Risk Factors For Severity Of Thrombocytopenia In Full Term Infants: A Single Center Study

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Research

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Abstract

Background

Neonatal thrombocytopenia (NT) is a common finding in the neonatal intensive care unit (NICU). The main aim of this study was to assess the prevalence, rick factors and outcomes of severe NT in full term (FT) infants.

Method:

During the study period, all FT infants who met the inclusion criteria for NT on two occasions were included. Maternal data such as maternal age, weight, gestational age, mode of delivery, and history of systemic diseases were recorded. Furthermore, neonatal data such as gender, neonatal weight, causes/duration of admission, types of respiratory support used, blood count and outcomes for neonates admitted to the NICU were recorded.

Results

In total, 55 FT infants with NT met the inclusion criteria. In all, 29 (52.73%) cases had severe NT. The most common cause of NT was neonatal sepsis (20 cases, 37.03%), followed by a postoperative state (5 cases, 9.25%). Moreover, in cases of positive blood cultures, the most commonly isolated organism was *Escherichia coli* (6 cases, 10.90%), followed by *Klebsiella* (5 cases, 9.09%). Cases of severe NT, when compared to cases of mild/moderate NT associated with signs of bleeding and pulmonary/intraventricular hemorrhage (IVH) (P = 0.001), needed more platelet transfusions (P = 0.001) and had higher rates of mortality (P = 0.001).

Conclusion

Severe NT occurred in 52.73% of cases. The most common cause of NT was neonatal sepsis, followed by a postoperative state. Furthermore, severe NT, when compared to mild/moderate NT associated with signs of bleeding and pulmonary/IVH, needed more platelet transfusions and had increased mortality.

Introduction

Thrombocytopenia, generally defined as a platelet count $< 150 \times 10^9$/L, affects up to 35% of all patients admitted to the neonatal intensive care unit (NICU) [1, 2]. Early onset neonatal thrombocytopenia (NT) presenting in the first 72 hours of life is commonly associated with pregnancy complications, such as intrauterine growth restriction, maternal diabetes, maternal immune thrombocytopenic purpura (ITP), congenital infection or neonatal alloimmune thrombocytopenia (NAT) [3]. While late onset NT presenting

after 72 hours of age is usually secondary to sepsis or necrotizing enterocolitis (NEC), it is usually more severe and prolonged [4].

There are two main underlying pathologic mechanisms for NT: increased destruction/sequestration or decreased production of platelets. The underlying cause of NT can often be predicted by the timing of the onset of the thrombocytopenia and its natural history [5]. However, from a clinical point of view, many cases had a compound etiology for thrombocytopenia.

In most cases, NT is mild to moderate and resolves without intervention. Life-threatening bleeding, intraventricular hemorrhage (IVH) or pulmonary hemorrhage with a high risk of neurodevelopmental impairment may occur in severe NT [6, 7]. However, NT in full term (FT) infants occurs less frequency than in preterm infants, as it was 2% in one study cohort [8]. Moreover, the main risk factors in term infants were placental insufficiency, NAT and occult infection, which differs from preterm rick factors such as sepsis, TORCH infection, and NEC [9].

Furthermore, the outcome of NT depends on several factors, such as birth weight, gestational age, platelet count and the underlying cause [10]. The relationship between the risk factors for NT and degree of severity, especially in FT infants, is not well studied. Moreover, a clear correlation between degree of NT and resulting bleeding risk factors has not been demonstrated [11]. Therefore, the aim of this study to determine the risk factors and outcomes for severity of NT in FT infants

Methods

The current clinical study was performed at the NICU in the Pediatrics Department, in cooperation with the Department of Clinical Pathology, Sohag University, Egypt, during the period from January 2019 to the end of December 2019. Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Sohag University (Number 652, 2018), and written informed consent was obtained from all parents of the participating children.

Patients selection

All FT infants with a diagnosis of NT on two occasions, at the time of study, were included in the study, whether thrombocytopenia was discovered within the first complete blood counts (CBC) or later. Exclusion criteria included any preterm delivery <37 weeks gestational age or neonates who had multiple congenital malformations at birth. The severity of NT was determined according to Roberts et al. [4] and categorized into mild thrombocytopenia (platelet count 100–150 × 10^9/L), moderate thrombocytopenia (50–99×10^9/L), and severe thrombocytopenia (<50×10^9/L). Furthermore, cases were classified as early onset NT (presenting in the first 72 hours of life) and late onset NT (presenting after 72 hours of life).

Maternal data collection

Maternal data such as maternal age, weight, gestational age, mode of delivery and maternal diseases, including diabetes mellitus, pre-eclampsia, premature rupture of membranes (PROM), systemic lupus erythematosus, ITP, and positive consanguinity, were recorded.

Neonatal data collection and investigations

Furthermore, neonatal data such as gender, neonatal weight, APGAR score, causes of admission to NICU, duration of admission in NICU, types of respiratory support used, CBC measurements (done by Cell Dyn 3700, automated cell counter, Abbott Diagnostics, USA), and thrombocytopenic manifestations, such as purpura, ecchymosis, gastric bleeding, bleeding from puncture site, and pulmonary hemorrhage or IVH, were recorded. Detailed systemic examination focusing on skin examination, macrosomia, head circumference, intrauterine growth retardation, congenital anomalies, and dysmorphic features were recorded. Septic work-ups and blood cultures/sensitivities were done for all included cases. A TORCH screen was done (by ARCHITECT *i*1000SR, Abbott Diagnostics, USA) in suspected congenital infection. Chromosomal assays [12,13] were done in suspected chromosomal abnormities. In neonates suspected to have NAT from the presentation and clinic course of the illness, put in the idiopathic causes as the diagnostic tests not available in our lab. Neonatal outcomes for neonates admitted to the NICU were also recorded.

Statistical analysis

Data was analyzed using STATA version 14.2 (Stata Statistical Software: Release 14.2, College Station, TX: Stata Corp LP). Quantitative data was represented as mean and standard deviation and median and range. Data was analyzed using Student's t-test to compare the means of two groups. When the data was not normally distributed, the Mann-Whitney test was used. Qualitative data was presented as number and percentage and compared using either the Chi square test or Fisher exact test. P value was considered significant if it was <0.05.

Results

Patient characteristics

In total, 55 FT infants who met the inclusion criteria were included in this study. Thirty (54.55%) cases were delivered by Cesearn section and 25 (45.45%) cases by normal vaginal delivery. Of these, 33 (60.00%) were male and 22 (40.00%) female. The mean ± SD of the platelet count at diagnosis was 67.53±46.91 x 10^9/L. In this study, 29 (52.73%) cases had severe NT at diagnosis and 26 (47.27%) cases had mild/moderate NT. However, out 55 diagnosed cases, most of them remained asymptomatic (32 cases, 58.18%), 14 (25.45%) cases had tendency to bleed from the puncture sites, 2 (3.64%) cases developed pulmonary hemorrhage and 2 (3.64%) cases developed IVH. Other maternal and neonatal characteristics are described in Table 1.

Causes of neonatal thrombocytopenia

As shown in Table 2, the most common cause of NT was neonatal sepsis (20 cases, 37.03%), followed by a postoperative state (5 cases, 9.25%). Chromosomal assays were done for 6 patients, two had Down syndrome (3.70%), TORCH screen was done in 10 patients and no cases had congenital infection. However, in cases of positive blood cultures, the most commonly isolated organism was *Escherichia coli* (6 cases, 10.90%), followed by *Klebsiella* (5 cases, 9.09%). Early onset NT was found in 18 (32.72%) cases, while late onset NT was found in 37 (67.27) cases.

Risk factors for thrombocytopenia severity

As regards the classification of the degree of NT into mild, moderate, and severe, there were 19 (34.54%), 7 (12.72%) and 29 (52.73%) cases, respectively.

Moreover, as shown in Table 2, 35 (63.64%) cases of NT needed respiratory support, either CPAP or mechanical ventilation, due to the presence of respiratory problems beside the NT. The total duration of hospital stay was 8.67±3.95 days. Furthermore, in this study, 6 (10.90%) cases were declared, and 5 of them had severe NT.

However, there were no significant differences in severity of NT and in maternal risk factors, such as diabetes (P = 0.08), pre-eclampsia (P = 0.09), history of PROM (P = 0.62), and mode of delivery (P = 0.51). Furthermore, in this study, the presence or absence of neonatal sepsis did not increase the severity of NT (P = 0.13), as shown in Table 3.

Thrombocytopenia manifestations

As regards manifestations of NT in FT infants (Table 3), most mild and moderate cases were asymptomatic (25/26 cases, 96.15%), and only one case had gastrointestinal bleeding. In contrast, 22/29 (75.86%) cases who had severe NT were symptomatic from gastrointestinal bleeding, bleeding from puncture sites, or pulmonary/IVH (P= 0.001). Moreover, FT infants with severe NT needed more platelet transfusions compared to cases who had mild/moderate NT (P=0.001).

Thrombocytopenia related morbidity and mortality

As shown in Table 4, the need for invasive mechanical ventilation was associated with severe NT in 14/29 (48.28%) cases compared to only 1/26 (3.85%) cases in those who had mild/moderate NT needing mechanical ventilation (P= 0.001). Furthermore, the neonatal mortality was high in cases with severe NT (5 cases out of a total 6 cases declared) compared to only one case who died in those with mild/moderate NT (P= 0.001).

Discussion

In this study, we found that, out of 55 FT infants who developed NT during the study period, about half of them had severe NT at diagnosis and appeared after 72 hours of life in about two-thirds of cases. The most common causes of NT were neonatal sepsis and a postoperative state. Furthermore, severe NT,

when compared to mild/moderate NT, was associated with more morbidity (pulmonary or IVH), needed more platelet transfusions, and had increased mortality.

In our study, severe NT was found in 52.73% of total thrombocytopenic cases. This result was higher than other studies. Gupta et al. [14] found that severe NT accounted for 34.4% of cases. In another study, 20% of cases were classified as severe NT (6). However, Robert et al. [4] in a large cohort study, included 11 281 NICU admissions of term or preterm infants over 5 years found only severe NT was identified (2.4%). The reason for a higher incidence of NT in our study was probably because the incidence of sepsis in our group was high. This has been shown in other study as well [15]. In contrast to FT infants, in preterm babies, Christensen et al. found that about 73% of extremely low birth weight neonates, at some time during their NICU stay, had at least a one-time platelet count $< 150 \times 10^9$/L, and this incidence increased up to 85% among neonates with a birth weight $\leq$ 800 g [16]. Furthermore in our study, most cases of NT in term infants were late onset (after 72hours of life) in about two-thirds of the cases. This was not in agreement with another study in which the majority (84.1%) had early onset NT, but 76% of cases were born preterm [9].

NT occurs more frequently in association with certain factors, such as sepsis, birth asphyxia, babies born to mothers with pre-eclampsia and low birth weight, and this was seen in our study as well. In our study, the most common cause of NT was neonatal sepsis in about one-third of the cases. Furthermore, the most commonly isolated organisms in septic neonates were gram negative (*E. coli* and *Klebsiella*) in 55% of cases. These results agree well with Ree et al. [17], as they found that severe NT occurred in 20% of septic neonates and the most commonly isolated organisms were gram negative. The pathogenesis of NT in neonatal sepsis is not completely understood. It has been suggested that, in neonatal sepsis, endothelial damage activates reticuloendothelial removal of platelets. NT occurs as, ultimately, the rate of platelet production falls behind platelet consumption [2]. The second most common cause of NT in our study was a postoperative state. Although the definite causes of postoperative NT have not been established in the literature, many factors have been proposed, including post-transfusion dilution, infection-induced, drug-induced, heparin-induced, immune mediated and others [18].

In this study, most cases (58.18%) were asymptomatic. The most common presentations, occurring mostly with severe NT, were cutaneous bleeding from previous puncture sites and gastrointestinal bleeding. These results agree with a study by Baer et al. [6]. Furthermore, our results also agree with Park et al. [19], as they found that gastrointestinal hemorrhage in patients with aplastic anemia and severe thrombocytopenia was recorded in 5% of those for whom the lowest platelet count was 20×10^9/L, compared with 1% of those for whom the lowest count was $20 \times 10^9 – 50 \times 10^9$/L.

We found that pulmonary and IVH occurred exclusively with severe NT. This agrees with a study by Setzer et al. [20], and Bolat et al. [21] as they found that lower platelet counts correlated with a higher prevalence of IVH. It was not clear from research, until now, whether NT caused the IVH or it occurred after as a result of consumptive mechanisms. In contrast to our results, Baer et al. [6] found, in patients with severe NT, no relationship between the lowest platelet count recorded and the presence of pulmonary hemorrhage or

IVH. They speculated that factors other than NT are prominent in the pathogenesis of those varieties of neonatal bleeding, such as coagulation disorders. Duppre et al. [22] found that a cellular and humoral coagulation disorder had more of a role in the occurrence of IVH in neonates than thrombocytopenia.

In our study, there were no statistically significant differences between duration of hospital stay and severity of NT, which did not agree with Resch et al. [23], as they found the duration of NT is positively related to the severity of NT and the number of subsequent platelet transfusions. Furthermore, in this study, half of the neonates with severe NT required mechanical ventilation. This may explain the bad general condition of these patients, and the actual mortality may not only be related to severe NT but also the original disease, such as sepsis, postoperative state or disseminated intravascular coagulopathy.

The outcomes of NT in our study showed that mortality increased to 10.90% with severe NT. In a study by Resch et al. [9], a mortality rate of 10.8% was significantly associated with signs of bleeding ($P < 0.05$) and correlated with an increasing number of platelet transfusions ($P < 0.05$), but not with the severity of NT ($P = 0.4$). Furthermore, results from studies by Baer et al. [6] and Resch et al. [23] found no relationship between the lowest platelet count recorded and the mortality rate; however, a direct relationship was observed between the number of platelet transfusions received and the mortality rate. In our study, two-thirds of cases with severe NT received at least once platelet transfusion. This may be explained by the fact that ill patients receive more platelet transfusions or as adverse effects of platelet transfusions [24]. Therefore, we used the following restricted guidelines for administering platelet transfusions in our unit: (I) platelet count $\leq 100 \times 10^9$/L just going to or just having had surgery or having clinical bleeding, (II) platelet count $\leq 50 \times 10^9$/L and unstable (mechanical ventilation or vasopressors), and (III) platelet count of 20×10^9/L and stable [6, 21].

In conclusion, severe NT occurred in about half of cases diagnosed with NT in FT infants and appeared after 72 hours of life in about two-thirds of them. The most common causes of NT were neonatal sepsis and a postoperative state. Furthermore, severe NT, when compared to mild/moderate NT associated with signs of bleeding and pulmonary/IVH, required more mechanical ventilation, needed more platelet transfusions, and had increased mortality.

Abbreviations

FT: full term; ITP: immune thrombocytopenic purpura; IVH: intraventricular hemorrhage; NAT: neonatal alloimmune thrombocytopenia; NEC: necrotizing enterocolitis; NICU: neonatal intensive care unit; NT: neonatal throbmcytopenia.

Declarations

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Author' contributions

RAM, AMS, AEA, set up, designed and data collection of the research project. SPA contributed to all the necessary materials and laboratory facilities. RAM perform the discussion and interpretation of the data. All authors reviewed and

approved the final manuscript for publication.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The research related to human subject use complied with all the relevant national regulations and institutional policies. Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Sohag University, Egypt (Number 652, 2018).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Maternal and neonatal characteristics of studied population

Variables	Summary statistics
Mother's age/years (mean ± SD)	29.18±4.33
Mother's weight/kg (mean ± SD)	77.36±6.31
Positive consanguinity	13 (23.64%)
Mothers had Diabetes	9 (16.36%)
Mothers had Preeclampsia	6 (10.91%)
History of PROM	3 (5.45%)
Mode of delivery	
Normal vaginal delivery	25 (45.45%)
Cesarean section	30 (54.55%)
Neonatal Weight (Kg) (mean ± SD)	2.77±0.61
Gender (Male/female)	33(60.00%)/ 22(40.00)
Neonatal WBCs (mean ± SD)	13.57±4.83
Neonatal Hemoglobin (mean ± SD)	15.86±4.46
Neonatal Platelet count at diagnosis (mean ± SD)	67.53±46.91
Thrombocytopenia degree at diagnosis	
Mild	19 (34.55%)
Moderate	7 (12.73%)
Severe	29 (52.73%)
Manifestation of thrombocytopenia	
No	32 (58.18%)
Bleeding from puncture site	14 (25.45%)
Gastrointestinal bleeding	5 (9.09%)
Pulmonary hemorrhage	2 (3.64%)
Intraventricular hemorrhage	2 (3.64%)
Received Platelets transfusion	20 (36.37%)

Table 2 Distribution of studied population according to some different variables.

Variables	Summary (total 55 cases)
Diagnosis of thrombocytopenia	
Late onset sepsis	13 (23.63%)
Early onset sepsis	7 (12.72%)
Post-surgery	5 (9.09%)
IUGR and placental insufficiency	4 (7.27%)
Disseminated intravascular coagulopathy	3 (5.45%)
Maternal ITP	3 (5.45%)
DM, hypoglycemia	3 (5.45%)
Down syndrome	2 (3.63%)
SLE	2 (3.63%)
Post exchange transfusion	2 (3.63%)
Tetralogy of Fallot	2 (3.63%)
Birth asphyxia	2 (3.63%)
Metabolic disorders	2 (3.63%)
Idiopathic	5 (9.09%)
Onset of thrombocytopenia	
Early onset thrombocytopenia	18 (32.72%)
Late onset thrombocytopenia	37 (67.27)
Severity of thrombocytopenia	
Mild thrombocytopenia	19 (34.54%)
Moderate thrombocytopenia	7 (12.72%)
Severe thrombocytopenia	29 (52.73%)
Blood culture	
No gross	35 (63.64%)
E-coli	6 (10.90%)
Klebesiella	5 (9.09%)
Enterobacter	3 (5.45%)
Pneumococci	3 (5.45%)
Staphylococcus aureus	3 (5.45%)
Respiratory support	
Room air	15 (27.27%)
CPAP	25 (45.45%)
Mechanical ventilation	15 (27.27%)
Duration of hospital stay (mean ± SD)	8.67±3.95
Outcome	
Alive	49 (89.10%)
Dead	6 (10.90%)

Table 3 Relation between thrombocytopenia severity and maternal/ neonatal characteristics

Variable	Thrombocytopenia (total 55 cases)		P value
	Mild/moderate	Severe	
	N=26 (47.27%)	N=29 (52.73%)	
Mother's age/years (mean ± SD)	29.69±4.77	28.72±3.92	0.41
Mother's weight/kg (mean ± SD)	77.56±5.67	76.34 ±8.23	0.62
Positive consanguinity	6 (23.08%)	7 (24.14%)	0.93
Mothers had Diabetes	5 (19.23%)	3 (10.34%)	0.08
Mothers had Preeclampsia	5 (19.23%)	1 (3.45%)	0.09
History of PROM	1 (3.85%)	2 (6.90%)	0.62
Mode of delivery			
Normal vaginal delivery	13 (50.00%)	12 (41.38%)	0.51
Cesearn Section	13 (50.00%)	17 (58.62%)	
Neonatal Weight/kg (mean ± SD)	2.77±0.74	2.76±0.50	0.97
Neonatal WBCs (Mean ± SD)	13.38±4.45	13.74±5.22	0.96
Neonatal Hemoglobin gram/dL (Mean ± SD)			
	15.99±3.19	10.06±3.46	0.001
Neonatal sepsis			
No sepsis	19 (73.08%)	16 (55.17%)	0.13
Early onset sepsis	4 (15.38%)	3 (10.34%)	
Late onset sepsis	3 (11.54%)	10 (34.48%)	
Manifestation of thrombocytopenia			
No			
Bleeding from puncture site	25 (96.15%)	7 (24.14%)	0.001
Gastrointestinal bleeding	0	14 (48.28%)	
Pulmonary hemorrhage	1 (3.85%)	4 (13.79%)	
Intraventricular hemorrhage	0	2 (6.90%)	
	0	2 (6.90%)	
Platelets transfusion			
No	26 (100%)	9 (31.03%)	0.001
Yes	0	20 (68.97%)	

Table 4 Relationship between neonatal respiratory support, duration of hospital stay, outcome and degree of thrombocytopenia.

Variable	Thrombocytopenia (55cases)		P value
	Mild/moderate	Severe	
	N=26 (47.27%)	N=29 (52.73%)	
CPAP			
No	12 (46.15%)	18 (62.07%)	0.23
Yes	14 (53.85%)	11 (37.93%)	
Mechanical ventilation			
No	25 (96.15%)	15 (51.72%)	0.001
Yes	1 (3.85%)	14 (48.28%)	
Outcome			
Alive	25 (96.15%)	24 (82.76%)	0.001
Dead	1 (3.85 %)	5 (17.24%)	
Duration of hospital stay			
Mean ± SD	9.19±3.70	8.21±4.18	0.21