Prevalence and outcomes of thrombocytopenia in a neonatal intensive care unit

Prévalence et pronostic de la thrombopénie dans une unité de réanimation néonatale.

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RÉSUMÉ

Prérequis : La thrombopénie est une complication hématologique fréquente en unité de réanimation néonatale, sa prévalence varie de 18 à 35%. Généralement légère ou modérée, parfois elle est sévère mettant en jeu le pronostic vital et le pronostic neurologique

Objectif : Étudier la prévalence, les étiologies et les facteurs de risque de mauvais pronostic des thrombopénies dans une unité de réanimation néonatale.

Méthodes : Nous avons mené une étude rétrospective dans l'unité de réanimation néonatale de l'Hôpital Charles Nicolle de Tunis, sur une durée de quatre ans (Janvier 2010-Décembre 2013). Tous les nouveau-nés ayant présenté au moins un épisode de thrombopénie confirmée durant leur séjour hospitalier ont été inclus. Le mauvais pronostic était défini par les décès ou une hémorragie intraventriculaire ≥ grade 2 chez les survivants.

Résultats : Parmi les 808 admissions en unité de réanimation néonatale, 100 ont présenté au moins un épisode de thrombopénie, soit une prévalence de 12,4%. Douze nouveau-nés ont présenté deux épisodes de thrombopénie durant leurs hospitalisations, soit un total de 112 épisodes. La thrombopénie était précoce dans 74,1% des cas. La thrombopénie était légère dans 22,3%, modérée dans 36,7% et sévère dans 41% des cas. Le retard de croissance intra-utérin était la cause la plus fréquente des thrombopénies précoces. L'infection nosocomiale était la cause la plus fréquente des thrombopénies tardives.

Conclusions : La thrombopénie néonatale peut mettre en jeux le pronostic vital ou être responsable de séquelles. Une approche diagnostique, préventive et thérapeutique appropriée est nécessaire pour prévenir la mortalité et les séquelles neurologiques.

Mots-clés

Thrombopénie, nouveau-né, pronostic.

SUMMARY

Background: Thrombocytopenia is a common clinical problem in neonatal intensive care units, affecting about 20 to 35% of all admitted neonates. Even most episodes are mild or moderate, severe episodes could be life-threatening or responsible for sequelae.

Objectives: The aims of this study were to describe the prevalence, clinical diagnoses, and to determine risk factors for poor prognosis of thrombocytopenia in a neonatal intensive care unit.

Methods: We carried out a retrospective study in the neonatal intensive care unit of Charles Nicolle Hospital of Tunis, a tertiary neonatal care center, over a four years period (January 2010 to December 2013). All Neonates with at least one episode of confirmed thrombocytopenia were included. Poor prognosis was defined as death or intraventricular hemorrhage ≥ grade 2 in survivors.

Results: Of 808 admitted neonates, one hundred (12.4%) had presented at least one episode of confirmed thrombocytopenia, and 12 had presented two episodes of thrombocytopenia. A total of 112 episodes of thrombocytopenia were collected. Thrombocytopenia occurred in the first 3 days of life in 74.1% of cases. Thrombocytopenia was mild in 22.3%, moderate in 36.7% and severe in 41%. Intrauterine growth restriction was the most common cause of early thrombocytopenia. Nosocomial sepsis was the most common cause of late thrombocytopenia. We found that the outcomes of thrombocytopenic neonates depend on, birth weight, gestational age, platelet count, and the underlying cause.

Conclusions: Thrombocytopenia in neonates can be life-threatening, appropriate diagnosis, preventive and therapeutic approach is necessary to prevent death or neurological impairment.

Key-words

Thrombocytopenia; platelet count; newborn; outcomes.

Thrombocytopenia is a relatively common complication in neonates, affecting about 20 to 35% of all admissions in neonatal intensive care units (NICUs) [1,2]. Generally moderate, sometimes severe and potentially life-threatening. The main risk is bleeding, especially intracranial hemorrhage. Severe thrombocytopenia and serious hemorrhage are more likely in preterm and very low birth weight infants [3]. Outcomes depend mainly on the underlying cause. There is no published study reporting the prevalence and the outcomes of thrombocytopenia in Tunisian NICUs. The aims of this study were to describe the prevalence, clinical diagnoses, and to determine risk factors for poor prognosis of thrombocytopenia in a neonatal intensive care unit.

METHODS

We conducted a retrospective study in the NICU of Charles Nicolle Hospital of Tunis, a tertiary neonatal care center, over a four years period (1st January 2010 to 31 December 2013). Neonates, who presented at least one episode of confirmed thrombocytopenia during their hospital stay, were included. Thrombocytopenia was defined as a platelet count <150 × 10^9/L. Confirmed thrombocytopenia was defined as ≥ 2 platelet counts <150 x 10^9/L. We have considered sub-groups of thrombocytopenia according to the severity: mild (100-149 × 10^9/L), moderate (50-99 × 10^9/L), severe (< 50 × 10^9/L). We have considered early thrombocytopenia if occurred in the first 72 hours of life, late thrombocytopenia if occurred after. Indications of platelet transfusion in our NICU during the study period were as follows: (1) platelet count < 30 × 10^9/L and stable neonate, (2) platelet count < 50 × 10^9/L and unstable neonate, or (3) platelet count <100 × 10^9/L in neonates with active bleeding. Platelet transfusion was prophylactic if the indication was (1) or (2) and therapeutic if the indication was (3). Poor prognosis was defined as death or intraventricular hemorrhage (IVH) ≥ grade 2 in survivors. Data were collected from the maternal and the newborn's medical records.

Data presented as means, standard deviation (SD) for centrally distributed data. Categorical data were presented as percentages. The chi-square test was used to compare variables frequencies. Group means were compared by using Student's t test. Odds ratios (ORs) were estimated for risk factors associated with "poor prognosis". Epi Info 6.04d was utilized for statistical analysis. P-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 808 neonates were admitted to the NICU. One hundred neonates (12.4%) had presented at least one episode of confirmed thrombocytopenia during their hospital stay, and 12 neonates had presented two episodes of thrombocytopenia. A total of 112 episodes of thrombocytopenia were collected. General characteristics of neonates are presented in table 1.

Table 1 : General characteristics of neonates

Sex ratio (M/F)	1.56
Gestational age (weeks), mean ± SD	35.5 ± 4.05 (26-41)
Birth weight (g), mean ± SD	2437±1057 (780-5400)
Preterm (%)	63
VLBW (%)	24
IUGR (%)	37

VLBW: very low birth weight, IUGR: intrauterine growth restriction, SD: standard deviation.

Thrombocytopenia episodes occurred in the first 3 days of life in 74.1% (83/112). Thrombocytopenia was detected at a mean of 4 days of life (1-75). Thrombocytopenia was mild in 22.3% (25/112), moderate in 36.7% (41/112) and severe in 41% (46/112); the prevalence of severe thrombocytopenia was 5.7% (46/808).

The clinical diagnoses of the thrombocytopenia are listed in table 2.

Table 2 : Clinical diagnoses identified to explain the thrombocytopenic episodes

Clinical diagnoses	Number of episodes (% of total episodes)
Nosocomial sepsis	29 (18.6)
IUGR	26 (16.6)
EONS	23 (14.7)
DCI	22 (14.1)
PIH	18 (11.5)
Unexplained	15 (9.6)
Congenital rubella	6 (3.8)
Perinatal asphyxia	5 (3.2)
Necrotizing enterocolitis	3 (1.9)
Trisomy 21	2 (1.3)
Cytomegalovirus	2 (1.3)
Blood exchange transfusion	2 (1.3)
Congenital toxoplasma	1 (0.7)
Neonatal upus	1 (0.7)
Maternal idiopathic thrombocytopenic purpura	1 (0.7)

IUGR: intrauterine growth restriction, EONS: early onset neonatal sepsis, DIC: disseminated intravascular coagulation, PIH: pregnancy induced hypertension,

Materno-fetal conditions (intrauterine growth restriction (IUGR), early onset neonatal sepsis (EONS) and maternal pregnancy induced hypertension (PIH)) accounted for 42.8% (67/156) of the causes of thrombocytopenia; nosocomial sepsis represented 18.6% (29/156) of the causes. Disseminated intravascular coagulation (DIC) was observed in 22 patients, it was associated with nosocomial sepsis (18/22), necrotizing enterocolitis (NEC) (3/22), and with perinatal asphyxia in one case. In 14.3 % (16/112) thrombocytopenia was multifactorial. Thrombocytopenia had no explanation given in 15 cases. In 45.5% (51/112) of episodes,

thrombocytopenia was associated with cytopenia: anemia (45/112) and leucopenia (6/112); pancytopenia was found in seven cases.

The prevalence of bleeding was 32.1% (36/112). Among the bleeding neonates, 19 patients presented severe hemorrhage. IVH occurred in eight cases, all of them were premature. A total of 77 platelet transfusion was indicated in 40 patients. Platelet transfusion was prophylactic in 26% (20/77) and curative in 74% (57/77). Of the 40 platelet transfused patients, 20 received ≥ 2 platelet transfusions. Immunoglobulins associated with platelet transfusion were used twice in the case of neonatal lupus (drop of platelet account to 20× 10^9/L and to 10× 10^9/L on day tow and on day five of life, respectively). Red blood cells and fresh frozen plasma transfusions were required in 29 and 22 neonates, respectively.

The intrahospital mortality rate was 21%. Very low birth weight (VLBW), prematurity, nosocomial sepsis, and severe thrombocytopenia were predictors of "poor prognosis". No significant difference was found between "good prognosis" and "poor prognosis" groups as regards to prophylactic platelet transfusion.

Table 3 : Risk factors for poor prognosis.

	Good prognosis	Poor prognosis	OR	95% CI	P
VLBW	15	9	7.28	[2.8-18.9]	<0.001
Prematurity	27	20	6.1	[2.24-16.62]	<0.001
Nosocomiale sepsis	17	12	4	[1.57-10.15]	0.002
Severe thrombocytopenia	31	15	2.71	[1.08-6.74]	0.029

VLBW: very low birth weight, OR: odds ratio, CI: confidence-interval.

DISCUSSION

Our study showed a high prevalence of neonatal thrombocytopenia. Nosocomial sepsis, IUGR, EONS, DCI and PIH were the most common causes for thrombocytopenia. VLBW, prematurity, nosocomial sepsis, and severe thrombocytopenia were predictors of "poor prognosis".

Thrombocytopenia is relatively a common hematological disorder in NICUs. Previous studies have reported that 20% to 30% of all patients who are admitted to a NICU have at least one platelet count<150 × 10^9/L during their hospital stay [4,5]. We found that severe thrombocytopenia accounted for 41% of all episodes of thrombocytopenia; its prevalence was 5.7% of all admissions; similar results were reported [6,7]. In the present study, thrombocytopenia occurred often in the first 72 hours of life, and the majority of thrombocytopenic episodes were mild or moderate; our findings are consistent with previous reports [8]. In contrast, other studies reported that the majority of thrombocytopenic episodes were diagnosed after 72 hours of age [3,9]. The populations in these studies were mainly very preterm and extremely low birth weight infants, with high prevalence of later and severe thrombocytopenia.

IUGR and PIH and EONS were the most common causes for early thrombocytopenia in our population. Early thrombocytopenia is generally associated to materno-fetal conditions. Newborns of mothers with PIH with or without IUGR are at risk of thrombocytopenia due to disorders associated with placental insufficiency [10]. Chronic hypoxia leads to megakaryopoiesis dysfunction. Thrombocytopenia secondary to PIH and/or IUGR is mild or moderate, resolving within 2 weeks in the majority of cases. Severe thrombocytopenia within 72 h of life is rare. In this case, except EONS and perinatal asphyxia, fetal causes must be investigated: allo- or autoimmune thrombocytopenia, congenital infections (cytomegalovirus, rubella), chromosomal disorders (trisomies 18, 13 and 21 or triploidy), and inherited thrombocytopenia [11].

Late thrombocytopenia is almost usually due to sepsis or necrotizing enterocolitis [4,6]. In this situation, thrombocytopenia is frequently severe, progresses rapidly with a platelet nadir within 24-48 h, and it is often prolonged, persisting until sepsis or NEC is controlled [6,8]. Charoo et al reported that nosocomial sepsis is an important risk factor for late thrombocytopenia in the NICU, and that fungal and gram negative sepsis are frequently responsible of platelet count drop [12]. Bacterial sepsis damages the vascular endothelial lining, thus accelerating adhesion, destruction, and removal of platelets [13]. It can also cause DIC, immune-mediated destruction, and decreased production of platelets from infected marrow.

We found that 74% of platelet transfusions were given in a therapeutic setting; prophylactic platelet transfusion represented only 26% of all. Our finding are different from several studies reporting that platelet transfusions are frequently administered to non-bleeding neonates with platelet counts of >50 x 10^9/L [14,15]. We also found that prophylactic platelet transfusion was not preventive of «poor prognosis». Several studies showed that prophylactic platelet transfusion was not associated with reduce of the incidence of severe hemorrhage or death [3,6,16]. Over the last decade there has been a trend toward accepting lower platelet counts in neonates, particularly in stable and non-bleeding patients [17-19]. In fact, the risk of bleeding depends mainly on the underlying diagnosis. Thus it is higher in allo-immune thrombocytopenia, sepsis, NEC, and in very preterm infant. The risk is low even if severe thrombocytopenia for IUGR and PIH [4]. The benefits of prophylactic platelet transfusion remain speculative. On the other hand, platelet transfusion is not without risk. Thus

prophylactic platelet transfusion should be indicated in cases of serious risk of hemorrhage.

In our population, the mortality rate was high (21%). In fact, we found that EONS, nosocomial sepsis and DCI accounted for about half (47.4%) of causes of the thrombocytopenic episodes. We also found that VLBW, prematurity, nosocomial sepsis, and severe thrombocytopenia were predictors of “poor prognosis”. These risk factors were reported by others authors [6,20]. The increasing number of platelet transfusions administered in the NICUs was also reported as a risk factor for mortality [3,12,21-23]. Generally, multiple platelet transfusions are necessary for the sickest neonates admitted to NICUs, therefore the number of platelet transfusion is a marker of disease severity and predictive of mortality. However, authors speculate that multiple platelet transfusions themselves are harmful in this population [21].

Our study had limits; it was a monocentric study including a small cohort of patients. Even the study was retrospective, we had no missing data. This supports the reliability of our results.

CONCLUSIONS

Our study showed a high prevalence of thrombocytopenia in our NICU with high mortality rate in thrombocytopenic neonates. The outcomes of thrombocytopenic neonates depend on, birth weight, gestational age, platelet count and the underlying cause.

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