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Risk factors of platelet refractoriness after thrombocyte concentrate transfusion in pediatric acute leukemia

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***Abstract*---**Children with acute leukemia often require platelet transfusions, but the platelet count frequently doesn't reach a satisfactory response, which is known as platelet refractoriness. This study aimed to analyze the risk factors for platelet refractoriness after thrombocyte concentrate transfusion in children with acute leukemia. An analytical observational study with a prospective approach, with subjects with acute leukemia who met the inclusion and exclusion criteria, at Dr. Soetomo General Hospital. Analysis with Chi-square test; Odds Ratio (OR), 95% confidence interval, multivariate Backward Wald method with $p<0.05$. There were 30 subjects, consisting of 19 subjects (63.3%) with platelet refractoriness, 11 subjects (36.7%) did not have platelet refractoriness. The significant differences factors are

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fever, splenomegaly, and antibiotic use with p values of 0.007; 0.004, and 0.049. There was no difference between gender, sepsis, heavy bleeding, chemotherapy, history of thrombocyte concentrate transfusion, and immature platelet fraction with the incidence of platelet refractoriness (p>0.05). Splenomegaly had a 5.333 times greater probability of platelet refractoriness after thrombocyte concentrate transfusion compared to those without splenomegaly in children with acute leukemia, (p=0.008), (OR 5.333; 95% CI 1.554 – 18.304). Splenomegaly is a risk factor for platelet refractoriness after thrombocyte concentrates transfusion in children with acute leukemia.

***Keywords*---**Platelet Refractoriness, Transfusion, Thrombocyte Concentrate, Acute Leukemia, Children.

Introduction

Leukemia is blood cancer, originating from hematopoietic stem cells and progenitor cells that lose the capacity for self-renewal, differentiation, and apoptosis. It is one of the most common cancers occuring in childhood, representing nearly one-third of all cancer diagnoses in children under 15 years of age (Milan et al., 2019). There are 4,100 new cases of cancer in children every year in Indonesia. According to the Indonesian Basic Health Research in 2018, the prevalence of cancer in children under the age of one is 0.03 per mile, aged 1-4 years is 0.08 per mile, and aged 5-14 years is 0.31 per mile (RISKESDAS, 2018). The incidence of acute leukemia in children under the age of 15 is on average 4-4.5/100,000 children per year with a peak of incidence at the age of 2-5 years (KEMENKES, 2011). Children with leukemia often experience mild or severe bleeding associated with thrombocytopenia, which can be caused by infiltration of leukemia cells, side effects of chemotherapy, and infection. Chemotherapy causes myelosuppression which results in thrombocytopenia. Pediatric patients with acute leukemia are also immunocompromised, making them more susceptible to infection and fever that needs the use of antibiotics, which can also stimulate thrombolysis, causing thrombocytopenia. Platelet transfusions are needed to reduce the risk of bleeding-related death (Subash & Umesh, 2018). A study conducted by the National Cancer Institute stated that platelet transfusions are generally carried out as prophylaxis when the platelet counts drop below $20x10^9/L$. Several studies have also shown that a platelet count $<10x10^9/L$ for prophylactic platelet transfusion doesn't increase the risk of (Bercovitz & Josephson, 2012).

Platelet refractoriness can be simply defined as an unsatisfactory increase in platelet count after transfusion (Schiffer et al., 1986). Platelet count often doesn't increase even after a platelet transfusion. Platelet refractory can increase the risks of morbidity and mortality, bleeding, length of hospitalization, and higher costs (Stanworth et al., 2015). A study conducted by Kerkhoffs et al., found a relationship between platelet refractory and the occurrence of bleeding and decreased survival (Kerkhoffs et al., 2008). Platelets' failure to increase after platelet transfusion occurs in 25-70% of patients, especially in repeated

transfusions (Kerkhoffs et al., 2008). The incidence of platelet refractory in hematology/oncology patients varies from 7% to 34% (Forest & Hod, 2016). An observational study with reduced leukocyte blood components showed that 44% of platelet transfusions failed to produce a satisfactory response (Stanworth et al., 2015). A study at King Abdul-Aziz Medical City, Riyadh, reported that platelet refractory occurred in 16.7% of patients with hematological malignancies who underwent platelet transfusion (Abuelgasim et al., 2017). It is estimated about two-thirds of refractory platelets are non-immune, and another 20% is a combination of immune and non-immune. Immune factors are caused by antibodies to human leukocyte antigen (HLA) and/or human platelet antigen (HPA). Non-immune factors include sepsis, fever, splenomegaly, disseminated intravascular coagulation (DIC), drugs, graft-versus-host disease, bleeding, and veno-occlusive disease (Forest & Hod, 2016). Few studies still evaluate the risk factors for platelet refractory after transfusion of platelet concentrates in children with acute leukemia. This study is the first study to examine the risk factors for platelet refractory in children with acute leukemia at RSUD Dr. Soetomo Surabaya. Knowing the risk factors for platelet refractory in children with leukemia is important and expected to reduce costs, mortality, and morbidity due to unnecessary transfusion of platelet concentrates.

Materials and Methods

This was an analytical observational study with a prospective approach. It was conducted from April to June 2022 with a total of 30 subjects who were treated at the pediatric hemato-oncology inpatient care unit at Dr. Soetomo General Hospital Surabaya. Inclusion criteria were children with ALL (Acute Lymphocytic Leukemia) aged 1 month to 18 years, received a platelet concentrate transfusion in one episode of administration until platelet count examination 24 hours post-transfusion, and obtained written consent from parents/guardians to participate in the study. Exclusion criteria were patients with complete blood count 1 hour after transfusion and patients who received whole blood or fresh frozen plasma transfusions during the study.

Patients who met the inclusion criteria were recorded in patient characteristics, clinical conditions (sepsis, fever, splenomegaly, use of antibiotics, heavy bleeding, chemotherapy, gender, history of TC transfusion), and laboratory data (complete blood count and IPF/Immature Platelet Fraction) taken from interviews and medical records. Complete blood count and IPF were collected before transfusion with another complete blood examination 24 hours after platelet concentrate transfusion. IPF was measured at the Clinical Pathology Laboratory of Dr. Soetomo General Hospital using a Sysmex XN-3000 and Lysercell WDF reagent. Subject characteristics were processed by descriptive statistical tests in the form of frequency tables and cross-tabulations. Determination of the relationship with chi-square test and risk factors using logistic regression test (multivariate analysis). Statistical analysis was done using SPSS for Windows version 21.

Findings

There were 30 subjects who met all the inclusion criteria. All were gathered in the pediatric hematology-oncology inpatient room at Dr. Soetomo General Hospital.

Data recorded were patient characteristics, clinical conditions (sepsis, fever, splenomegaly, use of antibiotics, heavy bleeding, chemotherapy, gender, history of TC transfusion), and laboratory data (complete blood count and IPF/Immature Platelet Fraction). There were 30% of subjects who hadn't started chemotherapy, and 70% were undergoing chemotherapy. From 30 episodes of platelet concentrate transfusion performed in all 30 subjects, the average CCI (Corrected Count Increment) was $3.45x10^9/l$ (range $0x10^9/l$ - $19.4x10^9/l$). In this study, 19 subjects (63.3%) had refractory platelets with a mean CCI of $0.51x10^9/l$ (range $0x10^9/l$ - $4.45x10^9/l$) and 11 subjects (36.7%) were not platelet refractory with a mean CCI of $6.8x10^9/l$ (range $4.65x10^9/l$ - $19.4\ x10^9/l$). The average age is 7 years, with ages ranging from 1 month to 1 year were 3.3%, ages 1 year to 10 years were 73.4%, and ages 10 years-18 years were 23.3%. The subjects were 66.7% male and 33.3% female. Diagnoses of ALL were 93.3% and AML was 6.7%. Subjects characteristics were all stated in Table 1.

Factors associated with platelet refractory after platelet concentrate transfusion in children with acute leukemia were tested using the Chi-Square test. Factors that have significant differences include fever, splenomegaly, and the use of antibiotics with a p-value of 0.007; 0.004; and 0.049 respectively. The Odd Ratio (OR) was 17.143, meaning that fever had a risk of 17.143 times greater than the occurrence of platelet refractory. Splenomegaly with an OR of 14.222 makes it 14.222 times greater risk of platelet refractory. Antibiotics administration OR result was 9.000, which means that antibiotics had a 9 times greater risk of platelet refractory. There were no significant differences between gender, sepsis, heavy bleeding, chemotherapy, history of TC transfusion, and immature platelet fraction in the incidence of platelet refractory after platelet transfusion in children with acute leukemia ($p>0.05$).

A logistic regression test was conducted to determine the variables that were eligible to be included in the multivariate test analysis mode. Logistic regression analysis was performed using the Backward Wald method, which was carried out one by one simple regression between each independent variable and the dependent variable in Table 2. The multivariate analysis was resulting in splenomegaly factors having a significant effect on the occurrence of platelet refractory in children with acute leukemia ($p=0.008$), (OR 5.333; 95% CI 1.554 – 18.304). The Backward Wald method showed that respondents with splenomegaly were 5,333 times more likely to experience platelet refractory after platelet transfusion in children with acute leukemia than those without splenomegaly.

Discussions

Platelet refractory is an increase in post-transfusion platelets that is less than expected (Forest & Hod, 2016) and can be caused by non-immunological and/or immunological factors, such as ABO system antibodies, human leukocyte antigen, and/or human platelet antigen present on the donor platelet membrane (Delaflor-Weiss & Mintz, 2000; Shehata et al., 2009; Tinmouth et al., 2006). In this study, of 20 boys, 12 of them had platelet refractory. Meanwhile, 7 out of 10 girls' research subjects had platelet refractory. Gender had no significant difference with the incidence of platelet refractory in this study, with a p-value of 0.702. A study by Ferreira et al. in Brazil resulted from 16 subjects, 9 were

women, and 7 with history of pregnancy. Among patients with alloimmunization, three were due to pregnancy (43%), and two experiencing platelet refractory (29%) (Ferreira et al., 2011). This is contrary to this study which was dominated by boys. Research by Utomo et al also found that most pediatric patients with acute lymphoblastic leukemia treated in Dr. Soetomo General Hospital are boys (Utomo et al., 2017).

Table 1
Subjects characteristics and factors associated with platelet refractory after platelet concentrate transfusion

Variable	Platelet refractoriness	No refractory	*P value*	Odd ratio	95% CI	
	n=19	n=11			Min.	Max.
Gender			0.702	0.643	0.127	3.254
Boy	12 (60)	8 (40)				
Girl	7 (70)	3 (30)				
Sepsis			0.268			
Yes	4 (100)	0 (0)				
No	15 (57.7)	11 (42.3)				
Fever			0.007*	17.143	1.794	163.806
Yes	12 (92.3)	1 (7.7)				
No	7 (41.2)	10 (58.8)				
Splenomegaly			0.004*	14.222	2.324	87.028
Yes	16 (84.2)	3 (15.8)				
No	3 (27.3)	8 (72.7)				
Heavy bleeding			1.000	0.556	0.031	9.873
Yes	1 (50)	1 (50)				
No	18 (64.3)	10 (35.7)				
Use of antibiotics			0.049*	9	0.954	84.899
Yes	9 (90)	1 (10)				
No	10 (50)	10 (50)				
Chemotherapy			0.419	2.625	0.437	15.777
Not yet	7 (77.8)	2 (22.2)				
Undergoing	12 (57.1)	9 (42.9)				
TC transfusion history			1.000			
Yes	18 (62.1)	11 (37.9)				
No	1 (100)	0 (0)				
IPF			1.000	1.231	0.238	6.358
Low	6 (66.7)	3 (33.3)				
Normal	13 (61.9)	8 (38.1)				

All subjects with sepsis experienced platelet refractory but the bivariate analysis shown no significant difference between sepsis and platelet refractory after platelet concentrate transfusion. This is different from the study of Purba et al which stated that sepsis is an independent risk factor for platelet refractory in children with an OR of 2.96 (Purba et al., 2013). These can occur due to differences in the structure of bacteria that cause sepsis such as lipopolysaccharides and endotoxins that also activate platelets directly (Levi, 2005). A total of 12 study subjects with fever experienced platelet refractory.

Research by Subash et al. in Tamil Nadu, India in 198 transfusions given to 30 children with acute leukemia showed an association between fever and platelet count and fever as a cause of thrombocytopenia [OR= 6 (p < 0.05)] (Subash & Umesh, 2018). However, Kumawat et al, found that only 26.7% of patients who underwent transfusion with fever had refractory platelets (OR 5.2 and p-value = 0.08) (Kumawat et al., 2015). Results differenced could be that it was conducted on adult patients with aplastic anemia and AML and other factors that cause fever. From the results of multivariate analysis, fever's not a risk factor for platelet refractory due to other triggering factors such as infection or drugs. Concomitant fever significantly reduces the percentage of platelet recovery when components of randomized donor platelets are given but it doesn't significantly affect the percentage of platelet recovery when appropriate platelets are used (Petz et al., 2000).

Table 2
Risk factors for platelet refractory after platelet transfusion in children with acute leukemia

Variable	*P* value	Odd Ratio	95% CI	
			Minimum	Max
Gender	0.737	0.616	0.036	10.419
Sepsis	0.999	201856361.2	0	.
Fever	0.46	3.431	0.13	90.327
Splenomegaly	0.008*	5.333	1.554	18.304
Heavy bleeding	0,999	0	0	.
Use of antibiotics	0,076	13.43	0.759	237.537
Chemotherapy	0,156	7	0.476	102.918
TC transfusion history	0,08	0.25	0.053	1.177
IPF	0,386	4.054	0.171	95.899

In subjects with heavy bleeding, one had platelet refractory and one did not. The bivariate analysis yielded a non-significant difference, with a p-value of 1,000. In contrast to the study conducted by Purba et al, found that from 1403 platelet transfusions in 464 patients, heavy bleeding was one of the factors that increased the risk of platelet refractory [OR=8.41 (4.19-16.871); p=0.000] (Purba et al., 2013). In the TRAP study by Slichter et al, where 6379 platelet transfusions were given to 533 patients, moderate to severe bleeding was one of the factors that affect the increase of platelet count and platelet refractory by 12% (Slichter, 2005). These differences may be due to the variability of the subject's characteristics. Our study was conducted on children with acute leukemia, where we found only 2 subjects with heavy bleeding.

From 10 research subjects with the use of antibiotics, 9 experienced platelet refractory and 1 subject was not. In this case, the antibiotics that are often used are ampicillin sulbactam. Bivariate analysis was done to examine the difference between factor antibiotics and platelet refractory in children with acute leukemia. We found a significant difference, with a p-value of 0.049. Drug-induced thrombocytopenia is relatively common and is usually immune-mediated. The mechanism by which drugs induce platelet-specific antibodies or increase antibody binding to platelets varies. The most common are the formation of

hapten-dependent antibodies, drug-glycoprotein complex antibodies, autoantibodies, ligand-induced binding sites, drug-specific antibodies, and immune complex-mediated antibodies (Hod & Schwartz, 2008).

We found 6 subjects with low immature platelet fraction (IPF) experienced platelet refractory and 3 did not. Meanwhile, in those with normal IPF, we found 13 subjects with refractory platelets and 8 subjects who did not. The differential test between immature platelet fraction factor and platelet refractory in children with acute leukemia through bivariate analysis showed that the difference was not significant (p-value of 1,000). Immature platelets are the youngest circulating platelets and reflect the degree of thrombopoiesis. IPF can predict platelet count recovery after chemotherapy-induced thrombocytopenia in pediatric patients and assist in directing prophylactic platelet transfusion therapy. IPF is usually high where there is rapid platelet destruction (ITP, as noted, but also thrombotic thrombocytopenia purpura and DIC). IPF is usually low in thrombocytopenia disorders with low or suppressed bone marrow activity (Schmoeller et al., 2017). In a study conducted on 19 children undergoing chemotherapy and with severe thrombocytopenia, the IPF results showed no significant increase over the same period (Have et al., 2013). In this study, the results varied because not all of the subjects underwent chemotherapy. From those who were undergoing chemotherapy, there were 12 subjects with platelet refractory and 9 subjects without. Bivariate test results showed no significant difference (p-value 0.419). Thrombocytopenia that occurs during chemotherapy is usually associated with drug-induced bone marrow suppression and/or tumor replacement of the marrow. Amarullah et al in their study found that 8 out of 13 subjects that received chemotherapy had thrombocytopenia (Amarullah et al., 2013). Curtis et al. reported 2 patients with severe thrombocytopenia and hemorrhagic symptoms while on chemotherapy. Drug-induced immune thrombocytopenia should be considered in patients who experience a sudden decrease in platelet count when given chemotherapeutic agents, especially when there are sufficient megakaryocytes in the bone marrow (Curtis et al., 2006). ALL is a common malignancy in children, with a 70-90% rate of survival despite chemotherapy failure and relapse (Kapoor and Singh, 2018; Lanzkowsky et al., 2011; Pui et al., 2008). In a study by Cahyadi et al, it's stated that all pediatric ALL who died had thrombocytopenia (Cahyadi et al., 2022).

In this study, 16 subjects with splenomegaly had platelet refractory and 3 others did not. Through bivariate analysis, we found that there was a significant difference between splenomegaly and platelet refractory (p-value of 0.004 and an OR of 14.222). From the multivariate analysis, we obtained p = 0.008; OR 5,333; 95% CI 1.554 – 18.304, from the backward wald method meaning that platelet refractory probability incidence is 5.333 times greater in those with splenomegaly. It also means splenomegaly affects the incidence of platelet refractory after platelet concentration transfusion in children with acute leukemia. In line with the research of Purba et al., the risk of platelet refractory increased 4 times (OR=3.94) in children with splenomegaly (Purba et al., 2013). A study by Subash et al also showed an association between splenomegaly and platelet count. Splenomegaly was also associated with thrombocytopenia with OR=2.5 ($p < 0.05$) (Subash & Umesh, 2018).

The spleen is the biggest factor influencing the increase in post-transfusion platelet count. Platelet refractory in patients with splenomegaly occurs due to an increase in platelet sequestration which increases in proportion to the spleen enlargement. The risk of platelet refractory in pediatric patients is higher than adult because the spleen blood volume in children is relatively higher than in adults. In addition, the number of platelets in the spleen's associated with an increase in age and body weight (Purba et al., 2013). Musrtasyidah et al also did a study about refractory platelets which was also conducted at Dr. Soetomo General Hospital, the results obtained from 25 TC transfusions were 20% CCI-1h and 40% CCI-24h with platelet refractory. There was a significant difference between CCI-1h and CCI-24h (p=0.027). The study stated that non-immune factors (fever, bleeding, infection, splenomegaly, male gender) did not affect platelet refractory and the platelet count should be analyzed after 24 hours of TC transfusion to diagnose platelet refractory (Murtasyidah et al., 2021). These results are different from this study where fever, splenomegaly, and the use of antibiotics have significant differences, although in the multivariate analysis only splenomegaly came as a risk factor for platelet refractory with the incidence of platelet refractory being 19 subjects (63.3%).

Conclusion

Sepsis, fever, heavy bleeding, use of antibiotics, chemotherapy, history of platelet transfusion, gender, and IPF are not risk factors for platelet refractory after platelet transfusion in children with acute leukemia. Splenomegaly is a risk factor for platelet refractory after transfusion of platelet concentrate in children with acute leukemia 5.333 times greater than those without splenomegaly.

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