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PLATELET FUNCTION ASSESSMENT AMONG CHILDREN WITH CONGENITAL CYANOTIC HEART DISEASE PRESENTING IN TERTIARY CARE HOSPITAL LAHORE

Saima Irum[1], Zeeshan Ghous[1], Nauman Naseer[1]

1 King Edward Medical University/Mayo Hospital, Lahore, Pakistan

Address for Correspondence:
Dr. Zeeshan Ghous
Department of Cardiology King Edward Medical University/Mayo Hospital, Lahore, Pakistan
Email: zeeshanghouskhan@gmail.com

Contribution
SI conceived the idea and designed the study. Data collection and manuscript writing was done by SI, ZG, and NN. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: The objective of this study was to determine the frequency of platelet dysfunction in congenital cyanotic heart diseases patients presenting to a tertiary care hospital in Lahore.

Methodology: A cross sectional survey was carried out from March 2018 to February 2019 in children hospital Lahore. Patients of congenital cyanotic heart disease who fulfilled the inclusion were selected after taking informed consent. Aggregation ability of platelet rich plasma was tested by collagen (1.25µg/ml), ristocetin (1.2mg), epinephrine (5µM) and ADP (2.5µM).

Results: There were one hundred and eighty-seven patients of congenital cyanotic heart disease in our study. The minimum age was 1 year and maximum age was 15 years with a mean age 8.02 ± 4.31 years. Platelet dysfunction was diagnosed in 60.4% patients.

Conclusion: Platelet dysfunction was found to be high among patients of congenital cyanotic heart diseases.

Keywords: Congenital heart disease (CHD), Cyanotic Congenital Heart Disease (CCHD), tetralogy of fallot, cardiopulmonary bypass.

INTRODUCTION

A lot of functions are attributed to the platelets in the blood and it plays a vital role in the process of regulation of hemostasis. It not only provide hemostatic plug but also cause the acceleration of coagulation cascade.[1] in case of excessive bleeding then the platelet disorder is to be detected in a multistep manner and it is usually started with platelet count. If platelet count is normal then further testing is done such as platelet aggregation testing, platelet adhesion studies, platelet secretion studies, electron microscopy, and specific testing including flowcytometry, study of signal transduction path-ways, support of thrombin formation, genetics, and proteomics.[2] Function of the platelet is different in children as compared to adults so there are different parameters in each laboratory according to the age. A recent publication has showed a new diagnostic approach to detect platelet disorders in children.[3]

Congenital heart disease (CHD) is most common type of congenital disorder in newborn and is leading noninfectious cause of mortality in first year of life. The reported prevalence of congenital heart disease (CHD) at birth ranges from 6 to 13 per 1000 live births.[4] Whenever there is prolonged hypoxemia that causes secondary erythrocytosis and more stress in the vessel wall in patients with cyanotic congenital heart diseases, it can cause chronic endothelial dysfunction due to surface of platelets and hyperviscosity of the blood, which may result in thrombogenesis of microcirculation and increased risk of thromboembolism.[5,6]

Several disorders have been attributed to be associated with congenital heart disease which may include dysfunction of platelets and decreased fibrinogen levels. There may be decreased platelet count, and their activation resulting in fibrinolysis and coagulation when blood is exposed to the artificial surfaces and hemodilution due to priming volume in cardiopulmonary bypass process that may ultimately lead to the decrease in number of platelets count and their abnormal function and there is also decrease in the level of fibrinogen.[7] Therefore, pediatric patients undergoing cardiac surgery are at high risk of excessive bleeding and needing blood transfusion, which may increase postoperative morbidity and mortality.[8]

Moreover, children with cyanotic heart disease who have been planned for cardiac surgery have a lot of abnormalities in their coagulation profile preoperatively and postoperatively these patients need more supplementation of fibrinogen.[9] Therefore, it is considered that it might be related to the antifibrinolytic, anti-platelet activation, and anti-inflammatory effects of TXA.[10]

The rationale of my study is that cyanotic congenital heart disease (CHD) is associated with complex coagulation abnormalities including platelet dysfunction. While some studies indicate a reduction in platelet count and function, other report platelet hyperactivity in CHD. Platelet function has not yet been systemically investigated in children with cyanotic heart disease and also there is lack of availability of local data. With platelet dysfunction bleeding time is prolonged that may cause complications during and after surgery. This study may help us identify platelet dysfunction among cyanotic congenital heart disease in our country as these patients undergo repeated surgeries requiring blood transfusion that may not only help surgeons to manage these patients preoperative but also avoid postoperative complications.

METHODOLOGY

A cross sectional survey was done in the department of Haematology and Transfusion Medicine and Cardiology Department of the Children's Hospital and the Institute of Child Health, Lahore. The duration of the study was one year and was carried out from March 2018 to February 2019. Sample size of 187 cases is calculated with 95%confidance level, 5% margin of error and taking expected percentage of patients with congenital cyanotic heart disease. Consecutive children aged 2 month – 15 years of either gender having congenital cyanotic heart disease and platelet count of > 50,000/µL measured by CBC were enrolled in the study. Patients with a platelet count greater than 50 × 10^3 per µL often are asymptomatic. Patients with a count from 30 to 50 × 103 per µL (30 to 50 × 109 per L) rarely present with purpura, although they may have excessive bleeding with trauma.[11] Patients excluded were those who had acyanotic heart disease diagnosed on echocardiography, taking

Aspirin or clopidogril and having family history of platelet dysfunction.

After obtaining the informed consent from the parents and approval from ethical committee a detailed demographic history, relevant investigation were carried out. Platelet dysfunction was assessed by Platelet aggregation studies. A coronolog aggregometer were used for aggregation studies. Siliconized cuvetts were used for placing platelet rich plasma that will be adjusted to150-350 platelets/µL. Aggregation ability of platelet rich plasma was tested by collagen (1.25µg/ml), ristocetin (1.2mg), epinephrine(5µM) and ADP(2.5µM). Activating agent (50µL) was added at 1000 to 1200rpm speed to platelet rich plasma. After 5 minutes of stimulation results were interpreted as per operational definition (when there is a decrease in light transmission (due to inadequate platelet aggregation) with any one of the various reagents below normal range on Chrono-log aggregometer.) and platelet dysfunction was measured. The reference ranges for normal platelet aggregation below which platelets will be considered dysfunctional with various agonists are as follows:

- Collagen; normal reference ranges 63-84%
- Epinephrine; normal reference ranges 63-97%
- ADP; normal reference ranges 36-101%
- Ristocetin; normal reference ranges 60-100%

Responses below lower limit of reference range for any agonist were considered as absent.

Data analysis was done on software Statistical package for Social science (SPSS) version 17.0. Numerical variables like age, platelet aggregation rate was presented as mean ± standard deviations. Categorical variables like gender, platelet dysfunction was presented as percentages.

RESULTS

From one hundred and eighty-seven patients of congenital cyanotic heart disease the minimum age was 1 year, and maximum age was 15 years with mean ± standard deviation as 8.02 ± 4.31 years. There were 98 (52.4%) male patients and 89 (47.6%) female patients. The minimum platelet count was 150000 and maximum platelet count was 400000 having mean ± standard deviation as 279090.9 ± 76268.68, platelet dysfunction was diagnosed in 113 (60.4%) patients. There were 62 (33.2%) patients having tetralogy of fellot, 28 (15%) patients having complete transposition of great arteries, 27 (14.4%) patients having total anomalous pulmonary venous return, 14 (7.5%) patients having tricuspid atresia, 18 (9.6%) patients having pulmonary atresia, 11 (5.9%) patients having hypoplastic left heart syndrome, 18 (9.6%) patients having ebstein anomaly and 9 (4.8%) patients having persistent truncus arteriosis. Descriptive statistics of age, platelet count, gender, and diagnosis are presented in Table 1.

Table 1: Descriptive statistics of age, platelet count, gender, and diagnosis

Characteristics	Descriptive Statistics
Age (years)	
Range [Max-Min]	15 - 1
Mean ± SD	8.02 ± 4.31
Gender	
Male	52.4% (98)
Females	47.6% (89)
Platelet count	
Range [Max-Min]	400000 - 150000
Mean ± SD	279090.9 ± 76268.68
Platelet Dysfunction	
Yes	60.4% (113)
No	39.6% (74)
Distribution of diagnosis	
Tetralogy of fellot	33.2% (62)
Complete transposition of great arteries	15% (28)

Total anomalous pulmonary venous return/connection	14.4% (27)
Tricuspid atresia	7.5% (14)
Pulmonary atresia	9.6% (18)
Hypoplastic left heart syndrome	5.9% (11)
Ebstein anomaly	9.6% (18)
Persistent truncus arteriosis	4.8% (9)

Collagen was present in 39 (20.9%) patients, Epinephrine was present in 46 (24.6%), ADP was diagnosed in 32 (17.1%) patients, and Ristocetin was found in 53 (28.3%) patients (see Table 2).

Table 2: Frequency and Percentage of Collagen

	Present	Absent
Collagen	39 (20.9%)	148 (79.1%)
Epinephrine	46 (24.6%)	141 (75.4%)
ADP	32 (17.1%)	155 (82.9%)
Ristocetin	53 (28.3%)	134 (71.7%)

DISCUSSION

These Patients with cyanotic heart disease suffer from chronic hypoxemia that makes a lot of changes in the platelet function as well as structure of endothelium. Endothelium-derived relaxation factor is released from the endothelial cells, regulating relaxation of the vascular smooth muscle cells. These regulatory mechanisms are disturbed in case of endothelial dysfunction Conversely, Pedersen et al**.** indicated that Flow-mediated dilatation (FMD) is preserved in adults with cyanotic CHD.[6,12] Platelet function is the most severely affected parameter.[12]

In the present study, there were 33.2% patients with tetralogy of fellot, 15% patients with complete transposition of great arteries, 14.4% patients with total anomalous pulmonary venous return, 7.5% patients had tricuspid atresia, 9.6% patients had pulmonary atresia, 5.9% patients had hypoplastic left heart syndrome, 9.6% patients had ebstein anomaly and 4.8% patients had persistent truncus arteriosis.

In another study done by chaudhary et al.[13] showed a lower activated coagulation time among cyanotic heart disease children (127.95 ± 51.4 s) and a significantly lower clot rate 19.31±10.68 U.min (-1) p=0.009. Platelet function was deranged in 59% of patients with cyanotic heart disease. In this study platelet function was most severely affected in baseline parameter.

In a study by Gross S et al.[14] he tried to find out the find out the number of platelets count in cyanotic patients with different oxygen saturations. Previous literature showed that the mean platelet count in 102 children with congenital cyanotic heart disease was found to be 235,000/mm^3 ± 1 S.D. of 85,000/mm^3 as compared to 260,000 ± 70,000 in an age-matched group of normal children. In the cyanotic children, whose mean oxygen saturation was >80%, the mean platelet level was 315,000/mm^3 as compared to 185,000/mm^3 in the <60% oxygen saturation group. The age of the patient, and thus the duration of the disease, was also related to the platelet levels with significantly higher platelet counts in the children under 3 years of age. The mean age of the patients with platelet counts below 100,000/mm^3 was 4.7 years as compared to a mean age of 2.8 years in the patients with platelet levels greater than 400,000/mm^3.

When we look at the previous literature, a study by Maurer HM et al.[15] showed that approximately 11% of the children with CHD had mild bleeding symptoms, and 9% had prolonged bleeding times, despite normal platelet counts. In 14 of 37 children (37.8%) with cyanotic CHD and four of 28 (14.3%) with the acyanotic variety, platelet aggregation by adenosine diphosphate (ADP), noradrenalin, and connective tissue suspension was impaired.

In our study, collagen was present in 20.9% patients whereas collagen was absent in 79.1% patients. Epinephrine was present in 24.6% patients whereas epinephrine was absent in 75.4% patients. ADP was diagnosed in 17.1% patients whereas ADP was not diagnosed in 82.9% patients. Ristocetin was found in 28.3% patients whereas ristocetin was not found in 71.7% patients. Platelet dysfunction was diagnosed in 60.4% patients whereas platelet dysfunction was not diagnosed in 39.6% patients.

Remková, A et al.[16] compared two groups. Platelet count, endothelial function and coagulation profile of patients suffering from pulmonary arterial hypertension that was due to congenital heart defects was compared with the control group that contained healthy individuals. There were forty-one patients who suffered from Eisenmenger syndrome against total 91 patients. There was a decreased platelet count [190 (147–225) vs. 248 (205–295) 10^9 l^{-1}, $P < 0.0001$], higher mean platelet volume [10.9 (10.1–12.0) vs. 10.2 (9.4–10.4) fl, $P < 0.0001$], and significantly decreased platelet aggregation (induced by five agonists, in various concentrations) in those patients who had Eisenmenger syndrome when compared with control group. So they concluded that Eisenmenger syndrome is accompanied by platelet abnormalities.

In another study by Shebl SS et al.[17] tried to evaluate that patients with the congenital heart disease are more liable to bleed and tried to corelate the clinical presentation of these patients. They did their testing on total forty patients and control group of 20 children who were healthy individuals. Among forty patients half had cyanotic heart disease and half had acyanotic heart disease. There ages were varying between one to ten years. All were subjected to full clinical examination, complete blood count, oxygen saturation, echocardiography, bleeding and coagulation times, PT, PTT, FDPs, plasma soluble P-selectin, E-selectin, and platelet factor 4 (PF4). The results showed decreased platelet counts and prolonged PT and aPTT in both disease group patients but were more prominent in cyanotic congenital heart disease patients.

In our study, collagen was present in 20.9% patients whereas collagen was absent in 79.1% patients. Epinephrine was present in 24.6% patients whereas epinephrine was absent in 75.4% patients. ADP was diagnosed in 17.1% patients whereas ADP was not diagnosed in 82.9% patients. Ristocetin was found in 28.3% patients whereas ristocetin was not found in 71.7% patients.

CONCLUSION

In our study Platelet dysfunction was diagnosed in majority of the patients and most of the patients presented with Tetralogy of fellot.

REFERENCES

1. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. Physiol Rev. 2013;93:327–58.
2. Harrison P, Mumford A. Screening tests of platelet function: update on their appropriate uses for diagnostic testing. Semin Thromb Hemost. 2009;35:150–7.
3. Israels SJ, Kahr WH, Blanchette VS, Luban NL, Rivard GE, Rand ML, et al. Platelet disorders in children: a diagnostic approach. Pediatr Blood Cancer. 2011;56:975–83.
4. Cordina RL, Celermajer DS. Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease. Cardiol Young. 2010;20:242–53.
5. Giglia TM, Massicotte MP, Tweddell JS, Barst RJ, Bauman M, Erickson CC, et al. Prevention and treatment of thrombosis in pediatric and congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2013;128(24):2622-703.
6. Ignjatovic V, Kenet G, Monagle P. Perinatal and Paediatric Haemostasis Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Developmental hemostasis: recommendations for laboratories reporting pediatric samples. J Thromb Haemost. 2012;10(2):298-300.
7. Siemens K, Sangaran DP, Hunt BJ, Murdoch IA, Tibby SM. Strategies for prevention and management of bleeding following pediatric cardiac surgery on cardiopulmonary bypass: a scoping review. Pediatr Crit Care Med. 2018;19:40–7.
8. Cholette JM, Faraoni D, Goobie SM, Ferraris V, Hassan N. Patient blood management in pediatric cardiac surgery: a review. Anesth Analg. 2018;127:1002–16.
9. Vida VL, Spiezia L, Bortolussi G, Marchetti ME, Campello E, Pittarello D et al. The coagulative profile of cyanotic children undergoing cardiac surgery: the role of whole blood preoperative thromboelastometry on postoperative transfusion requirement. Artif Organs. 2016;40:698–705.
10. Goobie SM. Tranexamic acid: still far to go. Br J Anaesth. 2017;118:293–5.
11. Robert LG, Michael MB. Thrombocytopenia. Am Fam Physician. 2012;85(6):612-22.
12. Pedersen CM, Schmidt MR, Mortensen B, Contractor H, Bøtker HE, Kharbanda RK, et al. Preserved flow-mediated dilation in adults with

cyanotic congenital heart disease. Pediatr Cardiol. 2009;30:965–70.
13. Chaudhary V, Chauhan S, Choudhury M, Kiran U, Talwar S, Kapoor PM. Sonoclot analysis in children with congenital heart disease. Asian Cardiovasc Thorac Ann. 2012 Oct;20(5):544-7.
14. Gross S, Keefer V, Liebman J. The platelets in cyanotic congenital heart disease. Pediatrics. 1968;42(4):651-8.
15. Maurer HM, McCue CM, Robertson LW, Haggins JC. Correction of platelet dysfunction and bleeding in cyanotic congenital heart disease by simple red cell volume reduction. Am J Cardiol. 1975;35(6):831-5.
16. Remková A, Šimková I, Valkovičová T, Kaldarárová M. Platelet abnormalities in adults with severe pulmonary arterial hypertension related to congenital heart defects (Eisenmenger syndrome). Blood Coagul Fibrinolysis. 2016;27(8):925-9.
17. Shebl SS, El-Shehaby WAN, Said YS, Darwish AH, Elfadaly NH, Amer E. Thrombo-hemorrhagic liability in children with congenital heart diseases. Hematol Oncol Stem Cell Ther. 2018 Sep;11(3):123-128.