SANAMED
2019; 14(3): 241–246
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.352
UDK: 616.155.2-053.31
ID: 281827596
Original article

THROMBOCYTOPENIA AS ONE OF THE REASONS OF PROLONGED STAY IN THE NEONATAL INTENSIVE CARE UNIT

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Primljen/Received 25. 07. 2019. god.

Prihvaćen/Accepted 02. 10. 2019. god.

Abstract: The aim of this paper was to present the occurrence and severity of thrombocytopenia, with intracranial and another bleeding in neonates with sepsis, analyze the risk factors for the development of thrombocytopenia and compare it with the length of hospitalization in the Neonatal Intensive Care Unit (NICU). Thrombocytopenia is a platelet count <150 x 109/L and is common in newborns during hospitalization in the NICU. In the early days of life, the most common causes of thrombocytopenia in newborns are conditions that lead to fetal hypoxia, intrauterine growth failure, maternal hypertension, and sepsis. In this study were included all newborns with thrombocytopenia, who were hospitalized in NICU, Children's Disease Clinic, University Clinical Centre in Tuzla, from 01. 01. 2014 to 01. 01. 2019.

In our results, 379 newborns had severe, 337 moderate, and 127 milder forms of thrombocytopenia, without a statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GW and ≥ 37 GW. Sepsis was the most common cause of thrombocytopenia, 300 children had early sepsis and 190 late. We found the statistically significant difference in intracranial hemorrhage of the second degree and pulmonary hemorrhage among neonates born < 37 GW in relation to newborns born ≥ 37 GW. A statistically significant effect of length of stay of our neonates in the Department of Neonatal Intensive Therapy and morbidity was shown in relation to the lower gestational age and lower platelet counts.

Conclusion: Timely diagnosis of the cause and development of thrombocytopenia with adequate and effective treatment can reduce the mortality and morbidity of newborns with perinatal risk for neonatal thrombocytopenia.

Key words: thrombocytopenia, newborn, sepsis, neonatal intensive care unit.

INTRODUCTION

Thrombocytopenia by definition is reduced platelet count < 150 x 109/L and frequent finding in neonates during hospitalization in the Neonatal Intensive Care Unit (NICU) (1). Despite a large number of studies, thrombocytopenia in the newborn is still in the focus of interest, due to possible complications resulting from a reduced number of platelets, such as various bleeding, especially intracranial and necrotizing enterocolitis, with possible fatal outcome (2).

In the first days of life, the most common causes of thrombocytopenia in neonates are antibodies mediated by platelet destruction, intrauterine growth retardation, and maternal hypertension, along with other factors associated with chronic fetal hypoxia. Antibodies mediated by platelet destruction are further classified into neonatal alloimmune thrombocytopenia when the mother's antibodies recognize fetal platelets as foreign and destroy them. However, it also could be a passive transfer of maternal autoantibodies that are produced in the mother due to the existence of an autoimmune disease, such as systemic lupus or immune thrombocytopenic purpura, when the platelets are also destroyed.

One of the main causes of thrombocytopenia in NICU is sepsis, during which middle-to-severe thrombocytopenia occurs in the period from 24 to 48 hours from the first signs of infection (3). Congenital infections, the causative agents of toxoplasmosis, measles, cytomegalovirus, herpes simplex virus, and fungal infections are also possible causes of thrombocytopenia in the neonatal period.

The thrombocytopenia pathogenesis and platelet count in neonatal sepsis have not yet been fully clarified, nor did the exact number of platelets, by which bleeding occurs. A possible mechanism of bleeding is damage to the blood vessel endothelium that activates the reticuloendothelial platelet damage system. Throm-

bocytopenia occurs when it is a higher consumption than platelet production, with the particular role of reduced serum thrombopoietin (1).

Thrombocytopenia, that occurs within the first 72 hours of birth is early, compared to late, which occurs after 72 hours of birth. In relation to the platelet count, it may be severe form < 30 x 109/L, a moderate form of 31 to 100 x 109/L, and a milder form of 101 to 150 x 109/L (4, 5).

The aim of this paper was to present the occurrence and severity of thrombocytopenia, with intracranial and another bleeding in neonates with sepsis, analyze the risk factors for the development of thrombocytopenia and compare it with the length of hospitalization in the Neonatal Intensive Care Unit.

SUBJECTS AND METHODS

All newborns with thrombocytopenia, who were hospitalized in the Department of Neonatal Intensive Care Unit, the Clinic for Children's Diseases, University Clinical Centre in Tuzla, in the period from 01. 01. 2014 to 01. 01. 2019 were included in this study. Data are collected from the history of neonatal disease. The research was approved by the Ethics Committee, University Clinical Centre in Tuzla.

Data on hypertension, the number and the order of pregnancy, and the way of ending the delivery were collected from the mother's history of the disease. Maternal hypertension was defined when systolic blood pressure was higher than 140 mmHg, diastolic 90 mmHg or more, in more than two measurements, or once measured with values greater than 160/110 mmHg.

The children's history of the disease has been reported data of gestational age, birth weight, gender, day of occurrence and duration of thrombocytopenia,severe bleeding and length of hospitalization.

Of the hematological data for each child, the initial platelet count was observed in the occurrence of sepsis and the lowest number of platelets over the duration of the sepsis. The clinical diagnosis of sepsis was confirmed by a positive finding of blood culture.

The exclusion criteria of this study were for newborns, who had a good general condition in the first 24 hours, with the excluded clinical diagnosis of sepsis, and were moved to another department, or had a contaminated blood culture, i.e. positive blood culture, without an increase in C- reactive protein and no antibiotic treatment in the first 72 hours.

All data were statistically processed and displayed using tables and images. The standard methods of descriptive statistics were used in the analysis. Absolute numbers and percentages were used to describe categorical data. The mean value ± standard deviation, or median, was used to describe numerical data. Statistical data analysis was carried out using the statistical program SPSS (version 17, StatSoft, Tulsa, USA).

RESULTS

This study included 843 newborns with thrombocytopenia, 536 (41.3%) born < 37 GW (week of gestation), and 307 (27%) born ≥ 37 GW. The prevalence of thrombocytopenia in preterm births was 6.5% (843/1296) compared to the previous 5 years. Most of our neonates, 489 (58.6%) had early thrombocytopenia. There was no statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GW and ≥ 37 GW. Table 1 isthe epidemiological date of newborns with thrombocytopenia born < 37 GW and born ≥ 37 GW (Table 1).

In our study, 379 newborns had severe, 337 moderate, and 127 milder forms of thrombocytopenia (Figure 1).

Table 2 shows the perinatal data of neonates with thrombocytopenia. The average mother's age of children with thrombocytopenia born < 37 GW was 24 ± 3.2, while for children born ≥ 37 GW was 28.2 ± 4.1 years. Hypertension had 61.8% of mothers in the group

Table 1. *Newborns with thrombocytopenia born < 37 GW and ≥ 37 GW*

Birth year	Total number of births (<37 GW / > 37 GW)	Newborns with thrombocytopenia born < 37 GW		Newborns with thrombocytopenia born ≥ 37 GW	
		(n; %)	Time of sepsis onset (early/late)	(n; %)	Time of sepsis onset (early/late)
2014	195 (130/65)	78 (40%)	50/28	40 (20.5%)	29/11
2015	180 (111/69)	87 (48.3%)	50/37	35 (19.4%)	19/16
2016	247 (149/98)	105 (42.5%)	75/30	60 (24.3%)	30/30
2017	332 (182/150)	116 (35%)	70/46	82 (25%)	40/42
2018	342 (172/170)	150 (44%)	85/65	90 (26.3%)	41/49
Ukupno	1296 (747/522)	536 (41.3%)	330/206	307 (27%)	159/128

Table 2. *Perinatal data of neonates with thrombocytopenia*

Perinatal data	Number of newborns with thrombocytopenia born < 37 GW	Number of newborns with thrombocytopenia born ≥ 37 GW
Mother's age (years)	24 ± 3.2 (14-47)	28.2 ± 4.1 (15-45)
Mother's hypertension	310 (57.8%)	190 (61.8%)
Number of pregnancy	2 (1-5)	2 (1-6)
Multiple pregnancy	92 (17.2%)	34 (11%)
Intrauterine growth of retardation	173 (32.3%)	148 (48.2%)
Caeserian section	328 (61.2%)	170 (55.9%)
Age of gestation (week of gestation)	30 ± 3.9 (24-36)	38.2 ± 2.1 (37-42)
Birth weight (gram)	1010 ± 234 (455-2500)	3550 ± 456 (2950-5010)
Gender (male/female)	80:55 (15:10%)	150:197 (49:64%)
Apgar score after 1 minute	4 (0-9)	6 (0-9)
Apgar score after 5 minute	8 (0-9)	9 (0-9)

*Data is represented by a number as n (%) or median (space)

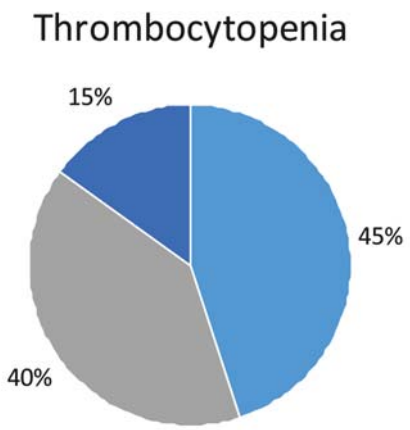
Table 3. *Causes of thrombocytopenia in neonates*

Causes of thrombocytopenia	Number of newborns with thrombocytopenia born < 37 GW	Number of newborns with thrombocytopenia born ≥ 37 GW	P values
Sepsis	300 (55.9%)	190 (62%)	0.268
Early onset of sepsis	180 (33.5%)	120 (39%)	0.112
Late onset of sepsis	120 (22.3%)	70 (11%)	0.534
Perinatal asphyxia	530 (98%)	268 (87.2%)	0.065
Necrotizing enterocolitis	88 (16.4%)	10 (30.7%)	0.068
Chromosomal abnormalities	13 (2.4%)	20 (6.5%)	0.876

Table 4. *Hemorrhagic diathesis in neonates with thrombocytopenia*

haemorrhage	Number of newborns with thrombocytopenia born < 37GW	Number of newborns with thrombocytopenia born ≥ 37GW	p
Intracranial haemorrhage grade I	54 (10%)	30 (9.7%)	0.322
Intracranial haemorrhage grade II	250 (46.7%)	250 (81.4%)	0.040*
Intracranial haemorrhage grade III	32 (5.9%)	37 (12%)	0.644
Cutaneus bleeding	98 (18.2%)	60 (19.5%)	0.342
Pulmonal haemorrhage	169 (31%)	20 (6.5%)	0.003*
Haematuria	2 (0.3%)	1 (0.3%)	0.675
Gatrointestinal haemorrhage	23 (4,2%)	10 (3%)	0.546

of births ≥ 37GW. In both groups, children with thrombocytopenia were from second pregnancy, and in the group of children < 37 GW, 17.2% were from multiple pregnancies. Although 48.2% of children with thrombocytopenia who was born ≥ 37 GW had an intrauterine delay in growth, the incidence of cesarean section was greater in the birth group ≥ 37 GW. Newborns with thrombocytopenia in the group < 37 GW are born in 30 ± 3.9 GW, with a birth weight of 1010 ± 234 grams, and in the group ≥ 37 GW at 38.2 ± 2.1 GW and 3550 ± 456 grams. The higher incidence of males was seen in the group of children < 37 GW and lower Apgar score.



* Severe thrombocytopenia 45% (platelets < 30 x 109/L), moderate 40% (platelets 31 to 100 x 109/L), mild 15% (platelets > 101 to 150 x 109/L).

Figure 1. *Thrombocytopenia in our neonates*

The causes of neonatal thrombocytopenia are shown in Table 3. Sepsis was the most common cause of thrombocytopenia, 300 children had early sepsis and 190 late. Thrombocytopenia was associated with sepsis, necrotizing enterocolitis, perinatal asphyxia, and chromosomal abnormalities, with no statistically significant difference between neonates born <37 or ≥ 37 GW.

In Table 4, the rates of intracranial and another bleeding of neonates with thrombocytopenia in relation to gestational age are shown. We found the statistically significant difference in intracranial hemorrhage of the second degree (p = 0.04) and pulmonary hemorrhage (0.003) among neonates born < 37 GW in relation to newborns born ≥ 37GW.

A two-factor analysis of the variance of neonates with thrombocytopenia has shown the effect of the platelet count and gestational age on the length of hospitalization in the NICU and the state of morbidity (Figure 2). Newborn infants are divided by gestational age into two groups (1group < 37 GN, 2 groups ≥ 37 GN) and platelet counts (group 1 < 30 x 109/L, group 2 from 31 to 100 x 109/L, and 3rd group 101 to 150 x 109/L). The effect of interaction between gestational age and platelet count was not statistically significant, F (2,290) = 1.44, p = 0.74. A statistically significant influence of the length of stay in NICU and morbidity of newborns in relation to younger gestational age and lower platelet count F (0.873) = 2.91, p = 0.002 was determined.

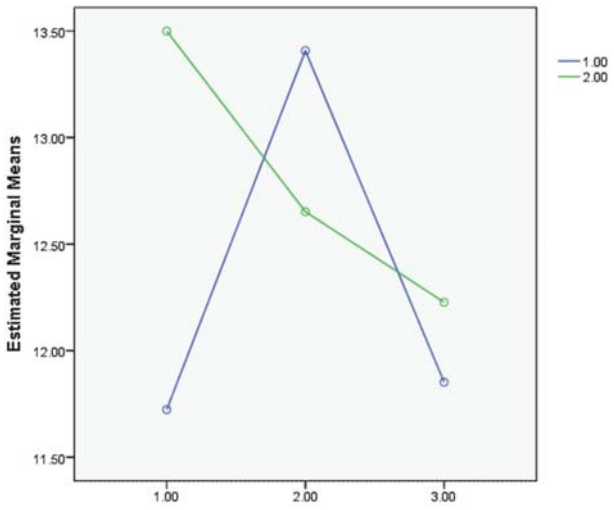


Figure 2. *Effect of the platelet count and gestational age on the length of hospitalization in NICU of the neonates with thrombocytopenia*

DISCUSSION

Thrombocytopenia in the neonatal period is a common problem. During our research, it was recorded in more than half of newborns (68.3%). In 45% of newborns, severe thrombocytopenia has been diagnosed. Most of our neonates, 489 (58.6%) had early thrombocytopenia, but without a statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GN and ≥ 37 GN. The Dutch authors presented similar results in their research (6).

The average of mother's age of children with thrombocytopenia born < 37 GN was 24 ± 3.2, while for children born ≥ 37 GN was 28.2 ± 4.1 years. Hypertension had 61.8% of mothers in the group of children born ≥ 37 GN. In both groups, children with thrombocytopenia were from second pregnancy. In the group of children < 37 GN, 17.2% were from multiple pregnancies. A higher percentage of 48.2% of children with thrombocytopenia born ≥ 37 GN had intrauterine growth retardation, while a higher incidence of cesarean sections had newborns in the group of ≥ 37 GN. Newborns with thrombocytopenia in the group < 37 GN are generally born in 30 ± 3.9 GN, with a birth weight of 1010 ± 234 grams, and in the group ≥ 37GN at 38.2 ± 2.1 GN and 3550 ± 456 grams. The higher incidence of males was seen in the group of children < 37 GN and lower Apgar score. According to the data of a large retrospective cohort study (7), Resch et al. proved that neonatal thrombocytopenia is directly related to maternal hypertension and the elderly age of birth, also more frequent in prematurely born children, with lower birth weight and lower Apgar scores, which we had during our research.

Thrombocytopenia was associated with sepsis, necrotizing enterocolitis, perinatal asphyxia, and chromosomal irregularities, with no statistically significant difference between neonates born <37 GN or ≥ 37. Bleeding was diagnosed in 443 (50%) infants. The incidence of caesarean section in newborns with sepsis

and thrombocytopenia can be explained by the higher incidence of maternal hypertension and the risk of birth naturally. It is known that maternal hypertension, in addition to being a risk factor for the development of neonatal thrombocytopenia, is a possible risk factor for intrauterine growth retardation. Also, maternal hypertension leads to fetal hypoxia and causes suppression of fetal megakaryocytopoiesis and platelet production. According to a study by British authors (8) and central venous catheters, they cause mechanical damage to the blood vessel, which directs the flow of blood in the other direction into the vascular wall sections that damage the megakaryocytopoiesis process.

Inthe newborns with thrombocytopenia intracranial, bleeding in the skin, pulmonary and gastrointestinal bleeding and hematuria were often, but statistically, a significant difference was found in intracranial hemorrhage of the second degree ($p = 0.04$) and pulmonary hemorrhage (0.003) among neonates born < 37 GN in relation on newborns born ≥ 37 GN.

The association between the number of platelets and clinically manifest bleeding complications is still not fully clarified. The incidence of association of major manifest bleeding and severe thrombocytopenia in several different authors ranges from 15% to 50% (9, 10). The risk of occurrence of manifest bleeding is associated with lower gestational age, but a small number of platelets is not yet an indicator or measure of severe manifest bleeding in a child (10, 11).

In several different studies, the association between thrombocytopenia and gram-negative sepsis was found (12, 13). The number of platelets is significantly lower in gram-negative sepsis and sepsis caused by fungi, compared with gram-positive sepsis. According to research by Ahmed F et al. the duration of thrombocytopenia in gram-positive sepsis is also lower compared to gram-negative (14). The pathogenesis of thrombocytopenia in neonatal sepsis has not yet been fully clarified. Thrombocytopenia should be a predictor of the severity of sepsis, the more gram-negative than gram-positive, as it causes intravascular disseminated coagulopathy (12). An important mechanism of action of endotoxin in gram-negative bacteria is important.

During our research, a statistically significant difference was found on the length of stay in NICU and morbidity of neonates compared to younger gestational age and lower platelet counts, as was confirmed by other authors in their research (13, 14, 15).

However, further and more detailed research is needed to help determine the exact number of platelets as a predictor of possible bleeding and prevention of sepsis and mortality in newborns, as well as longer hospitalization in the NICU.

CONCLUSION

Thrombocytopenia is often diagnosed in the neonatal period. Most episodes are mild or moderate and usually pass without major clinical consequences for the newborn. However, severe thrombocytopenia also causes serious consequences and is associated with longer hospitalization and more frequent child mortality. Early birth, sepsis, and perinatal asphyxia are the most common causes of neonatal thrombocytopenia. A timely diagnosis of the cause of thrombocytopenia with adequate and effective treatment can reduce the mortality and morbidity of newborns with perinatal risks for the development of neonatal thrombocytopenia.

Abbreviations

NICU — Neonatal Intensive Care Unit
GW — week of gestation

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

TROMBOCITOPENIJA KAO JEDAN OD RAZLOGA PRODUŽENE HOSPITALIZACIJE NA ODELJENJU NEONATALNE INTENZIVNE NEGE

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Cilj ovog rada je bio uporediti pojavu i težinu trombocitopenije, uz intrakranijalno i druga krvarenja kod novorođenčadi sa sepsom, te analizirati faktore rizika za nastanak i razvoj trombocitopenije i dužine hospitalizacije na Odeljenju neonatalne intenzivne terapije.

Trombocitopenija je broj trombocita < 150 x 109/L i čest je nalaz kod novorođenčadi tokom hospi-

talizacije na Odeljenju neonatalne intenzivne terapije. U prvim danima života najčešći razlozi trombocitopenije kod novorođenčadi su stanja koja dovode do fetalne hipoksije, intrauterinog zastoja u rastu, majčina hipertenzija i sepsa. U ovo istraživanje su uključena sva novorođenčad sa trombocitopenijom, koja su bila hospitalizovana na Odeljenju neonatološke intenzivne terapije, Klinike za dečije bolesti, JZU UKC Tuzla, u periodu od 01. 01. 2014. do 01. 01. 2019. godine.

Rezultatima smo pokazali da je 379 novorođenčadi imalo tešku, 337 umerenu, a 127 blaži oblik trombocitopenije, bez statistički značajne razlike u učestalosti trombocitopenije između grupa novorođenčadi rođenih < 37 GN i >37 GN. Sepsa je bila najčešći razlog trombocitopenije, 300 dece je imalo ranu, dok 190 kasnu sepsu. Kod novorođenčadi rođene < 37 GN u odnosu na novorođenčad rođenu > 37 GN nađena je statistički značajna razlika kod intrakranijalnog krvarenja drugog stepena i plućnog krvarenja.Utvrđen je statistički značajan uticaj dužine boravka na Odeljenju neonatalne intenzivne terapije i morbiditeta novorođenčadi u odnosu na mlađu gestacijsku dob i niže vrednosti trombocita.

Zaključak: Pravovremeno dijagostikovanje razloga nastanka trombocitopenije uz adekvatno i pravovremeno lečenje može smanjiti smrtnost i morbiditet novorođenčadi sa perinatalnim rizicima za nastanak neonatalne trombocitopenije.

Ključne reči: trombocitopenija, novorođenčad, sepsa, Neonatalna Intenzivna terapija.

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