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Neonatal Thrombocytopenia in the Neonatal Intensive Care Unit of Bahrami Children's Hospital: Clinical Diagnoses, Management and Short-Term Outcomes

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ABSTRACT

Background and Objective: Neonatal thrombocytopenia (NTP) is one of the most common neonatal hematological disorders. The causes of NTP are very various, leading to large differences in the clinical profile of the affected neonates. Therefore, the aim of this study was to investigate the characteristics, clinical diagnoses and short-term outcomes of NTP in Bahrami Children's Hospital, Iran.

Methods: This descriptive retrospective cross-sectional study was conducted on all neonates admitted to the neonatal intensive care unit (NICU) of Bahrami Children's Hospital in 2017-2019. The infants diagnosed with NTP, defined as a platelet count of less than 150000 on at least 2 occasions, were retrospectively evaluated. Data on patients' NTP and short-term outcomes were reported. Incomplete medical records were excluded from the study.

Findings: Out of 2000 neonates, 210 patients were diagnosed with NTP with a prevalence of 10.5%. Totally, 60% and 71.4% of infants were premature and underweight, respectively. Moreover, 30 and 20.9% of infants had premature and severe NTP, respectively. The most common clinical diagnosis was sepsis (68.1%). The mean length of stay in NICU was 12.3±9.5 days. Additionally, 20.9% of infants had at least one episode of severe hemorrhage, received a platelet transfusion, and 10.4% of infants expired during their NICU stay.

Conclusion: The prevalence of NTP was 10.5%. Despite the relatively high prevalence of preterm birth, low-birth weight and sepsis, the majority of our neonates recovered. Prospective studies are recommended to investigate the role of each predisposing factor in the development and outcome of NTP.

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Introduction

Neonatal thrombocytopenia (NTP) defined as a platelet count less than 150×10^9/L regardless of gestational age is one of the most common neonatal hematological disorders [1]. The incidence of NTP in neonates ranges from less than 1% to 5%; however, it develops in greater than 50% of those admitted to neonatal intensive care unit (NICU) [1-3]. The mechanisms underlying NTP in neonates and adults have a similar trend, i.e. increased platelet consumption and/or sequestration due to immune-mediated or non-immune causes and decreased platelet production due to poor bone marrow function or a combination of both [4].

The etiology of NTP includes a broad range of maternal, perinatal and neonatal causes, which can be classified based on factors such as the onset of NTP (early vs. late), gestational age (term vs. preterm), underlying mechanism and general condition of the neonate [1, 3]. Causes of NTP are best separated by time of presentation into fetal, early-onset, and late-onset. Early-onset NTP (presenting within the first 72 h of life) is related to chronic fetal hypoxia (as observed in intrauterine growth restriction (IUGR), pregnancy-induced hypertension or maternal diabetes), hypoxic-ischemic encephalopathy, perinatal or congenital infections, NAIT and maternal ITTP. On the other hand, most cases of late-onset NTP (presenting after the first 72 h of life) are associated with late-onset sepsis and necrotizing enterocolitis (NEC) [1, 4, 5].

Although a temporal association has often been observed between NTP and bleeding, the causality of the relationship is still a matter of debate [5]. Mild-to-moderate NTP (platelet count $50\_149\times10^9$/L), which accounts for the majority of NTP in neonates is generally self-limited, mostly resolving within 14 days [1]. On the other hand, severe NTP is potentially associated with an increased risk of bleeding ranging from mucocutaneous hemorrhages to pulmonary and/or gastrointestinal bleeding and intracranial hemorrhage (ICH) [6]. A recent study has shown that the location of cerebral hemorrhage and the resulting neurological damage depends on when NTP occurs during development [7]. According to different guidelines, a neonate with a platelet count less than 20×10^9/L should receive a platelet transfusion, regardless of age or clinical condition [1].

Detection of NTP is a useful initial assessment for sick neonates as it is considered one of the complications of the disease process. However, if not detected and managed properly, NTP can result in devastating complications. Due to the paucity of local studies on the profile of NTP in Bahrami Children's Hospital, the aim of the current study was to determine the frequency of known etiologies and predisposing factors of NTP and evaluate the short-term outcomes of these neonates.

Methods

Design and participants

This descriptive retrospective cross-sectional study was conducted at the NICU of Bahrami Children's Hospital; a Tertiary Pediatric Center affiliated with the Tehran University of Medical Sciences, Tehran, Iran.

Medical records of all neonates admitted to the NICU from 2017 to 2019 were retrospectively evaluated. Neonates with a platelet count of less than 150000 on at least 2 occasions during the NICU stay and with NTP diagnosed by the attending neonatologist were included in the study using a convenient sampling method. Asymptomatic patients with only one episode of NTP and those with incomplete medical records were excluded from the current study.

Data collection

Medical records of eligible patients were reviewed to extract gender, gestational age at birth, birth weight, age at NTP diagnosis, clinical diagnoses of NTP, platelet count, duration of hospitalization, treatment modalities and short-term outcomes. Preterm birth was defined as delivery before 37 weeks of gestational age and was further categorized into moderate-late preterm (32-36 weeks), very preterm (28-31 weeks) and extremely preterm (<28 weeks). Regarding birth weight, neonates were classified into normal birth weight (≥2500 g), low birth weight (LBW) (<2500 g), very low birth weight (VLBW) (<1500 g) and extremely low birth weight (<1000 g). The pattern of onset of

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NTP was divided into early- (presenting < 72 hours of life) or late (presenting after 72 hours) onset. Based on the platelet counts, the severity of NTP was classified into mild (platelet count 100–150 × 109/L), moderate (50-99×109/L) and severe (< 50×109/L). Short-term outcomes were defined as the frequency of major bleeding events (the total number of patients receiving platelet transfusions, pulmonary hemorrhage, gastrointestinal bleeding and intraventricular hemorrhage (IVH)) and mortality.

Statistical analysis

Statistical analyses were performed using SPSS statistical software (version 22 for Windows, IBM Corp). Quantitative data were represented as mean±standard deviation or median (inter-quartile range) and were compared across groups using an independent-sample t-test or ANOVA. Qualitative data were represented as numbers and percentages, comparisons being made using Chi-square/ Fisher's exact test. P-value less than 0.05 was statistically considered significant.

Results

Out of 2000 neonates admitted to the NICU during the study period, a total of 210 patients were diagnosed with NTP, accounting for a prevalence rate of 10.5%. The analyses were performed on 210 NTP neonates (males=108 and 102=females).

The mean age of 1-27-day infants at diagnosis of NTP was 10 ±9 days. Gestational age ranged from 23 to 40 weeks and 60% of patients were preterm. The mean birth weight was 2072.5±703.31 g (ranging from 930 to 3500 g), and 150 neonates (71.4%) were LBW. The median age at diagnosis was 5 days. Sixty-three (30%) of neonates had early-onset NTP, i.e. diagnosis was made during the first 72h of life, and the rest had late-onset. The majority of neonates (79.1%) had mild to moderate NTP, while 20 (20.9%) had severe NTP at diagnosis. Mean platelet count was 102000.2±26000.77 (per mm3). Demographic, clinical and paraclinical data are presented in Table 1. The clinical diagnoses identified to explain the thrombocytopenia were sepsis (68.1%), followed by IUGR (8.6%), NEC (5.7%), pregnancy-induced hypertension (5.2%), gestational diabetes (4.7%) and hypoxic-ischemic encephalopathy (3.8%). Table 2 shows the frequency of the clinical diagnoses based on the onset of NTP.

The length of NICU stay ranged from 1 to 37 days with a mean of 12.3± 9.5 days. In terms of outcome, 20 neonates (9.5%) had at least one episode of major bleeding and more than half of them had IVH. Out of IVH 12 neonates, 10 and 7 cases had sepsis and severe NTP. Forty-four neonates (20.9%) received platelet transfusion, 10 of whom died. The majority of infants had improved clinical symptoms as well as were discharged and followed up in an outpatient setting. On the other hand, 22 patients (10.4%) died. A summary of the outcomes of the study population is illustrated in Table 3.

Table 1. Demographic, clinical and paraclinical variables of the study

Variables		N (%)
Sex	Male	108 (51.4%)
	Female	102 (48.6%)
Gestational age	Term	84 (40%)
	Moderate to late preterm	102 (48.6%)
	Very preterm	18 (8.6%)
	Extremely preterm	6 (2.8%)
Birth weight	Normal	60 (28.6%)
	Low birth weight	150 (71.4%)
Onset of thrombocytopenia	Early	63 (30%)
	Late	147 (70%)
Severity of thrombocytopenia	Mild	76 (36.2%)
	Moderate	90 (42.9%)
	Severe	44 (20.9%)

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Table 2. Clinical diagnoses based on onset of thrombocytopenia episodes

Pattern of onset of neonatal thrombocytopenia	Causes of thrombocytopenia	N (%)
Early-onset thrombocytopenia (≤72 h), n=63	Intrauterine growth restriction	18 (28.5)
	Pregnancy-induced hypertension	11 (17.5)
	Gestational diabetes	10 (15.9)
	Early-onset sepsis	10 (15.9)
	Hypoxic-ischemic encephalopathy	8 (12.7)
	Neonatal alloimmune thrombocytopenia	3 (4.7)
	Congenital anomalies	2 (3.2)
	Maternal immune thrombocytopenic purpura	1 (1.6)
Late-onset thrombocytopenia (>72 h), n=147	Late-onset sepsis	133 (90.5)
	Necrotizing enterocolitis	12 (8.1)
	Metabolic diseases	2 (1.4)

Table 3. Outcome of neonatal thrombocytopenia

Type of outcome		N (%)
Major bleeding events	Intraventricular hemorrhage	12 (5.7)
	Gastrointestinal bleeding	6 (2.8)
	Pulmonary hemorrhage	2 (0.9)
Patients receiving platelet transfusions		44 (20.9)
Mortality		22 (10.4)

Discussion

The results of the present study demonstrated that the prevalence of NTP at NICU during the study period was 10.5%, and neonatal sepsis was the most common clinical diagnosis to explain the NTP. Seventy percent of neonates had late-onset NTP. Twenty neonates (9.5%) had at least one episode of major bleeding and 12 of them had IVH. Forty-four neonates (20.9%) received platelet transfusion. The majority of neonates (89.6%) were discharged and 22 patients (10.4%) died.

Although the frequency of NTP reported by different studies is highly variable, it is known to be significantly higher among VLBW preterm neonates, especially those admitted to the NICU [1, 2]. In the current study, the prevalence of NTP in NICU was 10.5%, which is lower than the reports by Ulusoy et al. (12%) and Ayadi et al. (12.4%) [8, 9]. On the other hand, Bolat et al. reported a prevalence of 9.4%, which is higher than that in ours. This difference may be due to different definitions and methods of diagnosis of NTP [10].

The approach to NTP is based on several key factors such as the general condition and gestational age of the newborn and etiology, mechanism and severity of NTP [1]. The onset of NTP is one of the most commonly used factors for the classification of etiologies, subdividing causes into early-onset and late-onset [5]. Based on this classification, early-onset and late-onset NTP were reported in 30% and 70% of our neonates, respectively. In contrast, Ayadi et al. reported early-onset NTP in 74.1% of their study population [10].

Overall, neonatal sepsis was the most common clinical diagnosis in the current study. One explanation is that our center doesn't have a maternity ward and most neonates are referred to us after the first 72 hours of life. However, Ulusoy et al. also stated that sepsis was the most common etiology of NTP in 2007-2009, whereas IUGR was the leading cause in 2010 [8]. Chakravorty et al. suggested NTP in 53 of 901 neonates admitted to the NICU over 3 years with late-onset sepsis and NEC being the most common causes [11]. Moreover, sepsis was the most common etiology in a study by Tirupathi et al. [12]. The pathogenesis of NTP in neonatal sepsis is not completely understood. One of the major mechanisms leading to low platelet counts in neonatal sepsis is disseminated intravascular coagulation (DIC) resulting in reticuloendothelial removal of platelets [13]. It has been found that NTP is one of the most predictive and independent risk factors for sepsis-associated mortality in VLBW neonates [14]. Additional multi-

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center studies are required to clearly define the relationship between neonatal sepsis, NTP and outcomes in high-risk neonates.

Analysis of the causes according to early- and late-onset NTP revealed that IUGR and late-onset sepsis were the most common causes in early- and late-onset NTP, respectively. In addition, Ulusoy et al. reported similar results [8]. In preterm neonates, chronic fetal hypoxia caused by IUGR, pregnancy-induced hypertension, preeclampsia and maternal diabetes leads to increased erythropoiesis, which, in turn, suppresses platelet production in the bone marrow, resulting in early-onset NTP [1, 2]. In these situations, NTP is usually mild-to-moderate and resolves spontaneously within 10 days [5]. On the other hand, in healthy term neonates, the early-onset NTP mainly occurs because of immune-mediated mechanisms, i.e. fetal or neonatal platelet destruction due to the maternal antiplatelet alloantibodies or less commonly, autoantibodies (ITTP) [2, 5]. In NAIT, the NTP is often severe, associated with a high risk of intracranial bleeding [11]. In the ongoing study, only 3 cases of NAIT were reported. This might be explained by the fact that the population of the present study consisted of newborns admitted to the NICU due to various underlying pathologies. Moreover, NAIT-associated NTP typically occurs during the first 72 h of life but most neonates o the current study had late-onset NTP.

NTP is usually mild or moderate with severe NTP occurring on average in 2-25% of neonates [5]. In the present study, the prevalence of severe NTP was almost 21%, which falls within the range. The major concern about the severity of NTP is the increased risk of bleeding. In neonates, severe NTP has been associated with major bleeding events, including IVH, pulmonary hemorrhage or gastrointestinal bleeding [8, 15, 16]. However, these findings do not imply a causal relationship [5]. Von Lindern et al. expressed a significant association between NTP, irrespective of the severity and IVH but found no differences in the incidence of IVH after stratifying for the severity of NTP [17].

The risk of bleeding is higher in neonates with NAIT, sepsis or NEC, especially in very preterm neonates [1-5]. In the current study, major bleeding (IVH, gastrointestinal bleeding and pulmonary hemorrhage) occurred in 9.5% of neonates, which is roughly similar to that of Ulusoy et al. [8]. This study is also in accordance with the present study in terms of the high prevalence of preterm birth, LBV and sepsis. In the ongoing study, it was found that only 7 of 12 neonates with IVH had severe NTP; hence, prospective studies are needed to evaluate the role of severity of NTP on the incidence of IVH.

Management of NTP is based on the use of prophylactic and therapeutic platelet transfusions; however, there is no evidence that prophylactic transfusions are effective to prevent bleeding [5]. It has been reported that in 20 to 25 % of neonates, one or more platelet transfusions are ordered [18]. In the current study, 20.9% of neonates received platelet transfusion. The mortality rate in the ongoing study was 10.4%, which is higher than that in the study of Ulusoy et al. who had a mortality rate of 4.5% [8]. This difference might be due to the variety of study populations and also the high prevalence of sepsis in the present study. About half of expired neonates had platelet transfusions. According to Christensen et al., the mortality rate had no relationship with the lowest platelet count but was proportionate to the number of platelet transfusions received [19]. It might be concluded that platelet transfusion does not necessarily improve the outcome. Moreover, timely management of sepsis may reduce the need for transfusions.

Limitations of the study

Our study had some limitations. Because of the retrospective methodology of the current study, more detailed data regarding some variables could not be gathered. Moreover, patients with incomplete medical records were excluded from the ongoing study. As there was no control group, we could not precisely state the clinical diagnoses used to explain the NTP as "risk factors". Moreover, no association between risk factors and outcomes could be established. The present study can serve as baseline data for additional prospective, preferably multi-center studies.

Conclusion

The results of the present study represented that the most common etiologies of NTP were sepsis,

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followed by IUGR and NEC. Despite the relatively high prevalence of preterm birth, LBV and sepsis, the majority of neonates in the current study recovered. Cost-effective and early interventions such as antibiotic administration in case of infections are needed to decrease the prevalence of NTP. Prospective studies are recommended to investigate the role of each factor in the development of NTP.

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Ethical approval

The study was approved by the Ethics Committee of the Medical Faculty of Tehran University of Medical Sciences (Code: IR.TUMS.MEDICINE.REC.1397.830).

Conflict of interest

The authors declare no conflict of interest.

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