RESULT

A total of 42 subjects who met the inclusion criteria have participated in this study. We found that of 54.8% subjects who had undergone phlebotomy procedure >2 times with median age was 7 years and the most subject was female (52.2%). Subject's characteristic is listed in Table 1.

Table 1. Demographic characteristics of the study

Demographic characteristics at First Measurement	Value (n=42)
Age, median (range) years	7 (0-18)
Gender, n (%)	
Female	22 (52.4)
Male	20 (47.6)
Cardiac diagnosis, n (%)	
Increase pulmonary blood flow	
TGA	2 (4.8)
DORV	4 (9.5)
Decrease pulmonary blood flow	
Classic TOF	15 (35.7)
TOF with variant	7 (16.7)
Tricuspid atresia, VSD	3 (7.1)
Pulmonary atresia, VSD	6 (14.3)
Complex Cyanotic CHD	5 (11.9)
Phlebotomy Frequency, n (%)	
< 2 times	19 (45.2)
≥ 2 times	23 (54.8)
IDA at first admission, n (%)	
Yes	10 (23.8)
No	32 (76.2)
Malnutrition, n (%)	
Yes	19 (45.2)
No	23 (54.8)

TGA (transposition of the great arteries); DORV (double outlet right ventricle); CHD (congenital heart disease); TOF (tetralogy of fallot); VSD (ventricular septal defect); and IDA (iron deficiency anemia).

This study is evaluated the MCV and RDW changes in subjects who have undergone phlebotomy procedures that have been done within the last 6 months. Complete data was shown in figure 1 and 2. Total subjects who have undergone the phlebotomy procedure for the first time in this study was 42 subjects. At first measurement, mean difference of MCV pre-phlebotomy and post-phlebotomy was 1.45 (P=<0.05, 95%CI 0.78 to 2.12) and mean difference of RDW was 0.75 (P=<0.05, 95%CI 0.32 to 1.17). In the second measurement, the total subjects who undergone phlebotomy procedure were 23 subjects with a mean difference of MCV pre- and post-phlebotomy was 0.94 (P=<0.05, 95%CI 0.48 to 1.39). Meanwhile, the mean difference of RDW in the second measurement was 0.8 (P=<0.05, 95%CI 0.43 to 1.18). Total subjects at the third measurement were 9 subjects.

Mean difference of MCV level was 0.72 (P=0.31, 95%CI -0.7 to 2.23) and mean difference of RDW was 0.71 (P=0.04, 95%CI 0.04 to 1.39).

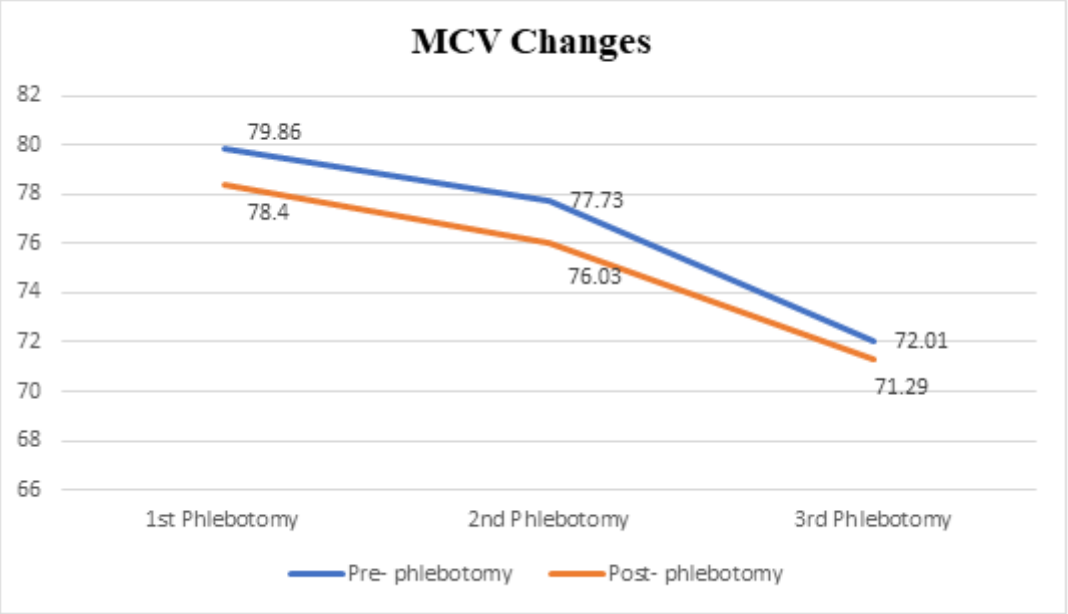

Figure 1. MCV changes in repeated phlebotomy

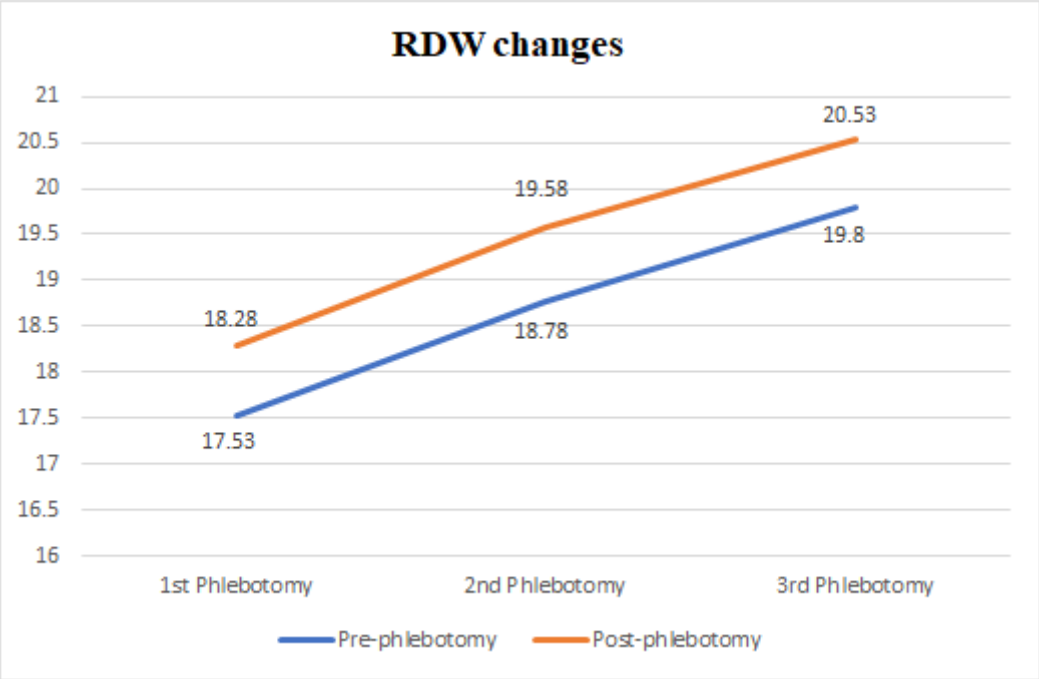

Figure 2. RDW changes in repeated phlebotomy

DISCUSSION

A study that examines the effect of phlebotomy among *Grown Up Congenital Heart Disease* (GUCH) patients showed significant reduction of MCV value after the phlebotomy procedure (-5.703; p=<-0.001). They also

found that in the group where the patients underwent repeated phlebotomy, the MCV level is even lower than the other group (78.37 ± 4.3 vs 85.41 ± 3.4; p=0.0007).[14] A similar study that assesses iron level changes in patients who had 4 serial procedures within 6 months found that iron level was decreased by 0.86 g/dL mL between the initial and final procedures. This reduction is linearly correlated with the decreased level of MCV from 91.12 ± 3.41 at the initial study to 90.48 ± 3.92 at the end of the study.[23] Another study that was conducted in Sanglah Hospital also showed that 45.2% of children with uncorrected CCHD who undergone ≥ 2 times phlebotomy procedures in 6 months had a lower level of MCV.[12] In this study, we found that the mean MCV level was decreased in the last procedure compare to the initial procedure. The mean MCV level of post-phlebotomy at the first measurement was 78.4 fL compare to 71.29 fL at the third measurement.

This study found that the majority of children with uncorrected CCHD have undergone phlebotomy procedures at least two times within 6 consecutive months (54.8%). Phlebotomy is known to reduce blood viscosity that can be seen changes in the hematocrit parameter, where the removal of 250-500 ml of blood during the phlebotomy procedure could decrease HCT value from a patient with the initial HCT more than ≥ 50%.[14] HCT reduction after phlebotomy reveals the benefit of phlebotomy in terms of balancing hemostasis and avoiding thromboembolism events in CCHD patients.[14-15]

Despite the benefit of phlebotomy procedures, patients with CCHD who underwent repeated phlebotomies are risky for developing iron deficiency anemia. These microcytic red blood cells are more rigid and less deformable therefore increase the symptoms.[16] Iron deficiency in children with uncorrected CCHD is associated with low-quality life, impaired exercise capacity, and also impaired oxidative metabolism as well deranged cellular immune mechanism which could lead to more morbidity and mortality.[17] Iron deficiency anemia is associated with increase risk of cerebrovascular event in CCHD children whom have HCT level over 60%. Initiation of iron supplementation since infancy to late childhood period could be appropriate in CCHD children to prevent iron deficiency anemia since the complications of thromboembolic and nutritional iron deficiency are more frequent in this group.[18] Olcay et al., showed that iron supplementation (3 mg/kg of ferrous sulfate per oral 3 times daily for a month) increased serum ferritin level and prevented the development of iron deficiency in the iron sufficient group.[19]

In children with CCHD, it is necessary to diagnose iron deficiency and appropriate management. Complete

blood count is useful, cheap, easy, and ready even in primary medical centers. In a world where cost-effectiveness became important phenomenon, we do imply that complete blood count can effectively be used in the follow-up of children with CCHD. In this study, iron deficiency anemia was diagnosed using RDW and MCV, affordable validated parameters for diagnosing iron deficiency.[20-22] When RDW and MCV are considered together, iron deficiency anemia could be diagnosed with 98% accuracy.[21]

Increasing in MCV level has been report in subjects with CCHD, but low MCV has also been reported in CCHD children that had iron deficiency anemia. The trend of high mean MCV in CCHD children is most likely as sequence of hypoxia activating hematopoiesis therefore providing rapid supply of young red cells which are likely to have higher MCV.[10]

Red distribution width increased when hematopoietic response amplified that found in cyanotic congenital heart disease. Previous studies showed that patient with CCHD who had RDW level increased was significantly associated with iron deficiency status accompanied by polycythemia. Increased RDW has also been shown as early signal of iron deficiency as result of anisocytosis.[18] In this study, we found RDW level increased at the third measurement. The mean RDW level in the post-phlebotomy procedure at the first measurement was 18.28% and in the third measurement, we found 20.53%.

In this study, we can find that the mean difference of MCV and RDW levels in the first measurement was higher than the second measurement, and in the third measurement, it became insignificant at the MCV level. The subjects in this study never underwent the phlebotomy procedure before, which caused the total amount of blood removed during the first phlebotomy procedure to become more than the second procedure.

The limitation of this study is there is a dispersion of phlebotomy timing for each patient due to different visit times to the polyclinic or hospital and not analysis others risk factor that associated with frequency of phlebotomy. In this study, we can be concluded that frequent phlebotomy procedures could decrease the MCV level and increase the RDW level among children with uncorrected CCHD which indicates iron deficiency. Further study should be performed to evaluate the causes and effects of these changes.

CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

FUNDING ACKNOWLEDGEMENTS

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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