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Risk factors of thrombocytopenia in term infants in Prof. Dr. I.G.N.G. Hospital Denpasar Bali

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Abstract

Thrombocytopenia is a condition in which platelet count below 150 x 109/L. Neonatal thrombocytopenia (NT) accounts up to 35% of all patients admitted to neonatal intensive care unit (NICU). The underlying cause of NT can often be predicted by the onset time of thrombocytopenia and course of disease. The purpose of this study was to determine the risk factors of thrombocytopenia in term infants undergoing treatment at Prof. Dr. I.G.N.G. Hospital.

Method: An observational analytical study using case-control design was conducted in 50 term infants from March 2021 to October 2021 in Prof. Dr. I.G.N.G. Hospital Denpasar Bali.

Result: Total 25 infants with thrombocytopenia in case group and 25 infants without thrombocytopenia in control group. Most of the infants were dominated by female gender (54%), mean gestational age was 38 (± 1) weeks, birth weight 2,940 (± 445) gram, cesarean section (56%). In addition, 48% of patients were vigorous babies. Early-onset neonatal sepsis (EOS) was 76% and late-onset neonatal sepsis (LOS) was 14%, most infants had neonatal pneumonia 58% and necrotizing enterocolitis (NEC) 48%. Mothers with preeclampsia were 26%. Multivariate analysis showed EOS was risk factor for NT (OR 4.69; 95% CI 0.9 – 22.0) and NEC (OR 4.17; 95% CI 1.2 – 14.4).

Conclusion: Early onset neonatal sepsis (EOS) and necrotizing enterocolitis (NEC) are risk factors for thrombocytopenia in term infants.

Keywords: Neonatal Thrombocytopenia; Term Infant; Risk Factor; Hospital

1. Introduction

Thrombocytopenia is condition in which the platelet count below 150 x 109/L[1, 2]. Neonatal thrombocytopenia (NT) is found in up to 35% of all patients admitted to neonatal intensive care unit (NICU)[3]. Based on previous studies, the prevalence of thrombocytopenia infants are very diverse. Severe neonatal thrombocytopenia was present in 34.4% of cases [2]. In previous study, 20% of cases was classified as severe neonatal thrombocytopenia [4, 5]. However, in large cohort study including 11,281 term infants in NICU, severe neonatal thrombocytopenia was only identified in 2.4% due to the high incidence of sepsis [3, 6].

There are two main pathological mechanisms underlying NT, namely increased destruction/sequestration and decreased platelet production. The underlying cause of NT can often be predicted by the onset of thrombocytopenia and the course of disease. However, many cases of thrombocytopenia caused by multiple etiologies [5].

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The frequency of NT occurs rarely in term infants than in preterm infants. In addition, the main risk factor in term infants are infection and NEC (Necrotizing Enterocolitis). Meanwhile the risk factors for NT in prematurity are sepsis, TORCH infection (Toxoplasmosis, Rubella, Cytomegalovirus, and Herpes) and NEC. The risk of spontaneous bleeding is minimal from mild (platelet 20×10^9/L to 100×10^9/L) to moderate (platelet 5×10^9/L to 20×10^9/L and severe (platelet $< 5 \times 10^9$/L). Mild to moderate NT will resolve without intervention [6, 7, 8]

The purpose of this study was to determine the risk factors for thrombocytopenia in term infants whom were treated in Prof. Hospital. Dr. I.G.N.G. Ngoerah Denpasar Bali because there is no such study in Bali.

This research has been approved by Research Ethics Commission Faculty of Medicine, Udayana University / Prof. Hospital. Dr. I.G.N.G. Ngoerah Denpasar with ethical clearance number 992/UN 14.2.2.VII.14/LT/2021.

2. Material and methods

This is an observational analytic study using case-control design. This study started from collecting data on term infants who were treated with thrombocytopenia as case group and data of healthy term infants as control, then the risk factors will be traced retrospectively from medical records. The research was conducted from March 2022 to May 2022.

The minimum total sample was 50 samples, 25 infants in case group and 25 infants in control group. All term infants with diagnosis of NT at period of study were included. Exclusion criteria in this study was preterm infants or term infants who had major congenital abnormalities.

Fifty infants with NT met the inclusion criteria. Data including birth weight, gestational age, mode of delivery and preeclampsia were recorded.

Data analysis was performed by using SPSS for Mac version 25.0. Descriptive analysis: data is presented in tabular form. Categorical data is presented in percentage form. Analytical analysis is divided into two parts, namely: bivariate analysis to assess the risk of neonatal thrombocytopenia by using chi-square test. Multivariate analysis was performed on variables that had p-value <0.25 in bivariate analysis. The analysis was performed by using logistic regression test.

3. Results

Total 50 subjects were analyzed in this study, majority of them were dominated by female 54% and vigorous babies 48%. The percentage of preeclampsia was 26% and without preeclampsia was 74%.

Table 1 Samples' characteristics

Characteristic	Case (n = 25)	Control (n = 25)	Total (n=50)
Gender (n, %)			
Male	11 (44)	12 (48)	23(46)
Female	14 (56)	13 (52)	27(54)
Gestational age mean (± SD)	38 (± 1)	38 (± 1)	
Birth weight mean (± SD)	2940 (± 445)	3028.92 (± 332.67)	
Mode of delivery (n, %)			
C-section	17 (68)	11 (44)	28(56)
Vaginal birth	8 (32)	14 (56)	22(44)
Neonatal asphyxia (n, %)			
Vigorous baby	14 (56)	10 (40)	24(48)
Moderate asphyxia	7 (28)	13 (52)	20(40)
Severe asphyxia	4 (16)	2 (8)	6(12)

Mother with preeclampsia (n, %)			
Yes	6 (24)	7 (28)	13 (26)
No	19 (76)	18 (72)	37 (74)
EOS (n, %)			
Yes	22 (88)	16 (64)	38(76)
No	3(12)	9 (36)	12(24)
LOS (n, %)			
Yes	3 (12)	4 (16)	7(14)
No	22 (88)	21 (84)	47(86)
Neonatal Pneumonia (n, %)			
Yes	12 (48)	9 (36)	21 (42)
No	13 (52)	16 (64)	29 (58)
NEC (n, %)			
Yes	17 (68)	9 (36)	26 (52)
No	8 (32)	16 (64)	24 (48)

Subjects whom experienced EOS was 76%, LOS was 14% and without LOS was 86%, 42% had neonatal pneumonia and 58% did not have neonatal pneumonia and 52% had NEC.

Table 2 Bivariate Analysis of Thrombocytopenia Risk Factors

Variable	**Case n = 25**	**Control n = 25**	**OR (CI 95%)**	**p-value**
EOS (n, %)	22 (88)	16 (64)	4.125 (0.961-17.704)	0.098
LOS (n, %)	3 (12)	4 (16)	0.716 (0.143 – 3.589)	1.000
Neonatal Pneumonia (n, %)	12 (48)	9 (36)	1.641 (0.529 – 5.093)	0.567
NEC (n, %)	17 (68)	9 (36)	3.778 (1.170-12.194)	0.048
Preeclampsia (n, %)	6 (24)	7 (28)	0.812 (0.229-2.882)	1.000

Multivariate analysis with logistic regression was performed on variables with p-value <0.25 in bivariate analysis. The results of analysis showed that EOS and NEC were statistically significant as risk factors for thrombocytopenia in term infants.

Table 3 Multivariate analysis

Variable	**OR**	**CI 95%**	**p-value**
EOS	4.696	0.999 – 22.086	0.050
NEC	4.172	1.205 – 14.440	0.024

4. Discussion

Neonatal thrombocytopenia (NT), is one of the most common hematological disorders in newborns. There are two main pathological mechanisms underlying NT, namely increased destruction/sequestration and decreased platelet production [5]. The etiology of NT varies according to the underlying disease. The most common causes of NT are sepsis

and necrotizing enterocolitis (NEC). The main risk factor in term infants namely infection and NEC (Necrotizing Enterocolitis). Meanwhile the risk factors for preterm infants including sepsis, TORCH infection (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes) and NEC [6,7].

In this study it was found that the proportion of thrombocytopenia in term infants was dominated by female gender (54%). This finding is similar to the study which found that the incidence of thrombocytopenia in term infants was higher in female (51.4%) than male (48.6%), but not significant different [2].

Early-onset neonatal sepsis (EOS) is perinatal infection that occurs immediately in postnatal period, namely infants aged 0-72 hours, while late-onset neonatal sepsis (LOS) is perinatal infection that occurs in infants aged >72 hours. Thrombocytopenia is hematological disorder that often found in infants. Most of the normal infants had mild to moderate thrombocytopenia. Neonatal sepsis is one of the main causes of thrombocytopenia in infants and can be severe that causes increased risk of bleeding within 24 hours of infection [12]. The exact mechanism of thrombocytopenia in neonatal sepsis is still unknown, but several theories suggest the occurrence of platelet consumption, which exceeds the amount of platelet production [8]. Thrombocytopenia is also a predictor of severe sepsis in infants [14].

Based on the results of statistical analysis, the risk factors for thrombocytopenia were EOS with OR 4.69; 95% CI 0.9 – 22.0 (p = 0.050). Early onset neonatal sepsis has risk of thrombocytopenia in term infants 4.696 times. This result is in accordance with Gupta et al. which showed that 65.29% of septic infants suffered thrombocytopenia [13]. In this study, LOS was not a significant risk factor for thrombocytopenia, because the number of subjects with LOS was less than EOS.

Necrotizing enterocolitis (NEC) is necrosis of gastrointestinal tract in infants that causes morbidity and mortality, especially those with gestational age of up to 32 weeks and birth weight less than 1500 grams, placental insuffiency, chorioamnionitis, intestinal ischemic, viral infection, blood transfusion, etc [16]. NEC is often the cause of late-onset neonatal thrombocytopenia that occurs after 72 hours of life. Thrombocytopenia always present in early stage of sepsis or NEC, platelet drops drastically and reach its lowest point within 24-48 hours. Platelet counts can reach 50 x 10^9 and frequent platelet transfusions are required [17]. The exact mechanism of excessive platelet destruction in NEC is unknown. Platelet activators such as platelet activating factors (PAF), arachidonic acid metabolites and coagulation factors stimulate endothelial cells and macrophages. This results in release of thromboplastin from necrotic gut to induce secondary mediators such as proinflammatory cytokines and nitric oxide. In infants with NEC, platelets will decrease and level of Tpo will increase. The more severe the NEC, the platelet count will also decrease due to impaired thrombopoiesis and the presence of megakaryopoiesis inhibitors such as platelet factor (PF-4). The decreased of immature platelet count indicates failure of thrombopoiesis[18,19].

Necrotizing enterocolitis was obtained with OR 4.17; 95% CI 1.2 – 14.4 (p = 0.024) which is 4.172 times risky for thrombocytopenia. This is consistent with Bolat et al. who found that 50–95% of infants with NEC will experience thrombocytopenia (platelet levels <150 x 10^9/L) within 24–72 hours of disease onset[11]. Similar results were also reported by Resch et al. who stated that thrombocytopenia was found in 50–95% of non-natives with NEC and had platelet count in range of 30 × 10^9/L - 60 × 10^9/L[8].

Neonatal pneumonia defined as inflammation of lung parenchyma in infants. Mostly are caused by microorganisms (viruses/bacteria) and few are caused by other causes (aspiration, radiation, etc.)[21]. Neonatal pneumonia is important cause of neonatal infection with significant morbidity and mortality [22]. Similar to sepsis, in pneumonia there is systemic inflammatory process destructs platelets that exceed the number of its production. The end result of infection is thrombocytopenia. In this study, neonatal pneumonia was not risk factor for thrombocytopenia, this was caused by the percentage of infants without pneumonia who had thrombocytopenia was higher (58%) than infants with pneumonia (42%).

Thrombocytopenia in infants is one of the frequent complications of preeclampsia. Roberts and Murray postulated that preeclampsia will cause hypoxia in fetus, thereby depress megakaryocytopoiesis and platelet production in the fetus [5]. In this study the number of subjects who had preeclampsia was not risk factor for the occurrence of NT.

5. Conclusion

Early onset neonatal sepsis (EOS) and necrotizing entercolitis (NEC) are risk factors for thrombocytopenia in term infants.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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