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Original Article

Incidence and risk factors of neonatal thrombocytopenia: a preliminary study

Nila Kusumasari, Rinawati Rohsiswatmo, Djajadiman Gatot, Darlan Darwis

Abstract

Background Thrombocytopenia is the most common hematological abnormality in the neonatal period. Hemorrhagic manifestations are found in 10% cases of thrombocytopenia. Neonatal thrombocytopenia commonly assumed due to sepsis, despite many risk factors that may caused thrombocytopenia.

Objective To obtain incidence and risk factors of neonatal thrombocytopenia.

Methods A cross sectional study was conducted in April 2009. Complete blood counts investigation was performed before age of 24 hours, medical conditions and risk factors of mothers and subjects were noted, as well as hemorrhagic manifestations. Subjects with thrombocytopenia were followed for 2 weeks. The risk factors consisted of hypertension in pregnancy, pre-eclampsia, eclampsia, intrauterine growth retardation, gestational diabetes mellitus, perinatal infection, asphyxia, sepsis, and necrotizing enterocolitis.

Results Neonatal thrombocytopenia was found 17 (12.1%) of 140 subjects, consisted of 88.2% early onset and 11.8% late onset. Significant risk factor of mother was pre-eclampsia (PR 3.97, 95%CI 1.70 to 9.25), while significant risk factors of neonates were asphyxia (PR 5.66, 95%CI 2.49 to 12.86), sepsis (PR 5.33, 95%CI 2.33-12.19) and necrotizing enterocolitis (p=0.014; PR 9.2 95% CI 5.17 to14.84). We found 29.4% hemorrhagic cases of neonatal thrombocytopenia (i.e.,. skin, gastrointestinal, intracranial hemorrhage).

Conclusions The incidence of neonatal thrombocytopenia was 12.2%. Significant risk factor of mother that caused thrombocytopenia was pre-eclampsia, while risk factors of neonates were asphyxia, sepsis and necrotizing enterocolitis. **[Paediatr Indones. 2010;50:31-7]**.

Keywords: *thrombocytopenia, neonates, risk factors*

Thrombocytopenia is the most common hemostatic disorder found in neonates. Thrombocytopenia is defined as platelet counts less than 150.000/μL.[1] Platelet count usually reaches more than 150.000/μL at 18-20 weeks of gestational age and remains constant until term months. Therefore, thrombocytopenia in neonates is an abnormal condition.[2] Several studies reported thrombocytopenia occurs in 0.16-0.9% of all newborns. Hemorrhage manifestations are not found in all thrombocytopenic neonates. Not more than 10% of hemorrhage manifestations are found in thrombocytopenic neonates.[3-6]

Currently, complete blood count (CBC) is not routinely performed in newborn babies; it is only performed in newborn baby with risk factors.[5] In Indonesia, health care centers still have limited facilities, so that pregnant women with complications have not been managed adequately. Cipto Mangunkusumo Hospital (CMH) as a national referral hospital caused most pregnant women with many complications came to this hospital. For those reasons, many newborn babies have asphyxia,

From the Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Reprint request to: Nila Kusumasari, MD, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital, Jl. Salemba no. 6, Jakarta 10430, Indonesia. Tel. +62-21-7443615.

intrauterine growth retardation (IUGR) or sepsis. In Perinatology Divison, the incidence rate of neonatal thrombocytopenia is not known. Complete blood counts are performed only in neonates with signs of infection, though many other risk factors caused neonatal thrombocytopenia. Those risk factors are not investigated further. The aims of this study were to obtain incidence rate and risk factors of neonatal thrombocytopenia.

Methods

This was a cross-sectional study carried out at the emergency room CMH and Perinatology Division in April 2009. Subjects were all newborn babies whose parents gave informed consent.

Sample size was calculated using the rule of thumb, i.e. 15 subjects per risk factors, yielded 135 subjects, who were recruited consecutively. After taking permission from the parents, medical conditions and risk factors of mothers and subjects, as well as hemorrhagic manifestations, were noted. Complete blood count was performed before the age of 24 hours. Subjects with thrombocytopenia were followed for 2 weeks. Subjects without thrombocytopenia but hospitalized were also followed for two weeks. The studied risk factors were pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia, intrauterine growth retardation, gestational diabetes mellitus (GDM), perinatal infection, asphyxia, sepsis, and necrotizing enterocolitis (NEC).

Statistical analysis was carried out using Fisher's test to show the association between neonatal thrombocytopenia and risk factors. A *P* value of less than 0.05 was considered as statistically significant. Risk factors with *P* value less than 0.25 were carried out logistic regression test. This study was approved by the Ethics Committee of Faculty Medicine, University of Indonesia.

Results

There were 140 newborns of 137 mothers were enrolled in this study, with simlar male and female subjecs. Most subjects were term babies (85.7%) with normal birth weight (75.7%). Mode of delivery by spontaneous was more common than assisted delivery **(Table 1).**

Table 1. The characteristics of study subjects

Charateristics	N	%
Sex		
Male	68	48.6
Female	72	51.4
Gestational age (weeks)		
<37	20	14.3
37-42	120	85.7
>42	0	0
Birth weight (grams)		
< 2500	29	20.7
2500-4000	106	75.7
> 4000	5	3.6
Mode of delivery		
Spontaneous	62	44.3
Vacuum extraction	6	4.3
Forceps extraction	7	5
Caesarean section	65	46.4

Table 2. Incidence of thrombocytopenia

Onset thrombocytopenia	N	%
Thrombocytopenia	17	
≤72hours of age	15	88.2
>72 hours of age	2	11.8

All subjects were performed CBC investigation before 24 hours of age with the median platelet counts was 283,000/μL (range 70,000-598,000/μL). Out of 140 subjects, thrombocytopenia was found in 17 (12.1%) subjects with platelet counts ranging from 63.000-148.000/μL. Based on the onset of thrombocytopenia, 15 of 17 subjects developed early onset thrombocytopenia (≤72 hours of age) and the rest developed late onset thrombocytopenia (>72 hours of age) **(Table 2)**.

The risk factors that commonly found in subjects with early onset thrombocytopenia were pre-eclampsia, perinatal infection, PIH, IUGR, GDM, asphyxia and sepsis, meanwhile subjects with late onset thrombocytopenia were asphyxia, sepsis and NEC **(Table 3, Table 4)**.

Among mother's risk factors, only pre-eclampsia was statistically significant in the occurrence of neonatal thrombocytopenia **(Table 5)**.

Out of 140 subjects, there were 21 (15%) subjects with pre-eclampsia. There was one case of pre-eclampsia followed by HELLP

Table 3. Data of neonates with thrombocytopenia at ≤72 hours of age

No	Discharged/ Hospitalized	Platelet count (x103/μL)			Hemorrhage	Risk factors		GA	Final diagnosis
		≤72h	Lowest	Normal		Neonate	Mother		
1	Discharged	146	-	250 (H-1)	-	Asphyxia	Pre-eclampsia	TB	
2	Discharged	70	-	186 (H-2)	-	-	Pre-eclampsia	TB	
3	Discharged	148	-	205 (H-2)	-	-	Pre-eclampsia	TB	
4	Discharged	128	-	196 (H-2)	-	-	-	PB	
5	Discharged	130	-	`185 (H-2)	-	-	Pre-eclampsia	TB	
6	Discharged	75	-	318 (H-1)	-	-	PIH		
7	Hospitalized	118	-	187 (H-3)	-	-	Pre-eclampsia, IUGR	TB	IUGR
8	Hospitalized	148	78 (H-6)	185 (H-8)	Hematemesis intracranial	Asphyxia, sepsis	Pre-eclampsia, GDM, perinatal infection	TB	Sepsis
9	Hospitalized	130	-	167 (H-3)	-	Asphyxia, sepsis	-	PB	Sepsis
10	Hospitalized	116	-	178 (H-4)	-	Asphyxia, sepsis	-	TB	Sepsis
11	Hospitalized	139	97 (H-3)	160 (H-8)	-	Asphyxia, sepsis	Perinatal infection	TB	Sepsis
12	Hospitalized	131	-	163 (H-2)	Hematemesis	Asphyxia, sepsis	-	PB	Sepsis
13	Hospitalized	145	78 (H-9)	182 (H-11)	Petechie hematemesis	Sepsis	Pre-eclampsia	TB	Sepsis
14	Hospitalized	132	-	-	-	Asphyxia	-	TB	PDA
15	Hospitalized	141	-	175 (H-6)	-	Sepsis	-	TB	Sepsis

Note: GA=gestational age; PDA=persistent ductus arteriosus; PB=preterm baby; TB=term baby

Table 4. Data of neonates with thrombocytopenia at >72 hours of age

No	Discharged/ Hospitalized	Platelet counts (x103/μL)			Hemorrhage manifestations	Risk factors		GA	Final diagnosis
		>72 h	Lowest	Normal		Neonate	Mother		
1	Hospitalized	63 (H-12)	-	157 (H-18)	Hematemesis	Sepsis, NEC	Perinatal infection	PB	Sepsis, NEC
2	Hospitalized	91 (H-14)	-	170 (H-18)	Hematemesis, intracranial	Asphyxia, sepsis, NEC	-	PB	Sepsis, NEC

Note: GA=gestational age; PB=preterm baby

Table 5. The association between mother's risk factors and neonatal thrombocytopenia

Risk factor		Thrombocytopenia		Total	P*	PR (95% CI)
		Yes	No			
Pre-eclampsia	Yes	7	14	21	0.005	3.97
	No	10	109	119		(1.70-9.25)
PIH	Yes	1	12	13	0.512	0.61
	No	16	111	127		(0.09-4.24)
IUGR	Yes	1	10	11	0.603	0.73
	No	16	113	129		(0.11-5.02)
GDM	Yes	1	4	5	0.48	1.69
	No	16	119	135		(0.28-10.34)
Perinatal infection	Yes	3	24	27	0.578	0.90
	No	14	99	113		(0.28-2.90)

*Fisher test; PR=prevalence ratio; 95% CI=95% confidence interval

Table 6. The association between neonates' risk factors and thrombocytopenia

Risk factor		Thrombocytopenia		Total	P*	PR (95% CI)
		Yes	No			
Asphyxia	Yes	8	11	19	0.000	5.66
	No	9	112	121		(2.49-12.86)
Sepsis	Yes	8	12	20	0.000	5.33
	No	9	111	`120		(2.33-12.19)
NEC	Yes	2	0	2	0.014	9.2
	No	15	123	138		(5.71-14.84)

*Fisher test; PR=prevalence ratio; 95% CI=95% confidence interval

Table 7. The association between pre-eclampsia, asphyxia, sepsis, necrotizing enterocolitis with neonatal thrombocytopenia

Risk factor	P*	PR (95% CI)
Pre-eclampsia	0.001	0.102 (0.026-0.398)
Asphyxia	0.000	0.079 (0.02-0.315)
Sepsis	0.103	0.288 (0.065-1.286)
NEC	0.999	0.000 (0.000-0.…)

*Logistic regresion test; PR=prevalence ratio; 95% CI=confidence interval

syndrome (hemolysis, elevated liver enzymes, and low platelets), but the infant had normal platelet counts. Asphyxia, sepsis and NEC were statistically significant in the occurrence of neonatal thrombocytopenia **(Table 6)**, but using logistic regression test, pre-eclampsia, asphyxia, sepsis, and NEC were not statistically significant **(Table 7)**.

Hemorrhage manifestations was found in 5 (29%) of 17 thrombocytopenic subjects. One subjects with gastrointestinal bleeding had platelet counts 100,000-<150,000/μL, where other four subjects with petechie, gastrointestinal bleeding, and intracranial hemorrhage had platelet counts 50,000-<100,000/μL. No subject experienced hematuria **(Table 8)**.

Discussion

This study used a cross-sectional design, that made it difficult to determine causality. The more risk factors of neonatal thrombocytopenia were studied, the larger the required sample size. We found that the incidence of neonatal thrombocytopenia was higher than in other studies (<1%)[3-6] because there might be different medical conditions and complications of pregnant women in our hospital. In this study, many pregnant women had pre-eclampsia or perinatal infection. Management of pregnancy with complications was also different due to limited facilities. Those were reasons for increased incidence rate of newborn with asphyxia and sepsis, followed by increased neonatal thrombocytopenia.

Subjects with thrombocytopenia mostly developed early onset thrombocytopenia (88.2%). Mild thrombocytopenia was found in 74.6% cases; the rest had moderate thrombocytopenia. No severe thrombocytopenia was found. Roberts et al stated that mild and moderate thrombocytopenia were more frequently found than severe thrombocytopenia.[7]

In this study, a statistically significant risk in the mother was pre-eclampsia [P=0.005; PR 3.97 (95% CI 1.70-9.25)], whereas pregnancy-induced hypertension, eclampsia, gestational diabetes mellitus, intrauterine growth retardation and perinatal infection were not. There were 33.3% subjects with thrombocytopenia from pre-eclamptic mothers. The platelet counts ranged from 70,000-148,000/μL. Besides pre-eclampsia, several subjects had other risk factors, such as GDM, IUGR or asphyxia which could induce neonatal thrombocytopenia. This was similar to the result of Brazy's study thrombocytopenia found in 36% neonates from pre-eclamptic mothers).[8] The platelet counts rarely reached <50,000/μL.[9] The pathophysiology of pre-eclampsia remains unknown.

Table 8. Hemorrhage manifestations of neonatal thrombocytopenia

No	Risk factor	GA	Platelet count (/µL)	Hemorrhage manifestations
1	Asphyxia, sepsis	PB	100,000 - <150,000	Hematemesis
2	Asphyxia, sepsis, pre-eclampsia,GDM, perinatal infection	TB	50,000 - <100,000	Hematemesis, intracranial
3	Sepsis, pre-eclampsia	TB	50,000 - <100,000	Petechie, hematemesis
4	Sepsis, NEC, perinatal infection	PB	50,000 - <100,000	Hematemesis, intracranial
5	Asphyxia, sepsis, NEC	PB	50,000 - <100,000	Hematemesis

Note: GA=gestational age; PB=preterm baby; TB=term baby

Recent studiessuggested that placental ischemia is an early event, leading to placental production of a soluble factor that caused maternal endothelial dysfunction, resulting in the clinical findings of hypertension, proteinuria and edema. Placental soluble fms-like tyrosine kinase 1 (sFlt1), an antagonist of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), is upregulated in preeclampsia, leading to increased systemic levels of sFlt1 that fall after delivery. The increased circulating sFlt1 in patients with preeclampsia is associated with decreased circulating levels of free VEGF and PlGF, resulting in endothelial dysfunction that can be rescued by exogenous VEGF and PlGF.[10,11]

This study found that all risk factors in neonates were significantly associated with neonatal thrombocytopenia. We found asphyxia in 13.6% of subjects and neonatal thrombocytopenia in 42.1% of them [*P*=0.000; PR 5.66 (95% CI 2.49-12.86). Andrew et al reported asphyxia in 53.1% of subjects, and 54.8% among them had thrombocytopenia.[12] These results may differ because Andrew used preterm babies as his subjects. The incidence of asphyxia was quite high in this study because the definition of asphyxia used was according to WHO (Apgar score below 7 at 1 minute).[13] No subject had an Apgar score of 0-3 for more than 5 minutes. Asphyxia caused impaired thrombocytopoiesis and platelet production.[7] Other risk factors (e.g. perinatal infection, sepsis, pre-eclampsia) also contributed to thrombocytopenia.

We found that sepsis was statistically significant risk factor [*P*=0.000; PR 5.33 (95% CI 2.33-12.19)] for neonatal thrombocytopenia. The incidence of sepsis was 14.3%, and 40% among them had thrombocytopenia. Thrombocytopenia occurred for 2-11 days. The risk factors of sepsis were premature rupture of membranes, urinary tract infection, stained amniotic fluid, prematurity and low birth weight. It was similar with the results of Modanlou's study reporting that there were 13.1% cases of sepsis and 62.5% among them developed thrombocytopenia. Thrombocytopenia occurred for 1-10 days. Risk factors which contributed to sepsis were premature rupture of membrane, perinatal infection and asphyxia.[14] Sepsis causes thrombocytopenia by several mechanisms, including disseminated intravascular coagulation (DIC), endothelial damage, immune-mediated destruction, platelet aggregation due to bacterial products adhering to platelet membrane, and decreased platelet production from infected bone marrow.[9]

Necrotizing enterocolitis is the most common gastrointestinal medical/surgical emergency occurring in neonates. Although it is more common in premature infants, it can also be observed in term and near-term babies. Necrotizing enterocolitis represents a significant clinical problem and affects close to 10% of premature infants. Although the pathogenesis of NEC remains uncertain, a large body of evidence suggests a multifactorial etiology, including the presence of abnormal bacterial flora, intestinal ischemia, reperfusion injury with activation of proinflammatory cellular cascades, and intestinal mucosal immaturity/dysfunction.[15] In this study we found that two subjects of premature neonates with late onset thrombocytopenia developed NEC. Perinatal asphyxia and sepsis affected the thrombocytopenia. Necrotizing enterocolitis was a satistically significant risk factor of neonatal thrombocytopenia [*P*=0.014; PR 9.2 (95% CI 5.17-14.84)]. In preterm neonates, impaired thrombocytopoiesis caused thrombocytopenia at birth or as was predisposing factor for thrombocytopenia when neonates were exposed to conditions which led to increased platelets consumption.[15]

The logistic regression test for the association between pre-eclampsia, asphyxia, sepsis, NEC and neonatal thrombocytopenia showed that no variable was statistically significant as a risk factor of neonatal thrombocytopenia. This might be due to the large number of studied risk factors with a small sample size. Therefore a prospective cohort study is needed to evaluate the association between risk factors and neonatal thrombocytopenia.

Andrew et al reported that thrombocytopenia increased the risk of hemorrhage. Asphyxia and DIC more frequently increased the risk of hemorrhage.[12] Mehta noted that significantly more thrombocytopenic neonates had hemorrhage manifestations than non-thrombocytopenic ones. There were 22% cases of hemorrhage in thrombocytopenic neonates in Mehta's study.[16] We found hemorrhage (petechiae, gastrointestinal hemorrhage, intracranial hemorrhage) in 29.4% of thrombocytopenic neonates. The presence of perinatal asphyxia and sepsis could increase the risk of hemorrhage.

In this study, two thrombocytopenic neonates developed intracranial hemorrhage. One infant had germinal matrix intraventricular hemorrhage. The infant had several risk factors (low gestational age, low birth weight, asphyxia, respiratory distress syndrome, sepsis) that also contributed to intracranial hemorrhage. Infants with gestational age below 32 weeks, birth weight below 1500 grams, asphyxia, respiratory distress syndrome, and sepsis had a higher risk of intracranial hemorrhage.[17] Respiratory distress syndrome was often accompanied by hypercarbia and hypoxemia which in turn could increase cerebral blood flow to compensate cerebral hypoxia. The increased cerebral blood flow and the immature structure of blood vessels may cause blood vessel rupture in the germinal matrix. This in turn will lead to GM-IVH in varying degrees.[18] The other infant had subgaleal hematoma and epidural hemorrhage. The infant was a term baby and large for gestational age with cranial birth injury and asphyxia. Cranial birth injury, besides thrombocytopenia, induced intracranial hemorrhage. Subgaleal and epidural hemorrhage are rarely found in neonates. Cranial birth trauma was more common to cause such hemorrhage.[19,20]

In conclusion, the incidence of neonatal thrombocytopenia in our study was 12.2%. The significant risk factor in the mother for neonatal thrombocytopenia was pre-eclampsia, whereas the risk factors in the neonates were asphyxia, sepsis, and NEC. We recommend performing complete blood count in neonates with risk factors of neonatal thrombocytopenia in order to prevent hemorrhage. Further cohort studies with larger sample size are needed to evaluate the association between neonatal thrombocytopenia and its risk factors.

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